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Room temperature ionic liquid based extraction and recovery of Rifampicin from water and its mechanistic study

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An attempt has been made to develop a fast, efficient and eco-friendly process for extraction of drug; Rifampicin (RF) from its aqueous solutions using room temperature ionic liquids (RTILs). RTILs *viz.* 1-butyl-3-methylimidazolium hexafluorophosphate, 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 1-butyl-3-methylimidazolium tetrafluoroborate and 2-Hydroxyethyl-trimethylammonium L-(+)-lactate have been used for removal of RF. Various factors such as hydrophilicity/hydrophobicity of RTILs, concentration of used RTILs and pH of drug solutions, affecting removal of RF from its aqueous solution have been studied to investigate mechanism of extraction process. Partition coefficient of RF between RTILs and aqueous phases as well as its extraction efficiency have also been calculated and analyzed. Results showed that hydrophobicity plays a major role in extraction of RF from its aqueous solutions. The addition of just 2 % of hydrophobic RTIL; [BMIM][PF_6] leads to almost complete precipitation (98.92 %) of RF in just 1 min. Also, it has been observed that extraction efficiency of [BMIM][PF_6] is maximum at pH = 8.

Keywords: Ionic liquids, [BMIM][PF_6], [EMIM][NTf_2], Rifampicin, [BMIM][BF_4], CL

Wastewater from industries like textile, dyeing, printing, pharmaceutics, cosmetics, food coloring, papermaking, etc. is a major contributor of colored effluents[1]. For instance, textile industry consumes large amount of water and different types of dyes and these dyes impart colors to effluent. Also, in pharmaceutical industries different types of drugs are being made and thus the drug contaminated water is being released in water bodies, which possess health hazards to human beings and aquatic animals. Several studies have shown that dyes contaminated wastewater and pharmaceuticals excreted by humans after therapeutic administration, enter the sewage networks and are often only partially removed by sewage treatment plants. The colors/drugs are toxic and main pollutants responsible for causing environmental problems as well as health hazards to human beings and aquatic animals[2,3]. There are number of conventional ways[4-18] for the removal of dyes from water. Also, a significant study is available on extraction of drugs from wastewaters[19-22]. But most of the methods used for extraction of drugs are of high operating cost, having less extraction efficiency and of time consuming. Hence, there is a need to develop environment friendly and economic method for the extraction of drugs from wastewaters. In the present study we have proposed a fast, efficient and an eco-friendly method for the extraction of drug; Rifampicin (RF) from its aqueous solution. In a study, Lin *et al.,*[22] have extracted 68.8% of RF from wastewaters using iron nanoparticles in approx. 20 min. But in the present study, we have extracted 98.92% of RF from its aqueous solution on addition of just 2% of [BMIM][PF_6] in merely 1 min. We are also successful in recycling the used extractant for its further use in another extraction processes.

RF is found to be an important antibiotic. It is commonly used for the treatment of all types of tuberculosis. RF is also being used to eliminate meningococci from the nasopharynx. Though RF is a known antitubercular drug, but it is found to be one of the toxic drugs as well[23]. Its toxicity is mainly hepatic and immunoallergic in character[24]. For instance, it affects the respiratory system, digestive system, functioning of kidneys and liver. RF may also cause headache, fever, unusual bleeding, irritation as well as dermatitis to eyes, skin and respiratory tract. Drugs and their metabolites usually contaminate the receiving surface waters[25-27], with potential implications for humans and wildlife[28]. Hence, in

order to avoid these issues, it is vital to remove RF from effluents discharged by various sectors like pharmaceutical industries, research laboratories, hospitals etc. In this paper, we have extracted RF form its 3×10^{-5} M aqueous solution using hydrophobic as well as hydrophilic room temperature ionic liquids (RTILs).

To acquire the desired goal, we have used hydrophobic RTILs; 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]), 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([EMIM][NTf_2]) and hydrophilic RTILs; 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]) and 2-Hydroxyethyl-trimethylammonium L-(+)-lactate ([(C_2H_4OH)-(CH_3)$_3$N][Lactate])/CL for the removal of RF from its aqueous solution. Factors affecting extraction process of drug such as hydrophilicity/hydrophobicity of RTILs, concentration of used RTILs and pH of drug solution have been investigated in order to study the systematic mechanism of extraction process.

Materials and Methods

Chemicals used

[BMIM][PF_6] (purum ≥97% HPLC), [EMIM][NTf_2] (≥98% ^{1}H-NMR), CL (≥95.0% (T)), [BMIM][BF_4] (purum ≥97% HPLC) and Rifampicin (Purity ≥97% HPLC), all were purchased from Sigma-Aldrich. All samples were prepared in doubly distilled water. All the experiments were performed in triplicate to check reproducibility of data. RTILs were vacuum desiccated and degasified before use. Rifampicin was used as received.

Methods

The stock solution of 3×10^{-5} M of RF was prepared by directly dissolving RF into distilled water. UV-visible spectrum of this solution was obtained using Thermo Fisher Scientific Evolution 160 UV-visible spectrophotometer at its characteristic wavelength 473 nm. 10 mL of solution was taken in four different glass vials. To each of solution, known concentrations of all four used RTILs were added directly. Vortex shaking of these mixtures for 1 min was done and then left undisturbed for another 1 min. Precipitation of drug was visibly evident at bottom of viols. UV-visible absorption spectrum of supernatant was observed to calculate the extraction efficiency by using formula:

$$E\,\% = \frac{C_i - C_f}{C_i} \times 100\% \quad \ldots (1)$$

Where, C_i and C_f represent initial and final concentrations of drug in an aqueous phase, respectively.

Partition coefficient ($P_{RTIL/W}$) of drug between RTILs and aqueous phases was estimated using equation

$$P_{RTIL/W} = \left\{\frac{C_i - C_f}{C_i}\right\} \times \frac{V_{aq}}{V_{RTIL}} \quad \ldots (2)$$

Where, V_{aq} and V_{RTIL} are the volumes of aqueous phase and RTILs, respectively.

In order to study the effect of pH on extraction efficiencies, pH of aqueous solutions was adjusted with HCl (0.1 M) and NaOH (0.1 M) solutions using pH meter (Cyberscan 510).

To confirm the identity of recovered RTIL, FTIR spectra of pure as well as recovered RTIL were recorded using Perkin-Elmer (RX1) FTIR spectrometer, in frequency range of (4400–350) cm^{-1}. The uncertainty in measurement of wave number υ was within ±0.01 cm^{-1}.

Results and Discussion

Effect of hydrophilicity/hydrophobicity of RTIL

To examine effect of hydrophilicity/hydrophobicity of RTILs on extraction efficiency of RF, 2 % of each RTIL was added to 10 ml of 3×10^{-5} M aqueous RF and vortex shaken for 1 min, which resulted in the precipitation of RF as shown in the photo given below.

In order to confirm the removal of RF in each RTIL, absorption spectra of supernatants left over were obtained (Fig. 1a). The values of $P_{RTIL/W}$ of RF against used RTILs are given in Table 1 and graphically shown in Fig. 1b. It is confirmed from Fig. 1 that hydrophobic RTILs show best removal

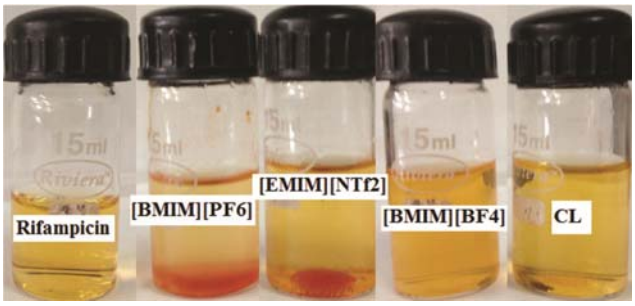

Table 1 — Partition coefficient, $P_{RTIL/W}$ of RF in each RTIL

Contaminants	[BMIM][PF_6]	[BMIM][BF_4]	[EMIM][NTf_2]	CL
Rh6G	4593.89	75.00	1170.45	56.38

efficiency. $P_{RTIL/W}$ of RF in RTIL/aqueous solution follows the trend (Fig. 1b)

$$P_{[BMIM][PF_6]/W} > P_{[EMIM][NT_2]/W} > P_{[BMIM][BF_4]/W} > P_{CL/W}$$

$P_{RTIL/W}$ of RF is more in hydrophobic RTILs, which further verified that hydrophobicity of RTILs plays an important role in the removal of drug. The values of $P_{RTIL/W}$ show that [BMIM][PF_6] has maximum removal efficiency of RF.

Effect of concentration of RTILs

A minimum amount of 1% of each RTIL was normalized to extract RF from its aqueous solutions. However, to observe effect of concentration of RTILs on removal efficiency, different amount of RTILs were used for the extraction of RF from their aqueous solution. UV-visible absorption spectra for removal of RF using different amounts of RTILs are shown in Fig. 2. It is clear from Fig. 2 that hydrophobic RTIL, [BMIM][PF_6] is more efficient in extraction of RF as compared to other RTILs. The addition of 2% of [BMIM][PF_6] leads to almost complete precipitation (98.92 %) of RF as shown in Figs 2 and 3.

The mechanism of precipitation followed two steps

Before forming hydrophobic interactions

On addition of RF in water, it gets solubilize by making hydrogen bonding with water. However, when hydrophobic RTILs are added to aqueous solution of drug, weak hydrogen bonding between drug and water molecules start breaking in order to make a space for the hydrophobe (RTIL). The whole

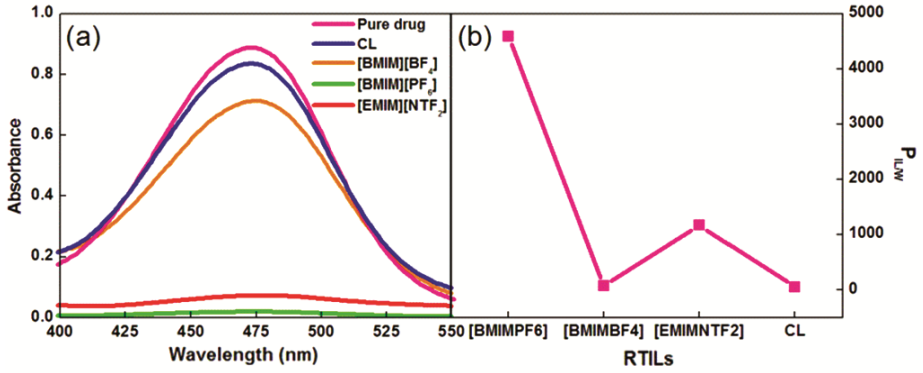

Fig. 1 — (a) UV-visible absorption spectra showing RF precipitation using 2% of each RTIL and (b) plot of $P_{RTIL/W}$ of RF against the used RTILs.

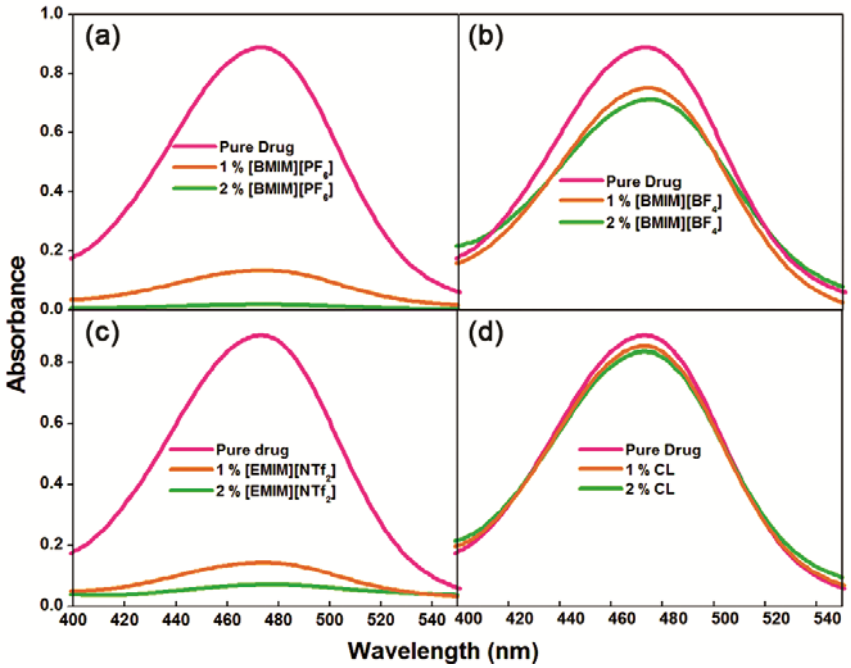

Fig. 2 — Absorption spectra for different amount of each RTIL.

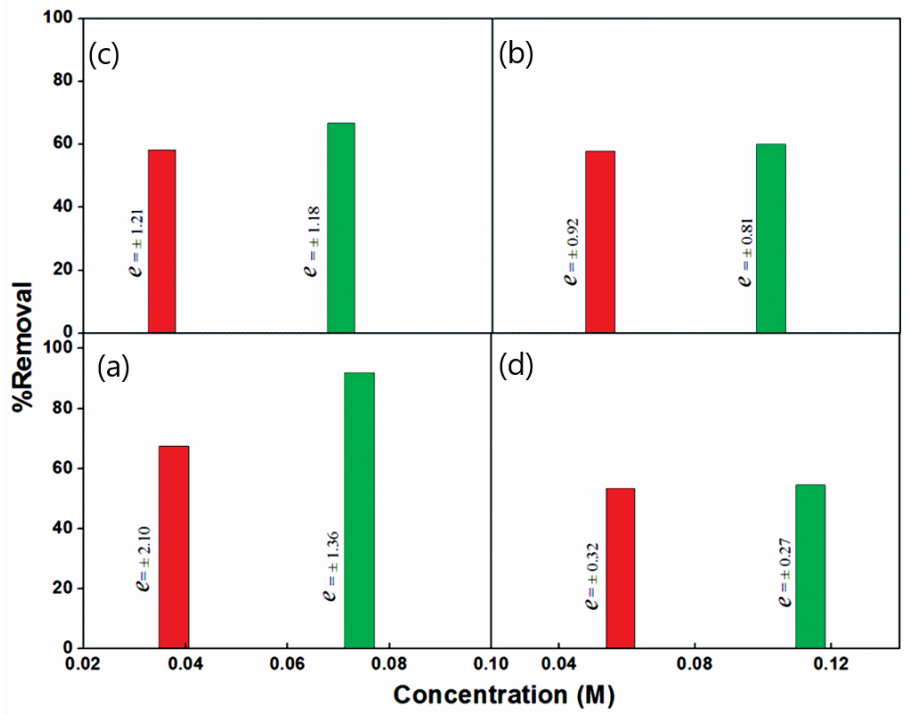

Fig. 3 — Plot of removal efficiency of different concentration of (a) [BMIM][PF_6], (b) [BMIM][BF_4] (c) [EMIM][NTf_2] and (d) CL, Color representation; red= 0.1 mL, green= 0.2 mL; Error = *e*.

reaction is endothermic (change in enthalpy, ΔH is positive), as heat is required in breaking of bonds. The presence of hydrophobic RTIL forces distorted water molecules to make new hydrogen bonds in order to have less contact with hydrophobe and as a result, water forms an ice-like cage structure called a clathrate cage around hydrophobe (Scheme 1). The system becomes more ordered that leads to decrease in entropy of the system; therefore ΔS becomes negative. ΔH of whole system may be positive, negative or zero, depending on whether the formation of new hydrogen bonds have completely, partially or over compensated the breaking of hydrogen bonds due to addition of hydrophobic RTIL. However, in mixing of hydrophobe and water molecules the entropy decrease become so large, that sign of change in enthalpy ΔH is insignificant in deciding spontaneity of reaction. Thus, according to Gibbs free energy formula $\Delta G = \Delta H - T\Delta S$, value of ΔG is positive with a large negative ΔS and small ΔH. The mixing of hydrophobic RTIL with water was not a spontaneous process.

Formation of hydrophobic interactions

On vortex shaking of 1 min, RF having less solubility in water, starts interacting with hydrophobic RTIL via hydrophobic interactions. This process leads

Scheme 1 — Schematic representation for the extraction process.

to increase in enthalpy (ΔH is positive), as due to hydrophobic interactions some of bonds of clathrate cage breaks down. Due to tearing of clathrate cage, entropy of the system increases, making ΔS positive. Therefore, with a large positive ΔS and small positive ΔH, value of ΔG is negative. Hence, hydrophobic interactions are spontaneous. Schematic representation showing mechanism of drug precipitation is given in Scheme 1. The immiscibility of RTIL in aqueous drug solution makes RTIL more efficient in extraction of RF.

Effect of pH of aqueous solution of RF

It has been seen that pH has no effect on efficiency removal of hydrophilic RTILs, whereas a slight effect on efficiency removal of hydrophobic RTILs has been

observed. Also, in comparison to [EMIM][NTf_2], [BMIM][PF_6] shows better extraction efficiency. So, the effect of pH of aqueous phase on the extraction efficiency of only [BMIM][PF_6] has been evaluated. The plot of absorbance vs. wavelength of supernatant left over after the precipitation of RF in [BMIM][PF_6] at different pH of aqueous phase is shown in Fig. 4.

Effect of pH value on the percent removal of RF using [BMIM][PF_6] and relationship between pH value and $P_{RTIL/W}$ of RF in [BMIM][PF_6]/aqueous solution is depicted in Fig. 5. Results show that [BMIM][PF_6] is capable of removing 99.17% of drug from its aqueous solution at pH = 8 with $P_{RTIL/W}$ of 5974.10, because of less solubility of drug in water near pH = 8.

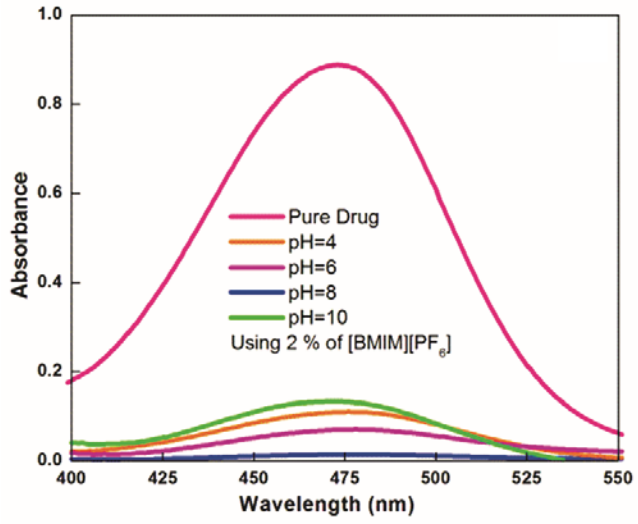

Fig. 4 — Absorption spectra at different pH of aqueous phase showing precipitation of drug in [BMIM][PF_6].

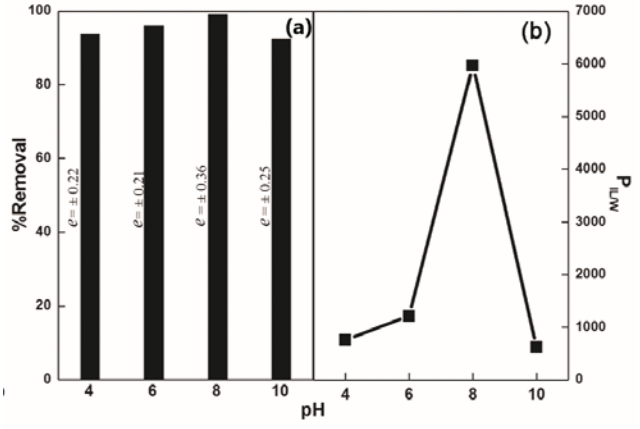

Fig. 5 — Plots of (a) pH value vs. % removal of drug by [BMIM][PF_6] and (b) pH value vs. $P_{RTIL/W}$ of drug in [BMIM][PF_6]/aqueous solution; Error = *e*.

Recovery and reuse of [BMIM][PF_6]

The used [BMIM][PF_6] can be separated from RTIL/drug precipitate by washing it with a specific solvent, in which one of the components of precipitate is soluble and other one is insoluble. A series of solvents were tried and 1-butanol was found to be best solvent for this recovery purpose. [BMIM][PF_6] remained insoluble in 1-butanol, while RF got solubilize due to their preferential solubility in 1-butanol. Hence, we have achieved 92% recovery of used [BMIM][PF_6] from RTIL/RF precipitate by washing it with 1-butanol. Identity of the recovered [BMIM][PF_6] was confirmed by comparing its FTIR spectra with spectra of pure [BMIM][PF_6] (Fig. 6), which were found to be identical. Recovered [BMIM][PF_6] was again used for extraction of RF via same procedure, and again recovered.

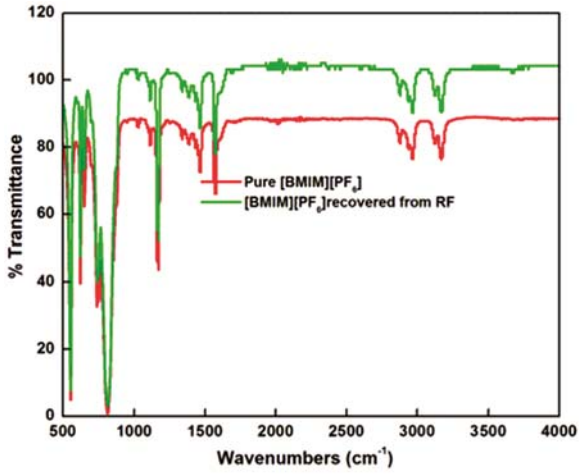

Fig. 6 — Comparison of FTIR spectra of pure [BMIM][PF_6] with recovered [BMIM][PF_6] from RF.

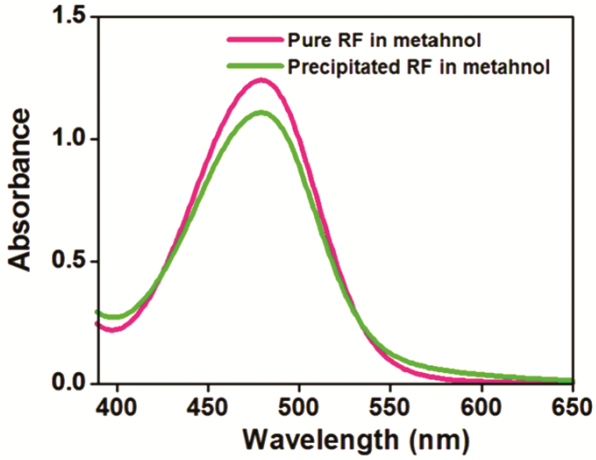

Fig. 7 — Absorption spectra for RF in methanol and precipitated (RF + RTIL) in methanol.

Also, to confirm the mechanism of extraction process, we have verified the identity of precipitated drug in [BMIM][PF_6]. Absorption spectra of pure RF in methanol as well as mixture of precipitated drug + [BMIM][PF_6] in methanol were observed (Fig. 7). Both absorption spectra were found to be same, which confirmed that identity of drug remains same. This further leads us to conclude that extraction process was due to hydrophobic interactions only.

Conclusions

Hydrophobic RTILs; [BMIM][PF_6] and [EMIM][NTf_2] are amazingly efficient in extracting drug; RF, from its aqueous solution in just 1 min. We have concluded that hydrophobicity is the key function of extraction processes. Also, we have been successful in recycling of almost 92% of used [BMIM][PF_6] and the recycled RTIL was further reused for extraction processes. So, we have made an attempt to develop a fast, efficient and eco-friendly process for extraction of drug from its aqueous solutions.

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