Investigation of Hydrophilic β–Blocker Drug Atenolol and Ionic liquid Surfactant Interactions Using Spectroscopic and Voltametric Techniques.

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ABSTRACT

Surfactants are the surface-active agents which self-aggregates and form micelle beyond critical concentration. These micelles are the simplified model of a membrane since it does not form a bilayer but in many cases, it possesses the spherical form. Considering the use of surfactants, surface-active ionic liquid (SAIL) surfactant such as 1-hexadecyl-3- methylimidiazolium chloride (HDMIC) with hydrophilic Atenolol (ATL) has been studied using UV-visible spectroscopy and Cyclic Voltammetric (CV) technique. Using both these techniques, free and bound form of ATL with HDMIC has been investigated at three pH levels of Britton Robinson buffer i.e. 3.5 pH, 7.4 pH, and 10.4 pH. The stoichiometry of interactions and their binding constant values of cationic and neutral ATL has been studied at pH < pKa and pH > pKa, respectively in presence of HDMIC where the binding constant value of ATL-HDMIC was found strong at 7.4 pH as 2018.315 M^{-1}. In Vitro evaluation of ATL in absence and presence of HDMIC using Cyclic voltammetry at scan rate range of 20mVs^{-1} to 300mVs^{-1} were performed in physiological condition (B-R buffer, 7.4pH). The results indicated that the process is diffusion-controlled, regardless with and without HDMIC. CV was used to examine the binding constant (K_b) and Gibbs free energy change (ΔG) for ATL-HDMIC complexes. These measurements suggests that electrostatic forces play significant role in formation of drug-surfactant complexes, highlighting the existence of cation- π and π- π interactions between ATL and HDMIC. The spectral result indicates the probability of location of drug on the micellar surface layer.

Key words: Atenolol, Micelles, Binding Constant, Electrooxidation, Diffusion

1. INTRODUCTION

It has been many decades, Ionic liquids have been utilized as solvents, co-solvents, and materials in various field such as pharmaceuticals, drug delivery system, biotechnology, and as microbial agents due to their green properties and their unique chemical properties (Moniruzzaman, Kamiya, Interface, & 2010, 2010) (Wells & Coombe, 2006)(Adawiyah, Moniruzzaman, Hawatulaila, & Goto, 2016). Their distinctive features have captured the attention of biochemists, ecologists, and medical scientists. Moreover, ILs are regarded as noble green solvents because to their exceptional qualities, which include strong solvation abilities, low toxicity, high thermal stability, and nonflammability (Łuczak, Jungnickel, Łącka, Stolte, & Hupka, 2010). Similar to conventional surfactants, ILs can self-aggregate in aqueous solution when they have long chains, creating surface active ionic liquids (SAILs) (Wang, Wang, Zhang, & Xuan, 2008). The classical surfactants can be replaced by SAILs and find an enormous importance in pharmacokinetic applications due to its amphiphilicity, allowing uses as emulsifier, detergents, paints, lubricants, etc (Kaur, Kumar, & Singla, 2022). SAILs consists of polar group and a nonpolar chain, similar to conventional cationic surfactants. These structural characteristic enables interaction with both hydrophilic and hydrophobic molecules (Hiemenz & Rajagopalan, 2016)(Ali, Uzair, Malik, & Ali, 2014).

One key ability of amphiphilic compound, such as SAILs, is their self-aggregation in solution to form micelles, with the critical micelle concentration (CMC).(Farn, 2007) (Molla, Rub, Ahmed, Liquids, & 2017). Micelles can effortlessly integrate organic compounds, polymers, or weakly soluble medications into their hydrophobic core, enhancing the solubility and bioavailability of diverse substances (M. Ahmed et al). Studying drug interaction with surfactant micelles is important because micelles can mimic cell membranes, providing insight into drug interactions with biological surfaces. However, drug interactions with SAILs remain largely unexplored despite extensive research with other surfactants (Caetano, science, & 2000)(Akhtar, Hoque, Thermodynamics, & 2008).

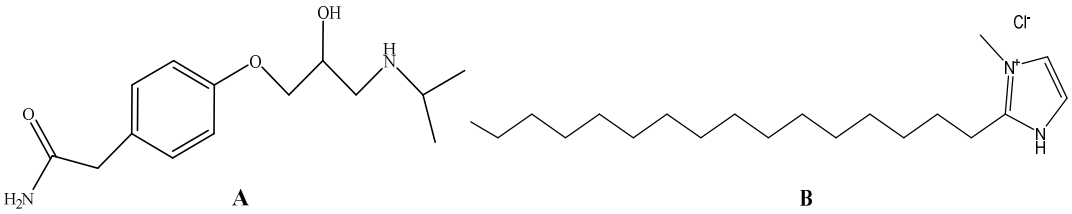

Figure 1. Structure of (A) Atenolol and (B)1-Hexadecyl-3 methylimidiazolium chloride

This study explores the interaction between Atenolol (ATL), a cardio selective β1-adrenergic receptor-blocking agent used for the treatment of cardiovascular disease, angina, hypertension and also migraines (Fumagalli, Maurizi, Marchionni, & Fornasari, 2020), and an Ionic liquid 1-hexadecyl-3- methylimidiazolium chloride monohydrate (HDMIC) having alkyl chain length of C_{16}. Several methods have been used to explore the interaction of drug with surfactants and can be found in the literature (Chhetri & Ali, 2024) (S. Ahmed, Alqurshi, Talanta, & 2018), (Goebel, Pharm, & 2007). Herein, spectrophotometry and electrochemical method (cyclic voltammetry) were employed due to their accuracy, selectivity and their cost-effectiveness. The binding of ATL with ILs micelles was analysed using spectrophotometer, while cyclic voltammetry investigated electro inactive species ATL on a bare glassy carbon electrode (GCE) using Britton-Robinson (B-R) buffer at pH level of, 7.4.

The findings highlight the importance of understanding drug-SAIL interactions to enhance drug solubility, bioavailability, and potential therapeutic efficacy. Despite extensive research on drug-surfactant interactions, studies on drug-SAIL interactions remain limited, emphasizing the novelty and relevance of this investigation.

2. MATERIALS AND METHODS

Atenolol (ATL) was sourced from TCI Chemicals, Japan, while the ionic liquid surfactant 1-Hexadecyl-3 methylimidiazolium chloride monohydrate (HDMIC) was procured from Acros Organics, Belgium.

The Britton-Robinson (B-R) buffer were prepared and used in the experiment. The desired pHs were adjusted using EUTECH pH 700. Absorption spectra of ATL upon binding with surfactants were measured using Shimadzu UV-VIS SPECTROPHOTOMETER (Japan), UV-1900i Series. The voltametric studies were

done using CH Instrument, USA (Model CHI 600D). All the experiment were conducted at room temperature (298.15K).

3. RESULTS AND DISCUSSION

Absorption studies

The UV absorption study of atenolol with and without HDMIC was conducted at pH 3.5, 7.4, and 10.4 due to the reason that pKa of ATL is 9.6 (Martínez, Maguregui, Jiménez, & Alonso, 2000). ATL exhibited peaks at 273 nm (π-π*) and 280 nm (n-π*), consistent with the previous study (Kale & Ottoor, 2019). In the absence of ionic liquids (ILs), ATL showed standard absorbance (shown in figure 1 (A)), but increasing HDMIC concentrations caused a hyperchromic shift at both wavelengths, as illustrated in Figure 2 (B).

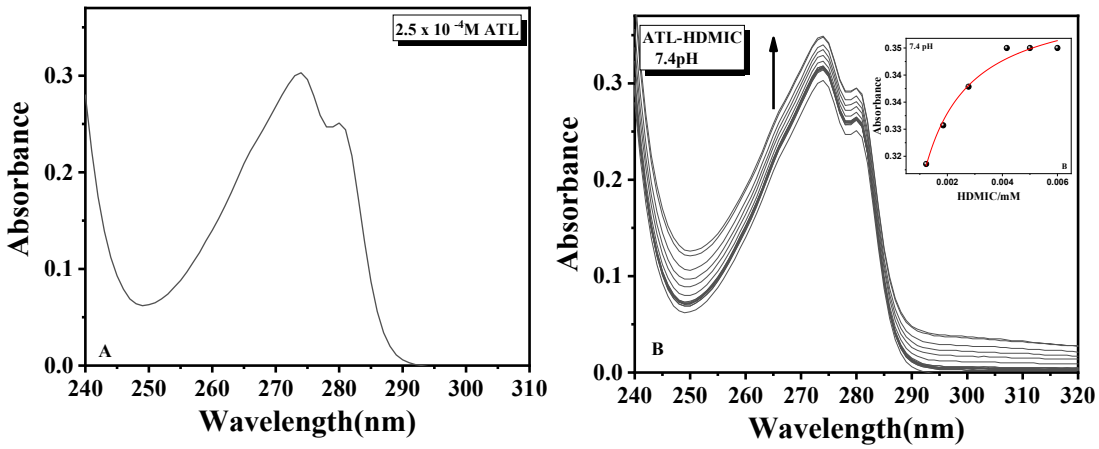

Figure 2. The UV- visible spectra of ATL in (A) Absence of HDMIC and (B) presence of HDMIC at pH of 7.4. Inset: plot of concentration of HDMIC and absorbance.

At pH 3.5 and 7.4, spectra remained unchanged up to 0.36 mM and 0.54 mM HDMIC due to repulsion between cationic ATL and HDMIC monomers. Beyond these concentrations, absorbance increased, indicating drug-micelle complex formation through π-π and cation-π interactions. At pH 10.4, neutral ATL showed no significant changes at low HDMIC levels, but absorbance rose with a ~1 nm redshift above 1.23 mM, signalling micelle incorporation.

Nonlinear absorbance increases were observed with HDMIC concentrations beyond 230 µM, 540 µM, and 1230 µM at pH 3.5, 7.4, and 10.4, respectively (shown by inset

of figure 2B). Using the modified Hildebrand equation, the binding constant ($K\,b$) values were determined (Santos, Del, …, & 2014).

$$A = \frac{A_o + A_{ATL:sur} K_b [micelle]}{1 + K_b [micelle]} \quad (1)$$

The calculated K_b values were 238.91 M^{-1}, 2018.31 M^{-1}, and 250.84 M^{-1} for pH 3.5, 7.4, and 10.4, respectively, indicating strongest binding at pH 7.4 due to favourable non-covalent interactions. The Gibbs free energy change (ΔG_{bin}) was also computed, further confirming the interaction strength and thermodynamic favourability of ATL-HDMIC complexation across different pH conditions.

$$\Delta G_{bin} = -RTlnK_b \quad (2)$$

Where K_b is the binding constant, R and T has their usual meaning. From the equation, the values of ΔG_{bin} were negative, signifying spontaneous interaction between ATL and HDMIC.

Electrochemical studies

Effect of scan rate

One of the frequently used techniques to confirm the formation of molecular complexes is Cyclic Voltammetry (CV). Therefore, to complement our previous spectroscopic findings, we conducted CV for ATL-surfactant complexations. CV was employed to investigate the surface inactive ATL, both with and without HDMIC at 7.4 pH. Figure 3 displays the cyclic voltammograms of 5 $\times 10^{-5}$ M ATL at pH of 7.4 pH at different scan rate with and without surfactants.

ATL exhibits an anodic peak at 0.55 V without corresponding reverse peak, confirming an irreversible oxidation process(Hegde, Kumaraswamy, & 2008). The oxidation peak shifts to less positive potentials with increasing pH due to the oxidation of ATL's secondary alcoholic group, emphasizing the electrode's catalytic role in this pH-dependent process; this fluctuation is consistent with the previous published data (Goyal & Singh, 2006).

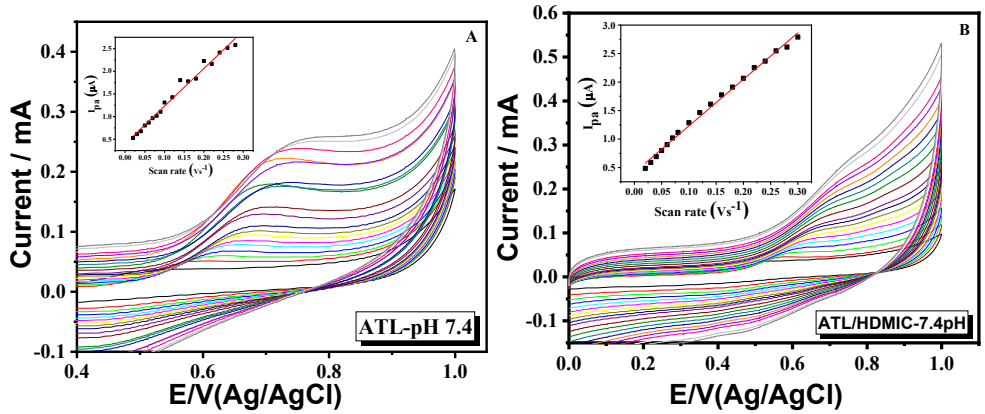

Figure 3. Cyclic voltammograms of variation of scan rate from 20mVs^{-1}to 300mVs^{-1} (A) ATL at 7.4pH inset: variation of current with increasing scan rate (B) ATL with 0.1mM HDMIC at 7.4pH. inset: variation of current with increasing scan rate.

For ATL (5×10^{-5} M), both with and without 0.1 mM HDMIC, there exist linear increase in the current with the square root of the scan rate ($v^{1/2}$), indicating a diffusion-controlled process(Khairy, Journal, & 2020). Regression equations for ATL without and with HDMIC were $I_{pa} = 36.090\ v^{1/2} - 0.0609$ ($R^2 = 0.9987$) and $I_{pa} = 5.778\ v^{1/2} - 0.4775$ ($R^2 = 0.9926$), respectively. Log-log plots of scan rate vs. peak current confirmed diffusion control, while the linear shift of peak potential (E_p) with ln(v), allows calculation of standard rate constant (K^0) and charge transfer coefficient (α) via the Laviron equation (Interfacial & 1979, n.d.).

$$E_p(V) = E^0 - \frac{RT}{\alpha nF}\ln\frac{RTK^0}{\alpha nF} + \frac{RT}{\alpha nF}\ln v \qquad (3)$$

The results without HDMIC**:** $K^0 = 0.9090\ s^{-1}$, $\alpha = 0.196$, $E^0 = 0.6525$ V and with HDMIC: $K^0 = 0.7409\ s^{-1}$, $\alpha = 0.169$, $E^0 = 0.6381$ V were obtained. Higher K^0 values without HDMIC indicate faster electron transfer kinetics in the absence of surfactant. HDMIC slows the reaction due to drug-micelle complexation and surfactant adsorption on the electrode, impacting ATL's electrochemical behaviour. Additional systematic studies were conducted to further investigate this effect.

Effect of Concentrations of HDMIC

Fig. 4 shows the effect of HDMIC on ATL's oxidation peak current (I_{pa}) and potential (E_p). Initially, I_{pa} decreased from 1.76 µA to 1.35 µA with a 0.1 V E_p shift, due to inactive ATL-surfactant complex formation. Further HDMIC addition caused linear increases in I_{pa} and E_p, indicating drug adsorption onto the electrode via cation-π and π-π

interactions. similar enhancement in I_{pa} was observed with tetradecyltrimethylammonium bromide monomers through cation- π interaction (Chhetri & Ali, 2023). The biphasic response arises from HDMIC micelle formation and ATL-surfactant complex kinetics. ATL initially disperses but later adsorbs as HDMIC monomers aggregate. With increased HDMIC concentration, surfactant monomers aggregate at the electrode, carrying ATL to the surface and further increasing peak current and potential. This could be attributed to various complex formations, surfactant adsorption, micellar formations, and interactions between ATL-surfactants and the surface of electrode (Rusling, 1997).

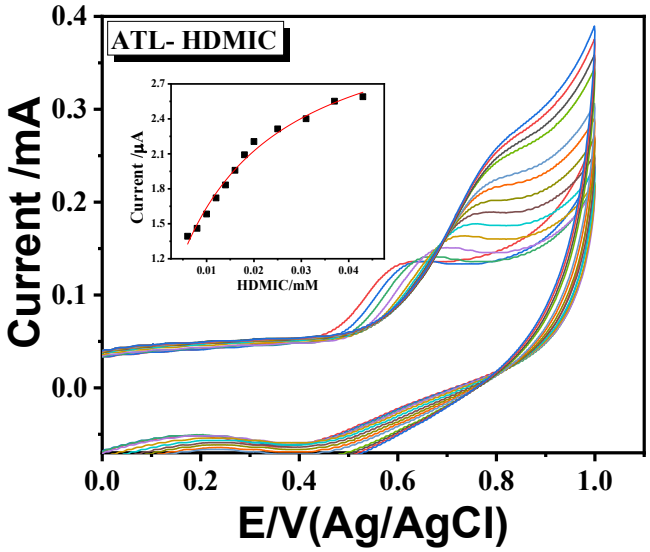

Figure 4. Cyclic voltammograms of ATL with different concentration of HDMIC. Inset: plot of concentration of HDMIC with current (Ipa).

To better understand ATL's binding with HDMIC, binding constant (K_b) was calculated from nonlinear plotting (inset of figure 4) and the value obtained was 58.687 M^{-1}. Negative Gibbs free energy (ΔG) value (-19398.4 kJ mol−1) confirmed spontaneous and stable ATL-HDMIC binding. These results highlight HDMIC's role in modulating ATL's electrochemical properties.

Conclusion

The study investigates pH-dependent interactions between Atenolol (ATL) and the ionic surfactant HDMIC using UV and CV. At pH 3.5, 7.4, and 10.4, ATL binds to HDMIC micelles through π-π and cation-π interactions, with the strongest binding at pH 7.4 Negative Gibbs free energy values (ΔG) confirm spontaneous binding. Cyclic voltammetry shows ATL undergoes irreversible, diffusion-controlled oxidation, with peak potential shifting based on pH and scan rate. Adding HDMIC initially decreases the peak current (I_{pa}) due to inactive ATL-HDMIC complex formation. At higher surfactant concentrations, I_{pa} and potential increase, indicating ATL-surfactant re-adsorption onto the electrode. HDMIC also slows electron transfer by forming mixed micellar aggregates, reducing the standard rate constant and charge transfer efficiency. These results highlight the role of HDMIC in modulating ATL's electrochemical behaviour and stability through molecular interactions.

Competing interests

The author(s) declare(s) that there is no conflict of interest associated with the submission of the research for publication. As a corresponding author, I confirm that that the manuscript has been read and approved for publication.

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Availability of data and materials

Not Applicable

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