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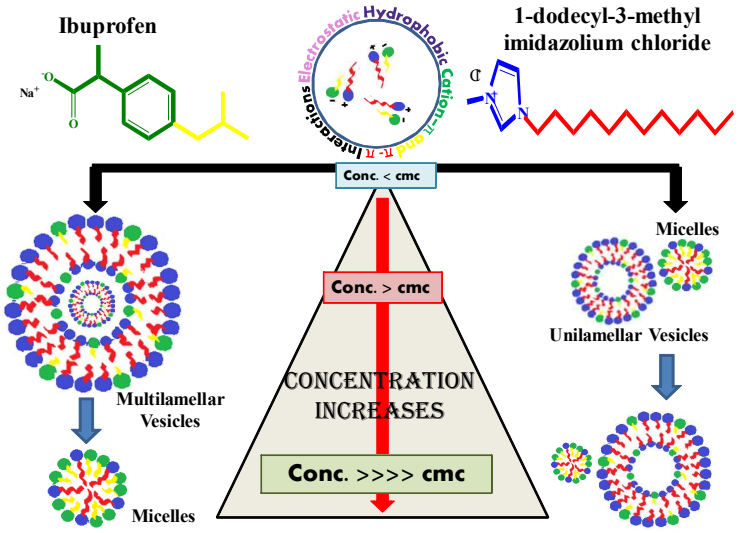

Interactions between 1-dodecyl-3-methylimidazolium chloride and Ibuprofen molecules in aqueous solution forms catanionic mixtures, with morphologies of mixed micelles dependent on solution composition.

Micellar Transitions in Catanionic Ionic liquid - Ibuprofen Aqueous Mixtures; Effects of Composition and Dilution

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Abstract

The present study aims to develop a basic understanding of the molecular interactions of an anti-inflammatory drug, Ibuprofen (Ibu) with surface active ionic liquid (IL), 1-dodecyl-3-methylimidazolium chloride (C_{12}mimCl) in aqueous medium, owing to their utility as the components of pharmaceutically active ionic liquids. Various techniques such as surface tension, steady-state fluorescence, UV-visible absorption, dynamic light scattering and ^{1}H NMR measurements have been employed to provide a comprehensive knowledge about C_{12}mimCl -Ibu interactions. The interactions between the ionic liquid and drug molecules are found to be highly synergistic both in the mixed micelles as well as in mixed monolayer due to the formation of catanionic mixtures. These mixtures are seen to display enhanced micellization and adsorption tendencies and varied aggregate assemblies in aqueous medium determined by amphiphile mixing ratio and the total mixture concentration. The dilution induced transformation of smaller micelles to larger aggregates is accounted to the solubility mismatch between the two components. The quantitative evaluation of the process of interaction between Ibu and the ILs has been done in terms of various quenching and binding parameters exploiting fluorescence measurements. The formation of highly surface active catanionic complexes ($C_{12}mim^{+}$ Ibu^{-}) of 1:1 stoichiometry stabilized largely by a combination of electrostatic, hydrophobic, cation-π and π-π interactions has been well established through spectroscopic investigations.

Keywords: 1-dodecyl-3-methylimidazolium chloride, Ibuprofen, Interactions, Micellar transitions, Binding constant, Catanionic complexes.

1. Introduction

Ionic liquids (ILs) are being increasingly reported as multipurpose materials,[1-5] with the interest capturing the attention of scientific fraternity even outside the disciplines of chemistry. The credit lies indeed to their 'designer' nature i.e. easily tunable behavior and essentially to their 'greener' aspects.[6-9] The journey of these ILs started with the first generation ILs[9,10] possessing unique physical properties such as decreased vapor pressure and high thermal stability, progressing to the second stage with advanced functional materials called second generation ILs[11,12] produced through a modification of both physical and chemical properties. And now these are heading towards their third generation where the active pharmaceutical ingredients are being explored to produce ILs with biological activity.[13-15] One of the reasons for the deployment of ILs in this regard is the possibility to tailor their physical, chemical and biological properties by developing specific features into the chemical structures of the cation or anion components that can offer unique attributes like desired hydrophobicity/hydrophilicity, acidity/basicity, viscosity etc. These ILs generally employ the use of one of the surface active ions like benzalkonium, alkyl imidazolium, docusate etc along with the pharmaceutically active second counterpart to provide for the necessary dual functionality and also to control the solubility, stability and bioavailability of the drug. Such active pharmaceutical ingredient based ionic liquids (API-ILs) appear in the literature as lidocaine docusate, rantidine docusate, didecyldimethylammonium ibuprofenate, benzalkonium saccharinate, benzalkonium ibuprofenate etc.[16,17] While these active ions may be pharmacologically independent, they may also act synergistically or antagonistically with one active ion counteracting the side effects of the other active ingredient. Hence, an appropriate combination of an anion / cation with a drug for a new pharmaceutical ingredient change requires the basic understanding of the interactions between the cationic and anionic moieties at the molecular level.

Keeping these in view, we have tried to explore the interactions between a non steroidal anti inflammatory drug (NSAID)[18], Ibuprofen (Ibu) and an anti film agent,[19] 1-dodecyl-3-methyl imidazolium chloride (C_{12}mimCl) in aqueous medium. The knowledge of these interactions could be helpful in the development of an API-IL based on above components providing us a formulation that can facilitate the entry of an anti-inflammatory drug in the biofilms. In addition to these, Ibuprofen possesses antipyretic and analgesic properties while C_{12}mimCl possesses

better surface active properties than conventional surfactants.[20] The interest in these interactions also stems from the fact that both the drug and the ionic liquid being amphiphilic are not only capable of forming micelle like aggregates but are also oppositely charged and thus may interact electrostatically as well as hydrophobically to form ion pairs i.e. ($C_{12}mim^{+}Ibu^{-}$) in the solution giving rise to catanionic mixtures with their morphologies dependent on mixture composition. Such catanionic mixtures from oppositely charged surfactants[21-25] and oppositely charged ionic liquids and surfactants[26-28] have been shown to exhibit varied aggregate assemblies such as spheres, rods, disks, ribbons, bilayers, vesicles, etc. and particular phase behavior typically at a equimolar ratios. However, similar catanionic drug-surfactant mixtures have been earlier explored for their use as drug delievery agents,[29-32] but hardly any study addressing the issue of physiochemical characterization of catanionic drug -IL mixtures appears in literature. One such report by Viau and coworkers[33] discusses the surfactant like behavior of salt free catanionic ionic liquids composed of short alkyl chain imidazolium cations (chain containing 4,6 and 8 carbon atoms) and ibuprofenate anions, where catanionic pairing of Ibu has been observed only for ILs with 8 carbon atom chain. The role of alkyl chain length of the imidazolium moiety in modifying the micellar morphology has been well established earlier also.[34] But, we were more interested in the evaluation of the longer chain IL-drug interactions over the whole mixing range and that too in aqueous medium so as to mimic body fluids (where excess salts may be present) in order to meet the requirements for the use of these API – ILs in pharmaceutical applications.

Briefly, this paper takes into account a detailed analysis of interactional phenomenon in the C_{12}mimCl-Ibuprofen mixtures in aqueous solution, ranging from monomeric to micellar regions through an appraisal of both binding and micellar parameters employing Surface tension, Fluorescence, UV-visible, DLS and ^{1}H NMR measurements. Firstly, the formation and stoichiometry of the $C_{12}mim^{+}Ibu^{-}$ ion pair complexes has been judged and the extent of interactions in these complexes have been quantitatively discussed in the light of binding constant and Stern-Volmer quenching constant. Secondly, the interactions between the ionic liquid and drug molecules were evaluated in the bulk (mixed micelles) as well as at the air/water interface (mixed monolayer) for both of these properties stand equally important for designing the composition of the mixture of desirable surface activity, optimal for a specific application. The knowledge on the structural transitions in these IL-drug mixtures have also been studied as a

function of the mixture composition and the dilution. These pseudo catanionic mixtures are seen to display interesting interfacial, micellar and phase behavior properties in aqueous medium, determined by amphiphile mixing ratio and the total mixture concentration.

2. Experimental

2.1 *Materials*

1-alkyl-3-methylimidazolium chlorides (C_8mimCl and C_{12}mimCl) were synthesized in the laboratory according to the procedure mentioned elsewhere,[35] which involved alkylation of 1-methylimidazole with the corresponding 1-chloroalkanes. The products were then recrystallized from ethyl acetate and dried under vacuum. The purity of the products was ascertained by ^{1}H NMR spectrum in $CDCl_3$. Ibuprofen sodium salt (Ibu) was obtained from Fluka and 1-butyl-3-methylimidazolium chloride was a product of Sigma Aldrich. All chemicals were used as received and were of analytical grade. An analytical balance (Sartorius analytic) with a precision of ±0.0001g was used for weighing the amount of different substances. The solutions were prepared by dissolving accurately weighed quantities in requisite volumes of deionised double distilled water. The structures of the ionic liquid (C_{12}mimCl) and the drug (Ibu) used in the present study are given in Figure 1.

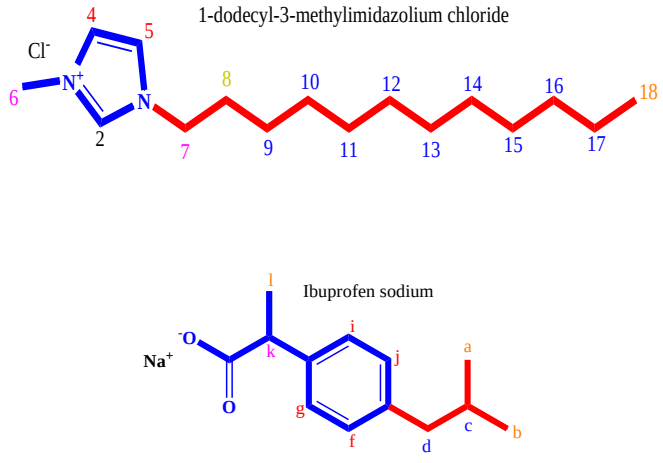

Figure 1 Basic structures of the Ionic liquid (C_{12}mimCl) and the drug (Ibu) used in the present study.

2.2 *Methods*

2.2.1 Surface Tension Measurements

The surface tension (γ) values were measured using a Du Nouy ring Tensiometer (Kruss Easy Dyne tensiometer) from Kruss Gmbh (Hamburg, Germany) equipped with thermostat, using a platinum ring at 298.15 ± 0.1K. The platinum ring used in the measurements was thoroughly cleaned every time by washing with doubly distilled water followed by heating through an alcoholic flame. The surface tension of doubly distilled water (72.8 mNm^{-1}) was used for calibration. The γ values for pure C_{12}mimCl, Ibu and their mixtures were measured by adding concentrated stock solutions (at ten times their cmc) of pure amphiphiles and their mixtures in aqueous solutions. All measurements were performed after giving the solutions, an overnight time for stabilization. The accuracy in the measurement of surface tension with tensiometer is ± 0.15 mNm^{-1}.

2.2.2 Fluorescence Measurements

The steady state fluorescence measurements were performed on Hitachi Fluorescence spectrophotometer, F-4600 using a 10 mm path length quartz cuvette at 298.15 ± 0.1K. The interactions between C_{12}mimCl and Ibu were studied using fluorescence spectroscopy in two ways. In one of the experiments we studied the micellar properties of the C_{12}mimCl + Ibu mixtures by employing an external probe, pyrene. For this, the concentration of pyrene used in all the measurements was approximately equal to 10^{-6} mol dm^{-3} with excitation at 335 nm and recording the emission spectra in the range of 350–500 nm using an excitation and emission slit width of 2.5 nm. The ratio of the intensity of pyrene emission, i.e. I_1/I_3 at 373 and 384 nm, respectively, was used for evaluating the polarity of the environment in which the pyrene was solubilised. Secondly, we studied the interactions between C_{12}mimCl and Ibu by considering the effect of varying amounts of C_{12}mimCl on the fluorescence emission spectra of Ibu recorded in the range of 250-400 nm at an excitation wavelength of 226 nm using an excitation and emission slit width of 2.5 nm. The titrations were performed by successive additions of stock solutions of C_{12}mimCl and Ibu directly into the quartz cuvette containing 2 mL of 0.1mM Ibu solution. After every addition, the solution was equilibrated for 5 minutes to reach the thermal equilibrium.

2.2.3 UV-visible Measurements

The absorption spectra were recorded on UV-1800, Shimadzu, UV-visible spectrophotometer with a quartz cuvette having path length of 1 cm. The absorbance of pure C_{12}mimCl, Ibu and their aqueous mixtures at varying mole fractions of the two components were recorded at 298.15 K in the range of 200-400 nm.

2.2.4 Dynamic Light Scattering (DLS) Measurements

DLS measurements were performed using a Malvern NanoZS zetasizer, equipped with a 532 nm laser beam. The samples of micellar solutions were properly filtered through 0.2 μm filters (Acrodisc) to avoid interference from dust particles. The scattered intensity for the various systems under study was obtained at an angle of 173° to the incident beam and data was collected at least five times for each independent sample. The apparent hydrodynamic diameters were then determined through Stokes-Einstein equation. The ζ-potential measurements were also carried out with the same instrument.

2.2.5 NMR Measurements

^{1}H NMR experiments were performed on a 300 MHz JEOL-FT NMR-AL spectrometer using D_2O as solvent. The NMR titration experiments were performed by titrating 2 mM of C_{12}mimCl prepared in D_2O with increasing equivalents of Ibu. Chemical shifts were given on the δ scale. The center of the HDO signal (4.650 ppm) was used as the internal reference.

3. Results and Discussion

Aqueous mixtures of two oppositely charged amphiphiles, the so-called catanionic mixtures are pseudo-three component systems and known to exhibit interesting phase behavior particularly at equimolar ratios. Considering this, a series of solutions of pure C_{12}mimCl and pure Ibu with concentrations 0.1mM, 1mM, 10mM, 50mM and 100mM were prepared. The equimolar solutions of both were then mixed in varying mole fractions ranging from 0.1 to 0.9. A visual inspection of these mixtures revealed interesting results as shown in Figure 2 for 1mM, 10mM and 50mM concentrations. The solutions with a total mixture concentration of 0.1mM and 1mM were clear and transparent throughout the entire mole fraction of C_{12}mimCl (x_{IL}= 0.1-0.9). In case of 10mM total concentration, the solutions were turbid for the anionic mole fraction range i.e. x_{IL}= 0.1-0.5 and clear for x_{IL}= 0.6-0.9 (cationic rich mole fraction range). However, in solutions with a concentration of 50mM, the turbidity appeared only in samples having 0.3-0.5 mole fraction of C_{12}mimCl. Further increase in the concentration also led to the disappearance of

turbidity (and increase in viscosity) in samples having x_{IL}= 0.3, 0.4 and 0.5 at total mixture concentrations greater than 100mM, 200mM and 750mM respectively. These observations indicated that the mixing of cationic IL with anionic drug did not led to the precipitation of insoluble salts which might be due to highly asymmetric chain lengths of the two components as is reported in case of cetyltrimethylammonium octylsulfonate.[25,36]

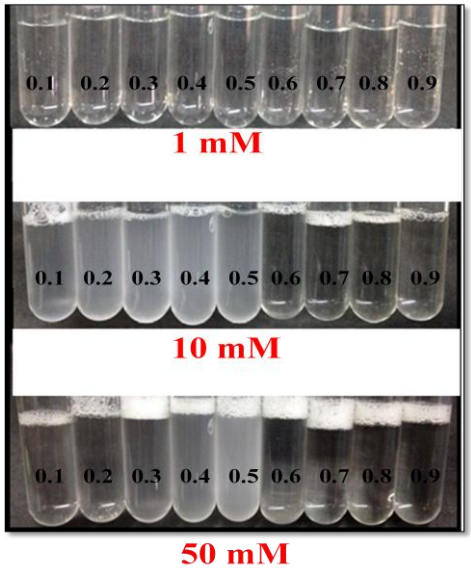

Fig. 2 (a)

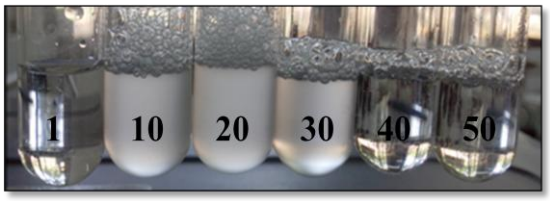

Fig. 2 (b)

Figure 2 (a) Phase behavior of C_{12}mimCl and Ibu mixtures in aqueous solution at varying mole fractions of C_{12}mimCl (x_{IL}) for total mixture concentration of 1mM, 10mM and 50mM.(b) Phase behavior of C_{12}mimCl + Ibu aqueous mixtures at x_{IL} = 0.2 for total mixture concentration of 1mM, 10mM 20mM, 30mM, 40mM and 50mM.

Based on above, we could differentiate two concentration regions as; firstly, at total mixture concentration ≤ 1mM, where all the cationic (C_{12}mimCl) rich or anionic (Ibu) rich samples exhibited similar behavior. At such lower concentrations, the interactions between the monomeric forms of both the molecules could be speculated as discussed further. Secondly, the regions at concentrations ≥ 1mM in which the anionic dominated mole fractions were initially turbid followed by its gradual disappearance at higher concentrations while the cationic rich mixtures were clear throughout. As in case of amphiphilic molecules, the changes in the turbidity are generally considered to be associated with the change in size and scattering factor of aggregates in the solution, the above observations can thus be visualized to be the result of the formation and the redissociation of some sort of C_{12}mimCl-Ibu aggregates, as both of the molecules being surface active can exhibit the tendency to undergo mixed micellization. Hence a complete analysis of the interactional phenomenon in the C_{12}mimCl-Ibu mixtures requires the evaluation of various changes associated with both the monomeric and micellar regions.

3.1 Formation of catanionic $C_{12}mim^+$ Ibu^- complexes in monomeric regions

To have a detailed picture of the interactions between C_{12}mimCl and Ibu monomers in aqueous solution and to account for the formation of catanionic complexes ($C_{12}mim^+$ Ibu^-), spectroscopic monitoring of their aqueous mixtures was carried out employing UV-visible and fluorescence measurements. The absorbance spectra of both pure C_{12}mimCl and Ibu at a concentration of 0.1mM were recorded from 200-400 nm range where Ibu is seen to exhibit an intensive peak with maximum absorption wavelength (λ_{max}) at 226 nm and a smaller but broader peak at 254 nm while no such peaks were observed for C_{12}mimCl (Figure S1, Supporting Information). This spectral characteristic of Ibu is consistent with previously reported data.[37] UV-visible measurements were employed to confirm the formation of catanionic $C_{12}mim^+$ Ibu^- complexes and to determine their stoichiometry by the method of continuous variations (Job's method). This involves measuring the absorbances of various samples obtained by mixing of equimolar solutions of both components (0.1mM of aqueous mixtures of each of Ibu and C_{12}mimCl were taken in present study) in varying volume fractions. The corrected absorbances (ΔA) of these samples are then plotted against the volume fraction of the C_{12}mimCl as shown in

Figure 3. This corrected absorbance represents the difference between the measured absorbance (A_{exp}) and the theoretical absorbance (A_{theo}) of the samples as

$$\Delta A = A_{exp} - A_{theo} \quad (1)$$

where A_{theo} is calculated taking into account the Beer-Lambert's law i.e. the two components do not interact with each other and hence the total absorbance of the mixture is equal to the sum of their individual absorbances as per the equation (2)

$$A_{theo} = \varepsilon_{IL}\, C_{IL}^{0}\, X_{IL} + \varepsilon_{D}\, C_{D}^{0}\, (1 - X_{IL}) \quad (2)$$

Here ε_{IL} and ε_{D} are the molar extinction coefficients and $C_{IL}{}^{0}$ and $C_{D}{}^{0}$ are the concentrations of the stock solutions of the ionic liquid (C_{12}mimCl) and the drug (Ibu) respectively, while X_{IL} represents the volume fraction of the ionic liquid. But the interaction between the two components leading to the formation of a new catanionic species (IL-D) makes the actual absorbance of the samples to be as

$$A_{exp} = \varepsilon_{IL}\, C_{IL} + \varepsilon_{D} C_{D} + \varepsilon_{IL-D}\, C_{IL-D} \quad (3)$$

where $\varepsilon_{IL\text{-}D}$ *is* the molar extinction coefficient of the complex ($C_{12}mim^{+}$ Ibu^{-}) and C_{IL}, C_{D} and $C_{IL\text{-}D}$ are the concentrations of the respective species in the mixture. As depicted in Figure 3, the presence of a maximum in the Job's plot for the IL-drug mixtures at $X_{IL} \approx 0.5$ corresponds to 1:1 stoichiometry for their binding. Further it also validates the presence of only one complex species i.e. $[C_{12}mim]^{+}$ $[Ibu]^{-}$ in the solution.

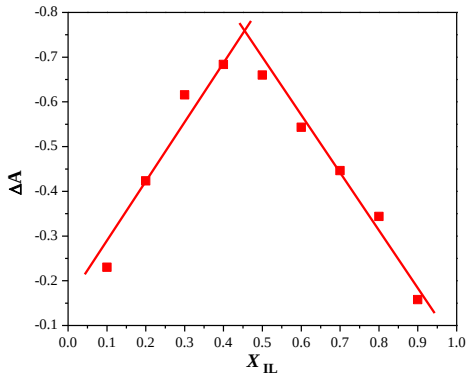

Figure 3 Job's plot depicting 1:1 stoichiometry for the catanionic $C_{12}mim^{+}Ibu^{-}$ complexes.

A further quantitative evaluation of these interactions in terms of binding constants was taken care of by fluorescence spectroscopy as Ibu itself gave a fluorescence emission spectrum[38] when excited at 226nm while the other component i.e. C_{12}mimCl showed no fluorescence in the region investigated. Moreover, the emission spectrum of a molecule is highly dependent on the polarity of the surrounding medium as compared to absorption measurements as the fluorophore stays for a longer time in the excited state and exposed to the relaxed environment with solvent molecules oriented around the dipole moment of the excited state.[39] Thus in fluorescence emission measurements, the amount of C_{12}mimCl was varied keeping the concentration of Ibu fixed at 0.1 mM and the corresponding changes in the fluorescence emission spectra for the peak maxima at 288.8 nm was noted and analyzed. The variation in the fluorescence emission spectrum of Ibu in its aqueous solution on addition of C_{12}mimCl is depicted in Figure S2, Supporting Information. A decrease in the fluorescence emission of Ibu signified the reduced availability of the fluorophores *i.e.* Ibu monomers, arising out of the complexation with C_{12}mimCl molecules. This quenching of Ibu fluorescence can be dynamic or static resulting from the collisions or the complexation between the fluorophore (Ibu) and the quencher molecules (C_{12}mimCl) respectively. Hence the fluorescence intensity data of Ibu both in the absence (I_0) and presence (I) of varying amounts of C_{12}mimCl [Q] at 288.8 nm was fitted to the following Stern-Volmer equation,[40]

$$\frac{I_0}{I} = 1 + k_q \tau_0 [Q] = 1 + k_{SV} [Q] \quad (4)$$

A good linear relationship was obtained for the I_0/I vs [Q] plots (Figure S3(a), Supporting Information) from where Stern-Volmer quenching constant (k_{SV}), was calculated and is given in Table 1. Further, taking average fluorescence life time (τ_0) of Ibu to be 10^{-8} s,[41] the collisional quenching rate constant (k_q) for the binding between Ibu and C_{12}mimCl were found to be greater than the maximum diffusion collision quenching rate constant (2.0×10^{10} $M^{-1}s^{-1}$) which signifies that the quenching was being mainly controlled by a static process rather than being a dynamic one. The corresponding free energies of quenching were evaluated employing equation (5) and were found to be negative for the systems under study suggesting that the quenching of Ibu fluorescence by C_{12}mimCl is a spontaneous process.

$$\Delta G_q = -RT \ln k_{SV} \quad (5)$$

Further, as both UV- visible and static quenching measurements signify the formation of 1:1 catanionic complexes between Ibu and C_{12}mimCl, the complexation equilibria and hence the binding constant can be represented as

$$C_{12}\text{mimCl} + \text{NaIbu} \leftrightarrow (C_{12}\text{mim})^{+}\,(\text{Ibu})^{-}$$

$$k_a = [(C_{12}\text{mim})^{+}\,(\text{Ibu})^{-}] \,/\, [C_{12}\text{mimCl}]\,[\text{NaIbu}] \quad (6)$$

The corresponding association constants for the complexation between IL and Ibu molecules can be determined from the spectral ratio between the fluorescence intensity of the bound (I) and the free ibuprofen (I_0) as per the equation[42]

$$\log[(I_0 - I)/I] = \log k_a + n \log [IL] \quad (7)$$

where n represents the number of binding sites and k_a is the apparent binding constant. A linear regression of the fitting curve of log (I_0-I)/I vs log of C_{12}mimCl concentration (Figure S3(b), Supporting information) provides the values of k_a and n as listed in Table 1. It is clear from the values of the binding constant that C_{12}mimCl exhibits larger binding affinity for the Ibu molecule as compared to its shorter chain analogues i.e. C_8mimCl and C_4mimCl. This increase in the k_a values with increasing chain length clearly emphasizes the role of hydrophobic forces in the formation of catanionic IL-Ibu complexes. The binding capacity (n) is found to be almost unity for all $C_n$mimCl + Ibu mixtures in accordance with UV-visible measurements. Further, from the values of k_a, the free energy change for the complexation between ILs and Ibu can be evaluated from the following equation:

$$\Delta G_a = -RT \ln k_a \quad (8)$$

The values of ΔG_a as listed in Table 1 have been found to be negative indicating the feasibility of formation of $[C_{12}\text{mim}]^{+}[\text{Ibu}]^{-}$ catanionic complexes under the given conditions. Both the k_a and ΔG_a is higher in magnitude in the C_{12}mimCl − Ibu mixtures as compared to C_8mimCl − Ibu and C_4mimCl − Ibu which suggests the greater feasibility and stability of the complex in case of former.

Table 1 Stern-Volmer quenching constants (k_{SV}, k_q), Binding constant (k_a), correlation coefficients (R_c), number of binding sites (n) and the corresponding free energy changes for quenching (ΔG_q) and binding (ΔG_a) for catanionic $C_nmim^+Ibu^-$ complexes.

System	k_{SV} ($\times 10^3$ M^{-1})	R_c	k_q ($\times 10^{10}$ $M^{-1}s^{-1}$)	k_a ($\times 10^3$ M^{-1})	n	R_c	ΔG_q (kJ mol^{-1})	ΔG_a (kJ mol^{-1})
Ibu + C_{12}mimCl	3.62	0.9987	36.2	1.543	0.90	0.9989	-20.3	-18.2
Ibu + C_8mimCl	1.65	0.9936	16.5	0.910	0.93	0.9953	-18.4	-16.9
Ibu + C_4mimCl	1.41	0.9995	14.1	0.227	0.78	0.9956	-17.9	-13.4

Hence on the basis of spectroscopic investigations we can conclude that the interaction between monomers of C_{12}mimCl and Ibu leads to the spontaneous formation of $[C_{12}mim]^+[Ibu]^-$ catanionic complexes stabilized largely by a combination of electrostatic as well as hydrophobic forces.

3.2 Formation of Mixed micelles in Catanionic C_{12}mimCl-Ibu (IL-drug) mixtures

As the cmc of a surface active substance is best regarded as a measure of its industrial utility, we here in investigated the behavior of aqueous mixtures of C_{12}mimCl and Ibu at varying mole fractions both in the bulk as mixed micelles and at the interface as mixed monolayer using fluorescence and surface tension measurements. For this, the propensity of both substances to form micelles individually was explored with conductivity and surface tension measurements, [Figures 4(a) and (b)] where the cmc values for both C_{12}mimCl and Ibu were found to be 14.22 mM and 187.63 mM respectively, being in good agreement with the literature values.[43,44] Ibu displays quite less capacity to form aggregates than C_{12}mimCl as revealed from its comparatively much higher cmc. This could also be due to the presence of a long alkyl chain in C_{12}mimCl giving it a high hydrophobicity.

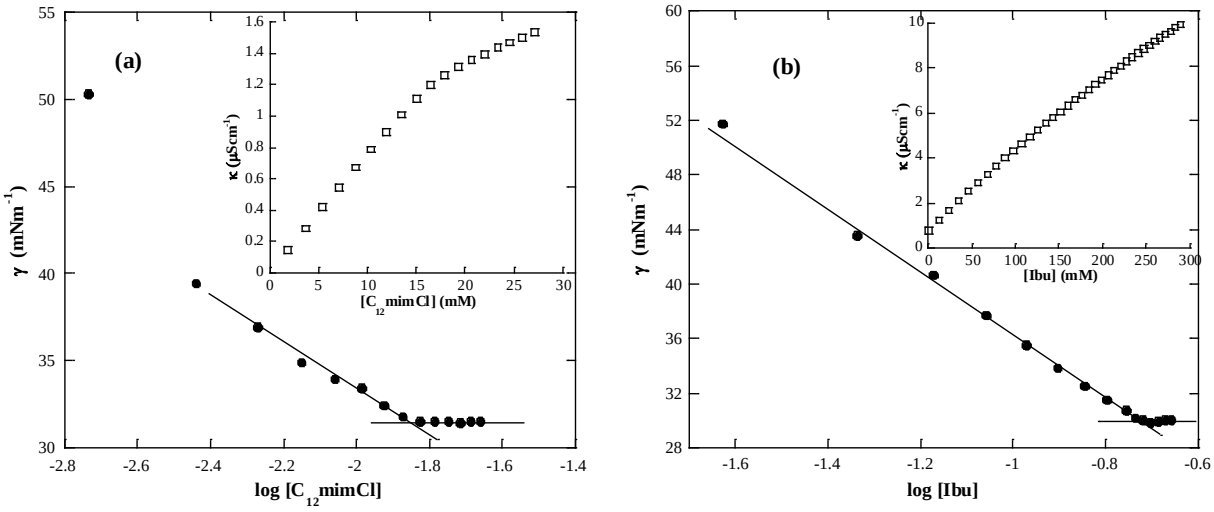

Figure 4 Plots showing variation of specific conductivity (κ) with molar concentration of amphiphile and variation of surface tension (γ) vs log of amphiphile concentration [inset] for (a) C_{12}mimCl and (b) Ibu.

Further conductivity, surface tension and fluorescence measurements were performed for C_{12}mimCl + Ibu mixtures at various mole fractions to deduce the mixed micellization behavior. The conductivity techniques were unable to detect the mixed micelle formation in these mixtures due to very less difference in pre-micellar and post-micellar slopes making the break at cmc indistinguishable. However, sharp breaks in the γ vs. log of concentration plots and I_1/I_3 ratio of pyrene emission spectrum vs. the concentration plots were obtained for all the mixtures [Figures 5(a) and (b)].

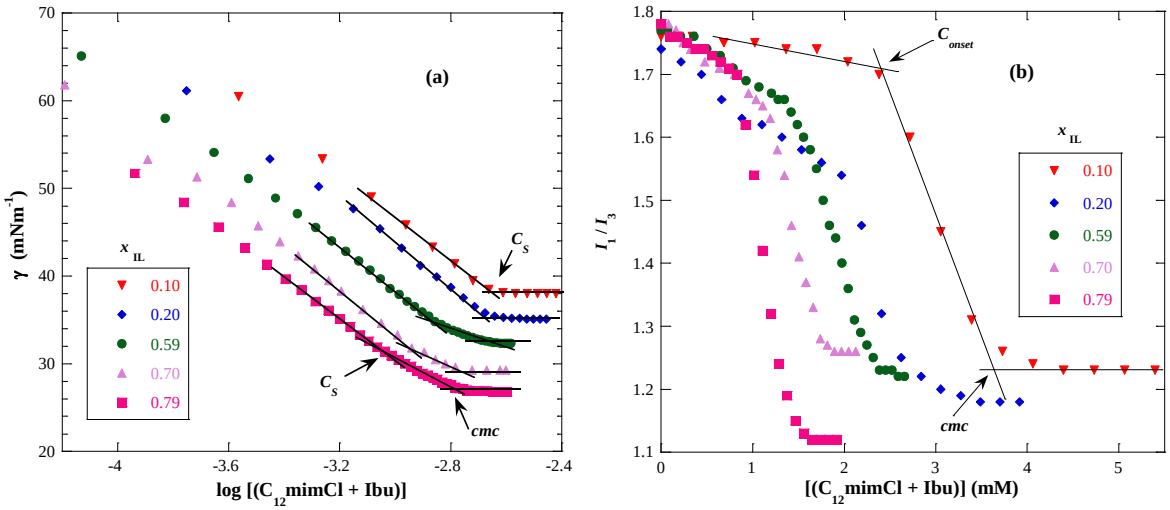

Figure 5 Plots showing (a) variation of surface tension (γ) vs log of total mixture concentration and (b) variation in the pyrene I_1/I_3 ratio with total mixture concentration for catanionic C_{12}mimCl + Ibu aqueous mixtures (For clarity reasons, the values of γ for x_{IL} = 0.70, 0.59, 0.20 and 0.10 have been shifted by +3, +6, +9 and +12 mNm^{-1} respectively).

For surface tension measurements, the anionic rich mole fractions displayed a single break while the cationic rich mole fractions exhibited two breaks in the γ vs. log of concentration plots. As per Table 2, the first break in all these mixtures coincided well with the point corresponding to the onset of aggregation (C_{onset}) from fluorescence measurements. Moreover in fluorescence measurements, the anionic dominated mixtures exhibited turbidity at their respective cmcs, but no turbidity was obtained in case of surface tension measurements corresponding to the first break. Hence the first break obtained from surface tension measurements was ascribed to be the saturation concentration (C_s) corresponding to the formation of surface aggregates in all these mixtures. The second break coincided well with those of fluorescence measurements and was depicted to be the critical micellar concentration (cmc) for the mixtures. The cmc values of anionic dominated mixtures were also determined from turbidity measurements (τ vs. concentration plots given in Figure S4, Supporting Information) and were found to be in good agreement with the fluorescence measurements. Insights in Table 2 clearly depicts very high micellization tendency of C_{12}mimCl + Ibu mixtures in aqueous solution on account of quite low cmc values in comparison to that of the individual components. This is quite expected as the mixtures of oppositely charged amphiphiles exhibit great synergistic activity owing to the strong electrostatic and hydrophobic interactions.

3.2.1Micellar parameters to deduce interactions between the components in mixed micelles

Considering the phase separation model, the ideality in the mixed micelle formation for these catanionic mixtures was evaluated in terms of ideal cmc (cmc^*) using Clint's model[45] as per the equation (9)

$$\frac{1}{cmc^*} = \frac{x_1}{cmc_1} + \frac{(1-x_1)}{cmc_2} \quad (9)$$

where x_1 represents the mole fraction of the C_{12}mimCl, cmc_1 and cmc_2 are the critical micellar concentration of the pure C_{12}mimCl and Ibu respectively. It is to be mentioned here that in exploring various micellar parameters for the mixtures, we considered the cmc values obtained

from fluorescence measurements to keep a consistency in results. As per Table 2, a non ideal behavior has been obtained for the mixtures in the whole mixing range as indicated by much higher ideal cmc values than the experimental ones. Since the structure of the head groups of the ionic liquid and the drug molecule are quite different, this non ideality on mixing seems to be justified. These observations were then further confirmed employing Rubingh's theory,[46] which not only provides the mole fraction of the components in the micellar form (X_1), but also measures the nature and strength of the interaction between the two amphiphiles in terms of interaction parameter (β^m), as per equations (10) and (11).

$$\frac{X_1^2 \ln\left(\frac{x_1 cmc}{X_1 cmc_1}\right)}{(1-X_1)^2 \ln\left[\frac{(1-x_1)cmc}{(1-X_1)cmc_2}\right]} = 1 \quad (10)$$

$$\beta^m = \frac{\ln(cmc\ x_1/cmc_1 X_1)}{(1-X_1)^2} \quad (11)$$

Equation (10) is solved iteratively for X_1, the mole fraction of C_{12}mimCl in the mixed micelle whose value is then substituted in equation (11) to obtain the value of β^m, a measure of the interaction between two different amphiphiles, relative to their self interaction under the same conditions before mixing. The β^m values were then further utilized to account for the deviation of the mixtures from ideal behavior in terms of the activity coefficients for C_{12}mimCl (f_1) and Ibu (f_2) using relations (12) and (13)

$$f_1 = \exp\{\beta_m (1 - X_1)^2\} \quad (12)$$

$$f_2 = \exp\{\beta_m (X_1)^2\} \quad (13)$$

A perusal of Table 2 indicates that the value of β^m comes out to be highly negative at all the mole fractions of C_{12}mimCl + Ibu mixtures, which indicates that interactions between the two components being investigated are more attractive or less repulsive than the self interaction of the two amphiphiles before mixing. These highly synergistic interactions between the oppositely charged IL and drug molecules arise due to the lessening of the electrostatic repulsions between the charged heads as well as strengthening of the hydrophobic interactions among the tails in a mixed micelle, thus favoring micellization at much reduced cmc values. This synergism in mixtures is generally aimed both from fundamental and applied point of view. Similar evidences of strong synergism have been reported earlier in several catanionic surfactant systems.[47-49]

Table 2 Micellar parameters for C_{12}mimCl + Ibu aqueous mixtures at varying mole fractions of C_{12}mimCl (x_{IL}); saturation concentration (C_S), critical micellar concentration experimental (*cmc*) and ideal (cmc^*), micellar mole fraction of C_{12}mimCl experimental (X_1) and ideal (X_{ideal}), interaction parameter (β^m) and activity coefficients of C_{12}mimCl (f_1) and Ibu (f_2) in the mixed micelles.

x_{IL}	ST[a]		Flu[b]		cmc^* (mM)	X_1	X_{ideal}	β^m	f_1	f_2
	C_s (mM)	*cmc* (mM)	C_{onset} (mM)	*cmc* (mM)						
0.10	2.34	-	2.36	3.61	84.54	0.52	0.59	-13.106	0.049	0.029
0.20	2.18	-	2.05	2.83	54.56	0.55	0.77	-12.968	0.072	0.020
0.59	1.44	2.14	1.42	2.32	22.90	0.61	0.95	-12.140	0.158	0.010
0.70	1.09	1.65	1.13	1.75	19.68	0.62	0.97	-13.668	0.139	0.005
0.79	0.98	1.40	0.84	1.46	17.64	0.63	0.98	-14.974	0.129	0.003

a; cmc determined by surface tension (error limit ± 0.04 mM).
b; cmc determined by fluorescence (error limit ± 0.05 mM).

However, in the anionic rich mole fractions, β^m tends to become less negative as the concentration of Ibu is being increased, while for the cationic dominated mixtures, the synergism is found to enhance with increase in drug concentration. This might be the result of different types of molecular interactions coming into play on the mixing of two amphiphiles having different structures and different properties.[50] These can be electrostatic repulsive interactions between ionic hydrophilic head groups, ion-dipole attractions between the ionic hydrophilic groups, the steric repulsions between bulky hydrophilic or hydrophobic groups, the attractive van der Waals interactions depending on the length, degree of branching and the closeness of packing of the hydrophobic groups, and the hydrogen bonding between hydrogen acceptor and donor groups in the two amphiphilic molecules. The values of both f_1 and f_2 (Table 2) have been worked out to be much less than unity confirming that the mixtures are behaving non ideally. As the concentration of the IL in the mixture increases, the activity of the Ibu molecules should decrease while that of C_{12}mimCl should increase in the mixed micelles, however contrary to the above, lessening of the activity coefficient of C_{12}mimCl in the cationic rich region is observed.

This might indicate some sort of hindrance being offered to IL molecules in the cationic dominated mixed micelles.

Further from Motomura's approximation,[51] the deviation of the micellar mole fraction (X_1) values from that in the ideal state, X_{ideal}, have been computed as per equation (14)

$$X_{ideal} = \frac{x_1\, cmc_2}{x_1\, cmc_2 + (1-x_1)\, cmc_1} \quad (14)$$

Higher values of X_{ideal} than X_1 in both anionic and cationic dominated mixtures indicate that the micelles are richer in the Ibu component again hinting at the lesser capacity of the C_{12}mimCl molecules to intercalate in the mixed micelles, which might be due to the bulkiness of the imidazolium head group.

3.2.2 Interfacial parameters to deduce interactions between the components in mixed monolayer

When a surfactant mixture is added to water, it first gets absorbed at the interface to form a mixed monolayer, which on further increasing the concentration eventually leads to the formation of mixed micelles in the solution. The composition of the adsorbed monolayer of the binary mixtures and interactions between the components have been evaluated using Rosen's approach[52] [equations (15) and (16)], in analogy with the derivation of Rubingh's equation for mixed micelles, where X_1, cmc_1, cmc_2 and cmc [in eqn (10) and (11)] get replaced by X_1^{σ}, C_1^{σ}, C_2^{σ} and C_{12}^{σ} respectively. The symbols C_1^{σ}, C_2^{σ} and C_{12}^{σ} represent the molar concentrations of pure C_{12}mimCl, pure Ibu and their mixtures at different mole fractions of C_{12}mimCl (x_{IL}), required to produce a surface tension reduction (γ = 45 mN m^{-1}) at the air-water interface.

$$\frac{(X_1^{\sigma})^2 \ln\left(\frac{x_1 C_1^{\sigma}}{X_1^{\sigma} C_1^{\sigma}}\right)}{(1-X_1^{\sigma})^2 \ln\left[\frac{(1-x_1) C_{12}^{\sigma}}{(1-X_1^{\sigma}) C_2^{\sigma}}\right]} = 1 \quad (15)$$

$$\beta^{\sigma} = \frac{\ln(C_{12}^{\sigma}\, x_1 / C_1^{\sigma}\, X_1^{\sigma})}{(1-X_1^{\sigma})^2} \quad (16)$$

An insight in Table 3 provides negative values of β^{σ} indicating that there is synergism between the components in the mixed monolayer too. However as expected, β^{σ} is more negative than β^{m} since the reduction of electrostatic repulsions between the charged head groups has a greater effect at the planar air/water interface as compared to the convex micellar surface.[52] Also, the accommodation of the two hydrophobic groups of the mixtures is easier at the planar interface than in the interior of a spherical micelle. This high synergism between the C_{12}mimCl and Ibu molecules makes their catanionic mixtures behave non ideally as indicated by the values

of activity coefficients for C_{12}mimCl (f_1^{σ}) and Ibu (f_2^{σ}) at the air /water interface in Table 3 [f_1^{σ} and f_2^{σ} have been derived in analogy with equations (12) and (13) replacing X_1 and β^{m} by X_1^{σ} and β^{σ} respectively].

Table 3 Interfacial parameters for C_{12}mimCl + Ibu aqueous mixtures at varying mole fractions of C_{12}mimCl (x_{IL}); interaction parameter (β^{σ}) and activity coefficients of C_{12}mimCl (f_1^{σ}) and Ibu (f_2^{σ}) in the mixed monolayer, surface excess (Γ_{max}), minimum area per molecule experimental (A_{min}) and ideal (A_{ideal}), surface pressure (π_{cmc}) and pC_{20}.[c]

x_{IL}	β^{σ}	f_1^{σ}	f_2^{σ}	Γ_{max} ($\times 10^{-6}$) (mol m^{-2})	A_{min} (nm)^2	A_{ideal} (nm)^2	π_{cmc} (mN)	pC_{20}
0.00				4.14	0.40		41.6	1.670
0.10	-15.705	0.027	0.014	2.17	0.76	0.43	45.5	3.692
0.20	-14.991	0.048	0.011	2.14	0.78	0.46	45.3	3.721
0.59	-13.994	0.106	0.006	2.09	0.79	0.59	45.2	3.793
0.70	-14.608	0.108	0.004	2.07	0.80	0.62	45.1	3.854
0.79	-15.225	0.111	0.003	2.03	0.82	0.65	44.9	3.907
1.00				2.31	0.70		39.0	2.761

[c] Maximum uncertainity limits in Γ_{max} , A_{min} and π_{cmc} are ±0.03, ±0.02 and ±0.2 respectively.

Next to have a comprehensive assessment of interfacial behavior of these IL-drug aqueous mixtures in comparison to the individual components, certain other surface active parameters like surface excess (Γ_{max}), minimum area per molecule (A_{min}) and the surface pressure (π_{cmc}) needs to be evaluated. The adsorption efficiency of the amphiphiles at the air/water interface is often discussed in terms of their bulk concentration which generates a surface tension reduction of 20 mNm^{-1} (C_{20}) from pure solvent i.e. water. Higher the value of the negative logarithm of this concentration (pC_{20}), the more efficient is the amphiphile. It is clear from the Table 3 that the adsorption efficiency increases in the order Ibu < C_{12}mimCl < Ibu + C_{12}mimCl aqueous mixtures. The presence of a longer alkyl chain and hence greater hydrophobicity in

C_{12}mimCl is responsible for its being more surface active than the Ibu molecules. However as the mixtures involve the adsorption of a catanionic pair containing both surface active ions, they are expected to be more active at the air / water interface than their individual counterparts. This adsorption efficiency among mixtures is found to enhance slightly with the increase in the concentration of the IL.

Further applying Gibbs adsorption isotherm to the tensiometric profiles, the maximum surface excess concentration, Γ_{max}, representing the amount of the amphiphile adsorbed at the interface and the minimum area occupied by a amphiphilic molecule, A_{min} at the air/ water interface were evaluated as per equations (17) and (18)

$$\Gamma_{max} = -\frac{1}{2.303\ nRT}\left[\frac{\partial\gamma}{\partial \log C}\right] \quad (17)$$

$$A_{min} = \frac{10^{20}}{N_A\ \Gamma_{max}} \quad (18)$$

where n, R and N_A represents the number of species at the air/solution interface, gas constant and Avogadro's number respectively at a temperature T. The Γ_{max} and A_{min} values for the pure C_{12}mimCl have been found to be in confirmity with the literature values.[43] In accordance with the larger size of the hydrophilic head group of the C_{12}mimCl molecule as compared to Ibu, the respective A_{min} values have been found to be larger in case of the former. For the catanionic mixtures, the Γ_{max} values decrease and the corresponding A_{min} values increase in comparison to that of the pure components. But with the change in the mole fraction of the mixtures, both Γ_{max} and A_{min} does not exhibit an appreciable change. This signifies that these mixtures involve the adsorption of bulkier catanionic $C_{12}mim^{+}Ibu^{-}$ pairs, which are expected to be more hydrophobic than both components. This is also manifested by the corresponding larger values of A_{min} in comparison to A_{ideal} for the mixtures at whole mixing range. These results signifying the formation of ion-pairs in mixtures are in corroboration with our earlier results from spectroscopic measurements.

Another parameter that directly provides the effectiveness of surface tension reduction is the surface pressure at the cmc i.e. π_{cmc}. It indicates the maximum reduction of surface tension caused by the dissolution of the amphiphilic molecules and is usually defined by relation (19)

$$\pi_{cmc} = \gamma_0 - \gamma_{cmc} \quad (19)$$

where γ_0 and γ_{cmc} represent the surface tension of the pure solvent and the surface tension of solution at the cmc respectively. As per Table 3, the aqueous IL-drug mixtures display higher values of π_{cmc} than their individual counterparts in accordance with their higher surface activity as mentioned earlier, although their efficiency to bring about surface tension reduction of water varies only slightly with the mixture composition.

3.2.3 Thermodynamic Evaluation of Catanionic Mixtures

Further, the thermodynamic evaluation of these catanionic IL - drug mixtures was done to reveal the spontaneity of the micellization and the adsorption phenomenon in terms of the standard free energy of micellization (ΔG_m^0) and adsorption (ΔG_{ads}^0) as per the equations (20) and (21), where X_{cmc} represents the cmc in mole fraction units.

$$\Delta G_m^0 = RT \ln X_{cmc} \quad (20)$$

$$\Delta G_{ads}^0 = \Delta G_m^0 - \left[\frac{\pi_{cmc}}{\Gamma_{max}}\right] \quad (21)$$

Negative values of ΔG_m^0 and ΔG_{ads}^0 (Table 4) clearly indicate the feasibility of both the micellization as well as adsorption processes for all the catanionic mixtures, however more negative values of ΔG_{ads}^0 than ΔG_m^0 specify that the adsorption of these mixtures at the air/water interface is a more favorable phenomenon and work needs to be done to transfer an amphiphilic molecule from air/water interface to the micelle through the solvent medium. Moreover higher values of ΔG_{ads}^0 and ΔG_m^0 for the mixtures in comparison to pure components signifies an increased adsorption and enhanced micellization because of newer stronger electrostatic and hydrophobic interactions among the oppositely charged components in a catanionic mixture. These adsorption and micellization tendencies are also found to enhance with increase in the concentration of more surface active (C_{12}mimCl) component. Further the thermodynamic stability of the surfaces can be judged from the free energy change (G_{min}) accompanying the transport of the solution components from the bulk phase to the surface phase from equation (22)

$$G_{min} = A_{min} N_a \gamma_{cmc} \quad (22)$$

Our observed values of G_{min} are higher for the mixtures reflecting the formation of thermodynamically more stable surfaces and the enhancement in surface activity. Similarly the stability of the mixed micelles is being confirmed by the negative values of excess free energy of mixing (ΔG_{ex}^0), obtained by using the values of activity coefficients f_1 and f_2 as per the relation (23)

$$\Delta G_{ex}^{0} = RT\ (X_1 \ln f_1 + X_2 \ln f_2) \quad (23)$$

Table 4 Thermodynamics of micellization and adsorption for C_{12}mimCl, Ibu and their aqueous mixtures at varying mole fractions of C_{12}mimCl (x_{IL}).

x_{IL}	ΔG^0_{ex} (kJmol^{-1})	ΔG^0_{m} (kJmol^{-1})	ΔG^0_{ads} (kJmol^{-1})	G_{min} (kJmol^{-1})
0.00		-14.106	-24.154	72.209
0.10	-8.109	-23.899	-44.867	119.79
0.20	-7.956	-24.503	-45.671	122.41
0.59	-7.159	-24.995	-46.622	125.81
0.70	-7.982	-25.694	-47.481	127.51
0.79	-8.652	-26.143	-48.261	131.01
1.00		-20.501	-37.384	140.67

Thus in micellar regions, the interactions of the IL with the drug molecules in aqueous medium leads to the formation of catanionic mixtures displaying more surface active properties and enhanced micellization tendencies at all compositions, hence being industrially, economically as well as environmentally beneficial.

3.3 Morphology of C_{12}mimCl-Ibu mixed aggregates

In further exploring the nature of species present in the aqueous solutions of these catanionic IL-drug mixtures, DLS measurements were undertaken to illustrate the changes in the morphology of the mixed aggregates from anionic rich to being cationic dominated ones and also to study the effect of dilution/concentration on the size of mixed micelles so as to associate it with the turbidity changes as discussed previously. It is worthwhile to mention that as the mixtures investigated here involve the presence of salt (sodium and chloride ions as counterions), the observed hydrodynamic diameters for the mixtures might be somewhat smaller than the actual ones because of the salt effect.[53]

The aggregate size distributions for both pure C_{12}mimCl and Ibu in aqueous solutions at varied concentrations of 10mM of each and at concentrations pertaining to five times cmc (70mM for C_{12}mimCl and 900mM for Ibu) have been given in Figure S5, Supporting Information. As observed at higher concentrations, both C_{12}mimCl and Ibu revealed the presence of two types of aggregates i.e. small micelles with hydrodynamic diameter (D_h) of 1-2 nm and larger aggregates with D_h in the range of 100-300 nm. For C_{12}mimCl, these larger aggregates have been ascribed to be unilamellar vesicles by Wang et al.[54] But the larger aggregates for Ibu molecules have not yet been characterised and the presence of small micelles is in accordance with the earlier reports.[44,55] However at concentration of 10mM of each, only large sized aggregates with D_h of 157.5 ± 5.7 nm for C_{12}mimCl and 187.1 ± 8.3 nm for Ibu were obtained. This behavior is peculiar of ionic surfactants and has been illustrated previously[53] where the hydrodynamic diameters are observed to go through a minimum at their respective cmcs.

3.3.1 Effect of Mixture Composition

From the aggregate size distributions for the various catanionic mixtures at a fixed total mixture concentration of 250mM, the hydrodynamic diameters were obtained for varying mole fractions as listed in Table 5. An appraisal of these D_h values showed a clear dependence on the mixture composition. The anionic dominated mole fractions revealed the existence of only small micelles with D_h between 3-20 nm, witnessing a micellar growth in mixtures with larger IL fractions, due to intercalation of more of C_{12}mimCl molecules in the micelles. As the mole fraction of IL exceeded the equimolarity, a clear transition was observed with the cationic dominated mole fractions showing the coexistence of small micelles (D_h =1-2nm) and the larger aggregates (D_h increased with increasing IL mole fraction). On the whole, it can be assumed that the mixed micelles which are dominated by Ibu molecules (as pointed earlier) firstly grow to a particular size by the intercalation of C_{12}mimCl molecules due to the decrease of electrostatic repulsions between the head groups, allowing the amphiphilic molecules to approach each other more closely and hence forming bigger micelles needing greater space for the hydrophobic chains. But further increase in the concentration of these IL molecules with bulky head groups and relative lessening of the Ibu concentrations leads to the generation of steric and electrostatic repulsions, hence causing the breakdown of micelles to smaller size and the excess of the IL molecules rearranging in the form of unilamellar vesicles, either alone or in mixed form with Ibu

molecules. This behavior is in concordance with our earlier discussions on the values of interaction parameter. Similar coexistence of two types of aggregates has also been reported recently by Viau et al for salt free catanionic complexes of short chain imidazolium ILs with Ibuprofen.[55]

Table 5 Hydrodynamic diameters (D_h) for C_{12}mimCl, Ibu and their mixtures at varying mole fractions of C_{12}mimCl (x_{IL}).

x_{IL}	0.00	0.10	0.20	0.30	0.59	0.70	0.79	1.00
D_h (nm)	1.59 ± 0.22	3.34 ± 0.85	7.08 ± 1.66	19.63 ± 5.82	10.38 ± 2.05	2.58 ± 0.41	1.95 ± 0.25	1.34 ± 0.19
	269.9 ± 22.7	-	-	-	34.89 ± 6.45	52.9 ± 8.3	169.4 ± 17.9	155.7 ± 25.6

3.3.2 Effect of Dilution

Further analysis of these catanionic mixtures in aqueous solution was performed to illustrate the effect of dilution on the mixed micellar size by studying the aggregate distributions for x_{IL} = 0.79 and x_{IL} = 0.20 at varying total mixture concentrations as shown in Figure 6. Here, the cationic dominated mixture (x_{IL} = 0.79) showed the coexistence of both the small micelles (D_h =1-5nm) and the larger aggregates (D_h =100-400 nm) at all the concentrations, with size of small micelles remaining almost same and that of larger ones increasing (Table S1, Supporting Information). This might indicate that the larger aggregates which are unilamellar vesicles are not purely formed by IL molecules rather are of mixed nature with Ibu molecules solubilised in them. However, prominent transitions in the size of micelles were observed for Ibu rich mole fraction (x_{IL} = 0.20), where only large aggregates with D_h extending upto 3000 nm (might be multilamellar vesicles) appeared at 10mM, the two types of aggregates (corresponding to size of unilamellar vesicles) coexisted at a concentration of 50mM and 100mM followed by a population of only smaller micelles at 250mM concentration. This could provide a reasonable answer for the disappearance of turbidity in anionic dominated mole fractions at higher concentrations as the increase in concentration leading to the transformation of larger aggregates to smaller micelles.

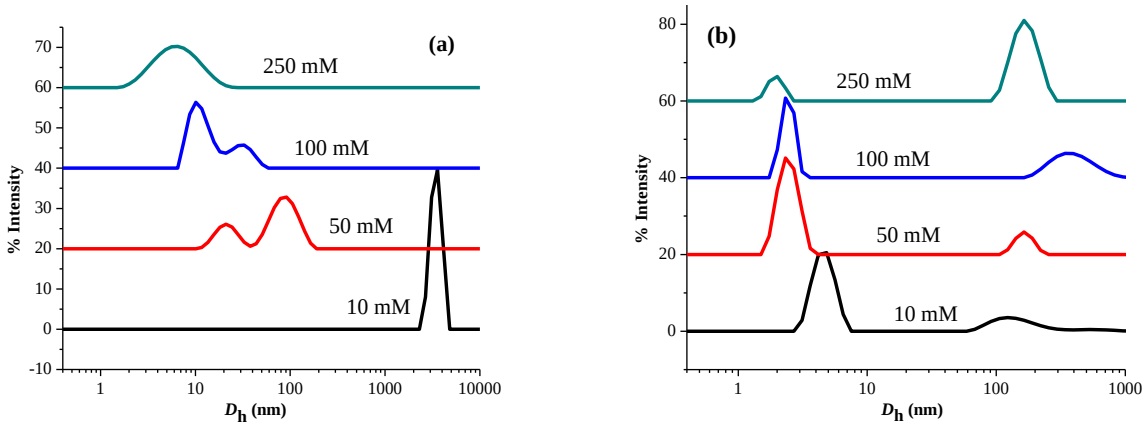

Figure 6 Aggregate size distributions for catanionic IL – drug mixtures with increasing total mixture concentrations at (a) x_{IL} = 0.20 and (b) x_{IL} = 0.79. The amplitudes for 50 mM, 100 mM and 250 mM mixture concentrations have been shifted upwards by +20, +40 and +60 units respectively.

This transition from micelle to vesicle/bilayers upon dilution in catanionic mixtures has been reported by many workers. Egelhaaf and Schurtenberger[56] have observed that in bile salt and lecithin mixed micelles, the monodisperse spherical micelles change to elongated, flexible cylindrical polymer-like micelles upon dilution. They have attributed it to the difference in the solubilities, i.e., cmc of bile salt and lecithin where on dilution the bile salt to lecithin ratio in the aggregates decreases which eventually lowers the average spontaneous curvature of the mixed micelles forcing them to grow. In another recent report on catanionic surfactant-hydrotrope mixtures, Hassan and coworkers[57] have ascribed this dilution induced transition from micelles to vesicles to be driven by the release of hydrotropes from the mixed micelles on account of the solubility mismatch between the two components. In our case too, since there lies a big difference between the cmc of C_{12}mimCl and Ibu, the same reason sounds to be true here also. At high concentrations, the micelles are dominated by Ibu molecules and the corresponding repulsion between the charges favours the formation of smaller micelles. But on dilution, the release of Ibu molecules from the mixed micelles will be much larger in comparison to its

cationic counterpart (having much lower cmc) forcing Ibu molecules to partition in the bulk , lowering the surface charge density of the micelle. This ultimately leads to micellar growth to higher aggregates because of the decreased average spontaneous curvature of the mixed micelles. The lowering of surface charge density for anionic dominated catanionic mixtures (x_{IL} = 0.20) has also been verified from ζ- potential measurements at total mixture concentrations of 100mM, 50mM and 10mM and found to be -21.5, -11.0 and -10.2 respectively. However, to be more sure about the mechanism of these transitions a detailed study using SANS and rheological measurements needs to be carried out and will thus constitute a part of our further studies.

3.4 ^{1}H NMR Measurements

^{1}H NMR measurements have been carried out to predict the changes in the environment of various protons of C_{12}mimCl and Ibu on interacting with each other. For this, the ^{1}H NMR spectrum of both pure C_{12}mimCl and Ibu were recorded in D_2O at a concentration of 2mM each. The corresponding spectrum obtained and the peaks assigned to various protons for both have been given in the Figures S6 and S7 (Supporting Information). It has been observed that the peak due to H2 of C_{12}mimCl did not appear in the spectrum probably due to its rapid H-D exchange as reported earlier.[58] Further addition of increasing equivalents of Ibu was done to the C_{12}mimCl solution (2mM) so as to get the catanionic mixtures with varying mole fractions and the corresponding ^{1}H NMR spectra were recorded for each mixture. The spectra showing the changes in the ^{1}H NMR signals for the various aromatic as well aliphatic protons at different mixture compositions have been given in Figures 7(a) and (b) respectively and the chemical shift (δ) values for the different protons of both the IL and Ibu have been summarized in Supporting Information Tables S2 and S3.

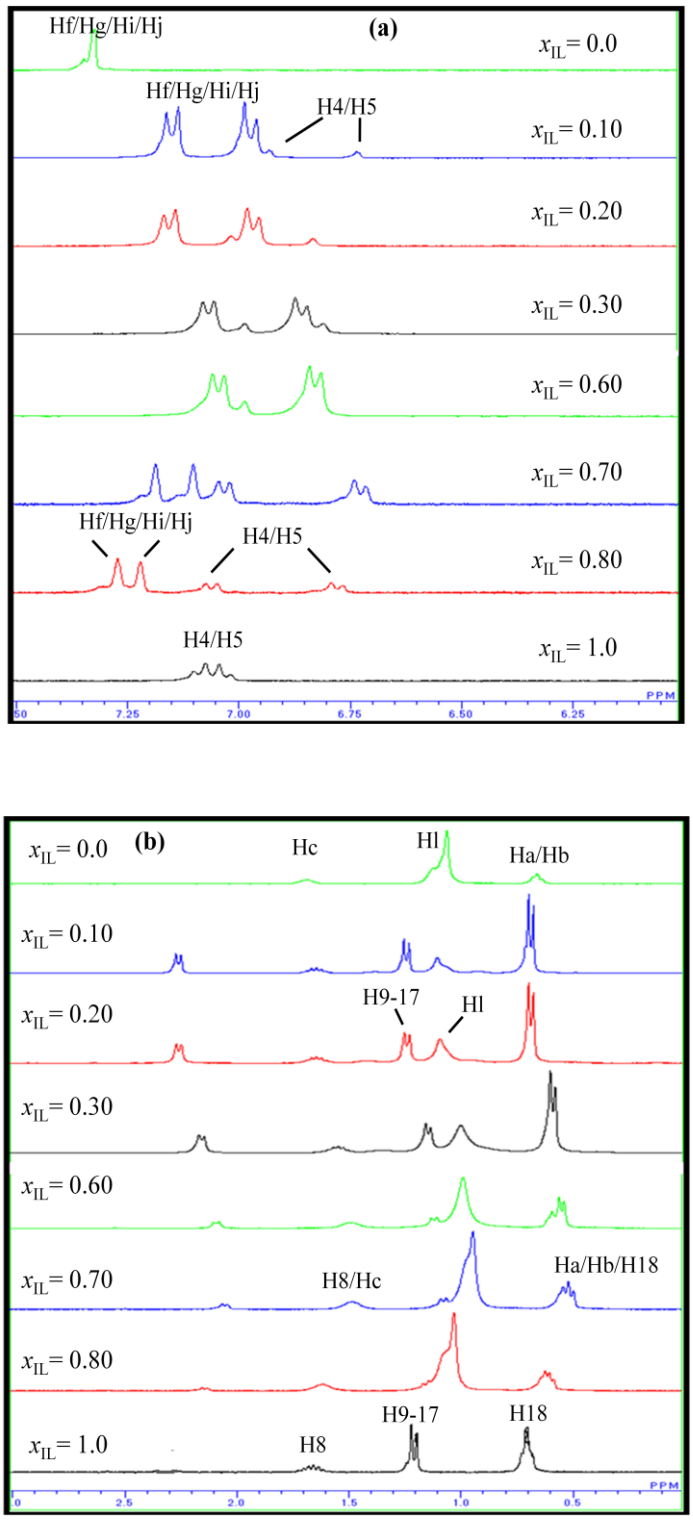

Figure 7 ^{1}H NMR spectra for pure C_{12}mimCl, pure Ibu and their catanionic mixtures at varying mole fractions in the (a) aromatic region and (b) aliphatic region.

The remarkable changes observed in the position of ^{1}H NMR signals (δ values) for the mixtures with respect to that of pure components provide a direct evidence of the existence of interactions between C_{12}mimCl and Ibu molecules. It is to be mentioned here that a definite assignment of the proton peaks and an actual phenomenon of the conformational changes occurring in the mixtures are difficult to predict on the basis of chemical shifts alone, the observations made here are predictive but well suffice to develop a basic understanding of the interactional phenomenon between IL and drug moieties. Insights in Figure 7(a) shows that the aromatic protons (H4 and H5) of C_{12}mimCl resonate at almost similar frequency but get largely separated and shifted upfield in the presence of Ibu molecules indicating a change in the environment for the two protons. Similar behavior was observed for the aromatic protons (Hf, Hg, Hi, Hj) of Ibu molecules which provides clue for the close proximity of these two molecules. Zheng et al[34] has also reported the upfield shifting of aromatic protons upon intercalation into the micelles. Here in our case too, although the concentrations of the pure components are well below their cmc, the mixtures tend to show aggregation at these concentrations as revealed earlier from surface tension measurements. Hence the separation of the ^{1}H NMR signals (in these catanionic mixtures) for the similar protons can be the result of conformational changes (more restricted environment) in both the molecules when in a mixed micelle. The restricted molecular motion of aggregates in comparison to IL monomers has also been established by Zhao and coworkers.[59] In accordance with our previous discussion and earlier reports,[59-61] there is a clear possibility of the existence of cation-π and π-π interactions between the imidazolium moiety of the IL and the benzene ring of the Ibu, in addition to the possibility of H-bonding between the cationic and anionic moieties with H2 of the imidazolium ring bonding with the carboxyl group of the Ibu molecules. Also from Figure 7(b), prominent upfield and downfield chemical shifts in the ^{1}H NMR signals of both the cationic and anionic moieties are an indication of the hydrophobic interactions between the aliphatic protons on the alkyl chains. The shielding of the aliphatic protons (H8, H9-17 and H18) is also a support to the presence of π-π stacking interactions. However more prominent shifts in the aromatic region are observed in comparison to the aliphatic ones as the head groups point towards the exterior of the micelle, being more exposed and less shielded than the alkyl protons.[59] A clear indication of the change in the micelle characteristics from being cationic rich (smaller micelles) to anionic dominated (larger

aggregates) is also provided by the downfield shifting of the signals on comparison of the ^{1}H NMR of mixtures from x_{IL}= 0.60 to 0.30. It can be observed that the peaks due to H4 and H5 appear splitted in cationic dominated mixtures while they get merged in anionic rich mixtures. This behavior is an indication of the change in the micelle morphology from micelles to vesicles as reported by Kumar et al.[62] Hence the results from ^{1}H NMR measurements highlight the interplay of cation- π, π-π and H-bonding interactions between the IL and IBu molecules within a mixed micelle.

Hence, the present study establishes the formation of highly surface active catanionic $C_{12}mim^+Ibu^-$ complexes, which when aggregating in the form of mixed micelles provide a diverse morphological behavior depending on the mixture composition and the dilution.

4. Conclusions

In the course of above study we looked at understanding the interactions between the surface active ionic liquid, C_{12}mimCl and the NSAID, Ibuprofen molecules in aqueous solution, from varied concentration regimes of monomers to micelles using a multi-technique approach. Fluorescence and surface tension measurements reveal the existence of highly synergistic interactions between the oppositely charged components both in the mixed micelle and in the mixed monolayer, with greater effect at the air/water interface on account of its planar geometry. The aggregate morphology is seen to vary from anionic dominated to cationic rich mixtures with former ones being larger than the latter. An assembly of molecules in the form of unilamellar vesicles in mixed form has also been predicted for cationic rich mixtures through DLS measurements. The appearance of turbidity in anionic dominated mole fractions at lower concentrations has been ascribed to the dilution induced transformation of smaller micelles to larger aggregates. This structural transition is thought to be driven by the release of Ibu molecules from the mixed micelles on account of the cmc (solubility) mismatch between the two components.

The formation of highly surface active catanionic complexes ($C_{12}mim^+$ Ibu^-) of 1:1 stoichiometry is well established through UV-visible spectroscopy although the complexes are pseudocatanionic ones due to the presence of counterions as salts in aqueous solution. The fluorescence emission measurements provide quantitative evaluation of this complex formation

in terms of binding constant and quenching constant values where an increase in alkyl chain length of imidazolium moiety is observed to produce significant changes. We conclude that hydrophobic interactions also play a very important role along with electrostatic interactions in the formation of these complexes. ^{1}H NMR studies too clearly visualize the role of other interactions such as cation-π, π-π, H-bonding etc in stabilising the mixed micelles. Hence, a comprehensive view of the interactions between C_{12}mimCl and Ibu molecules presented here will surely be of benefit to enhance our understanding for the development of ionic liquids with pharmaceutically active ingredients, thus enriching the field of third generation ionic liquids. In addition, the knowledge of these transitions from vesicles to micelles are of particular interest for they provide an easy way of encapsulating active agents by dissolving them in micellar phase prior to vesicle formation.

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Supporting Information

Figures S1−S6 contains supporting plots of UV-visible, fluorescence, Turbidity, DLS and ^{1}H NMR spectra. Results from DLS measurements illustrating the effect of dilution on the anionic and cationic dominated mole fractions have been given in Table S1 while Tables S2 and S3 provides the values of chemical shifts from ^{1}H NMR measurements of C_{12}mimCl + Ibu mixtures.

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