Polymerized Ionic Liquids as Antimicrobial Materials

Hamidreza Bagheri, Ali Mohebbi, Zahra Jayhani, and Mina Naderi

Abstract Ionic liquids (ILs) are salts composed of a large organic or inorganic cation in which an alkyl chain is replaced or inorganic or organic anions. Because of unique ILs properties, they have attracted significant attention from ecologists, medical scientists, and biochemists. Controlling the toxicity of ionic liquids by combining them with various substances is another important factor that has been investigated to make them better and easier to use in pharmaceutical applications. Therefore, the novel design and control of the molecular structure of these compounds can assist their antibacterial applications.

We reviewed antibacterial properties of ionic liquids derivatives including polymeric ionic liquids in pharmaceutical and medicine fields. ILs as drug formulation components in drug synthesis, their biological activities, and their possible applications in drug delivery systems were discussed. It was also discussed polymeric ionic liquids have higher antibacterial properties than conventional ionic liquids. The role of different factors including alkyl chain length and charge density, which affects the antibacterial properties of ionic liquids derivatives was scrutinized.

Keywords Antibacterial · Biological · Drug · Green solvent · Ionic liquid · Synthesis

1 Introduction

A solvent is a substance (usually a liquid) that dissolves something else and we use solvents for all kinds of things like cleaning products, chemical reactions, and so on. However, many solvents are hazardous and toxic. Green chemistry is employed to the design or creation of chemical processes and products with less dangerous

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substances (Ghalandari et al. 2020; Capello et al. 2007). This new chemistry branch looks for an alternative a new solvent with less harmful to the environment and human health to protect the ecosystem from hazardous conventional solvents (Bagheri et al. 2019a; Bagheri and Ghader 2017). Green chemistry basic principle is the design of processes to decrease waste production, decreasing harmful chemicals raw materials, and increasing the usage of more environmentally safe solvents. Supercritical fluids (SCF), ionic liquids (ILs), and water are known as green solvent (Bagheri et al. 2019b; Ivanković et al. 2017; McDowell and Bazan 2017). Many benefits are repeated about ionic liquids and supercritical fluids as green solvents to develop new processes. A supercritical fluid is a fluid state that its pressure and temperature is higher than its critical values and its properties is like liquid-like and gas-like (Bagheri et al. 2019c; Zhao et al. 2005). Two beneficial fluids, which are applied as supercritical fluid, are water and carbon dioxide (CO_2). CO_2 has moderate critical temperature and pressure, low cost, availability, and non-toxicity. However, supercritical water is highly corrosive. Due to the unique properties of supercritical fluids, they can be used instead of organic solvents in material processing and chemical reactions (Bagheri et al. 2018).

Wilkes and Zaworotko (1992) reported a kind of room-temperature liquid salts that is stable on air and moisture in 1992, for the first time. This type of liquid was named as "Ionic Liquid (IL)." Ionic liquids (ILs) are described as revolution in material science. Ionic liquids as a new class of solvent are unique topic from three decades ago and the number of published documents has grown rapidly (Aslanov 2011). These liquids have special properties like high thermal and chemical stability, low vapor pressure, good ionic and electrical conductivity, non-flammability, wide electrochemical range, and low melting point. The bonding between the two constituents of this substance is weak due to a difference in size between their anion and cation; therefore, they are liquid at $T < 100$ °C and have adjustable properties like solubility that can be changed by selecting appropriate constituent ions (Florio et al. 2019). ILs are low melting point organic salts, which causes to be liquids phase at ambient temperature. The thermal decomposition temperature of IL is in order of 474 K and their boiling points are not detectable. Furthermore, ILs specific gravities are in the range of 1.1–1.6; subsequently, they are heavier than water and useful in two-phase extraction (Somers et al. 2013). ILs can be composed of a large number of anions and cations. In most cases, there is a great inconformity in the size of ionic and at least one ion has a high asymmetry degree and weakly coordinating anions that this property causes low melting point. The ILs properties depend on the size and nature of both their anion and cation parts. Subsequently, by selecting of favorite anions and cations, many ILs are designed for various applications (Zec et al. 2018; Rogers and Seddon 2003). ILs have other scientific properties like outstanding thermal stability, organic and inorganic compounds, satisfactory dissolution properties with water, wide electrochemical windows, tunable viscosity, high ionic conductivity, and highly polar and no-coordinating (Marsousi et al. 2019; Bagheri and Mohebbi 2017; Sheikhi-Kouhsar et al. 2015; Welton 1999). The general properties of ILs and examples of anions and cations usually used in ionic liquids are given in Tables 1 and 2, respectively.

Table 1 Properties of ionic liquids

Property	Anion and or cation quite large
Liquid range	>200 °C
Freezing point	<100 °C
Viscosity	<100 cp
Thermal stability	High
Dielectric constant	<30
Molar conductivity	<10 Scm^2 mol^{-1}
Vapor pressure	Negligible
Specific conductivity	<10 m Scm^{-1}
Polarity	Mild

Modified after Somers et al. (2013)

Further investigations have indicated that ILs are very effective in electrochemistry (MacFarlane et al. 2007), biomass conversion (Passos et al. 2014), catalysis and chemical synthesis, fuel processing and production, development of liquid crystal (Coleman et al. 2012), biotransformation (Dominguez de Maria 2008), biotechnology (Lee et al. 2007), and many other areas (Smiglak et al. 2014; Welton 1999). ILs have unique and tunable properties, therefore, these solvents can be used in novel valuable topics like medicine, biomedical, and life sciences applications and effective drugs referring to ILs considered for approval by food and drug administration (FDA) (Deetlefs et al. 2016; Ferraz et al. 2011; Zhang et al. 2009). Research acting in the ionic liquids topic has reached a surprising level with a huge studies number (see Fig. 1). The publications number and its increasing trend indicate the main role of ILs in the field of life-science like proteomics and genomics, which have critical influence in medicine and pharmaceutical development.

The main purpose of this chapter is to describe the attention of many researchers in biological, medical, and chemical fields for progress in pharmaceutical using ILs. Consequently, we investigate the application of ILs applying in modern pharmaceutical industry. Moreover, our purpose is to discuss polymerized ILs as antimicrobial materials. Repeated and indiscriminate employment of substances like antibiotics has caused to pathogenic bacteria resistance, especially in hospitals. Engineers thus, by manipulation of the alkyl chain and placement of the appropriate matrix (Polymers, Nanoscaffolds, and so on) (Mecerreyes 2011) or manipulating the anionic part of these substances (such as ampicillin) (Ferraz et al. 2014), have developed substances that, by testing on microorganisms, are trying to detect their toxicity and eventually use them in medicine (Docherty and Kulpa Jr 2005).

2 Application of Ionic Liquids in Pharmaceutical Field

In general, there are four early phases in bacterial infection: the first phase is bacterial binding to host cells, the second phase is proliferation and formation of the colony, the third phase is invasion of host tissue, and the final phase is the destruction of host

Table 2 Some of anions and cations usually employed in ILs

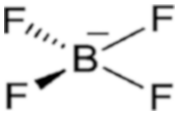
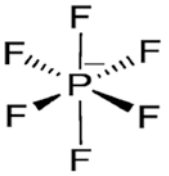
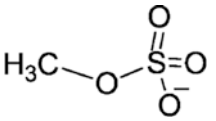
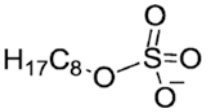
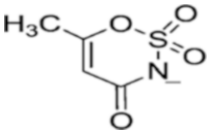
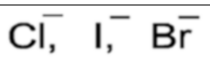
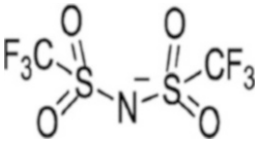
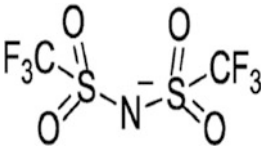
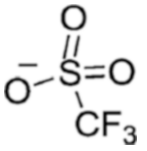
Anion	Typical abbreviation	Structure
Tetrafluoroborate	BF_4	
Hexafluorophosphate	PF_6	
Methylsulfate	$MeSO_4$	
Octylsulfate	C_8SO_4	
Acesulfamate	Ace	
Halides	–	
Bis((trifluoromethane)sulfonyl)amide	NTF_2	
Dicyanamide	DCA	
Trifluoromethanesulfonate	TfO	

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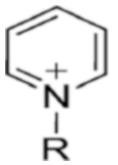
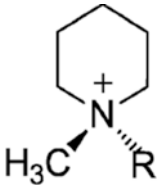
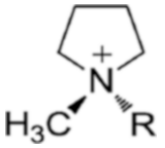
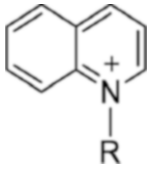
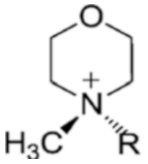
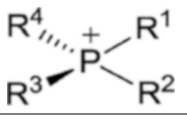
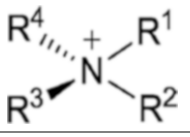
Table 2 (continued)

Cation	Typical abbreviation	Structure
Imidazolium	MIM	
Pyridinium	PY	
Piperidinium	PP13	
Pyrrolidinium	P11	
Quinuclidine	Qu	
Morpholinium	MO	
Quaternary phosphonium	–	
Quaternary ammonium	–	

Modified after Egorova et al. (2017)

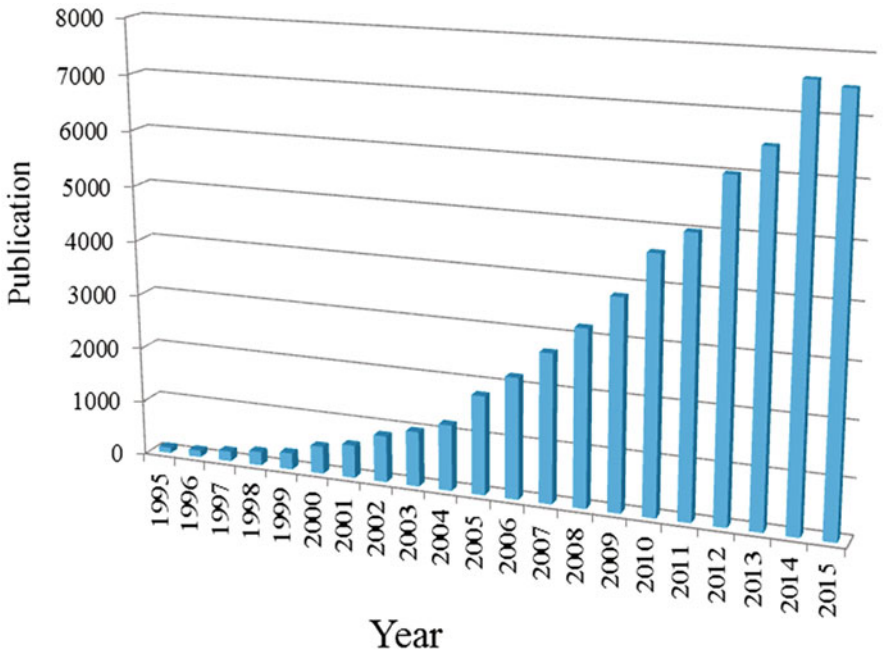


Fig. 1 Number of publications on the subject of ionic liquids. Modified after Egorova et al. (2017)

cells by toxins. Researchers by manipulating cations or anions of ionic substances are trying to design them in a way so that they can disrupt one or more of the mentioned phases; although, due to the rate of proliferation and colonization of microorganisms, it is better for the mentioned substance to have the ability to destroy colonies or at least disrupt their ability to reproduce. It is still unclear what is the reason for antibacterial and inhibitory effects of ionic liquids or to predict whether the reason for these effects is due to the type of bacteria (Gram negative or Gram positive) because the results for all species of a single class of bacteria were not the same (Docherty and Kulpa Jr 2005). Studies have shown that cationic groups play a key role because of their ability for electrostatic/lipophilic interactions with microorganism cell walls (Florio et al. 2019). In fact, polar groups' chemical composition and structure in the hydrophilic half of ILs could have a significant impact on their antimicrobial activity (Ferraz et al. 2014; Docherty and Kulpa Jr 2005). Although not yet proven, the antibacterial and toxic effects of ionic liquids are mainly driven by the alkyl branch by affecting the integrity of biological membrane (Florio et al. 2019) and the hydrophobicity of the cations, since there is an increase in the inhibition of growth with longer length alkyl chain (C_nH_{2n+1}) for all

microorganisms, the effect of toxic may be because of a common cellular structure (Docherty and Kulpa Jr 2005) and anions have an auxiliary role in modulating ionic liquids' activity such as their hydrophobicity (Docherty and Kulpa Jr 2005; Zhang et al. 2019). Consequently, we continue to explore some of the most conventional cations in creating ionic liquids and their combination with different anions and then we examine several anions.

2.1 Ionic Liquid Biological Activity

Ionic liquids as drug delivery, complementary components, and drug systems in the synthesis of drug can be used in pharmaceutical applications. H_2O is important for all conditions of living. Consequently, the solubility of IL in water and interaction between IL and water are main factors to determine the biological and environmental activities of IL. Most ILs, but not highly hydrophobic ILs, include some water. Furthermore, ILs can adsorb water from humid ambient. Moreover, ILs biological activity is depending on ILs hydration state. One of the drug tendencies in a salt is a usual method to enhance drug solubility; consequently, due to ILs are liquid salts, using of them leads to increasing ILs bioavailability (Egorova et al. 2017; Kurnia et al. 2014). Among ILs with several cations, the ionic liquids water solubility is impressed by the IL aromaticity and IL cation size and it decreases as follows: imidazolium > pyrrolidinium > pyridinium > piperidinium (Egorova et al. 2017). Some cations like pyridinium, imidazolium, ammonium, piperidinium, and pyrrolidinium can inhibit the activity of pathogenic and nonpathogenic fungi and bacteria (Elshaarawy et al. 2016; Papaiconomou et al. 2010; Dominguez de Maria 2008). In biological activity field, ILs can be used as anticancer agents. The ILs cytotoxicity depends on ILs structure and widely of varies, in the range of micromolar to millimolar. For example, pyridinium and imidazolium are more cytotoxicity than cholinium ILs. Once the ionic liquids toxic activity has become obvious, investigations on possible ILs using as anticancer agents have started. The main driving force of study on ILs anticancer agents is ILs high tunability (Egorova et al. 2017).

Studies have showed that the antibacterial effects of ionic liquids containing pyridinium are driven by alkyl branches and cation hydrophobicity (Docherty and Kulpa Jr 2005). This trend increases with increase in c-1alkyl chain (McCrary et al. 2013; Pernak et al. 2004). This process is applied to numerous bacteria like *Vibrio ficheri*, which inhibits the breathing of the organism; *Coccus* representing the Gram-positive bacterium and *yeast* representing Gram-negative bacterium; *B. subtilis*, which is a Gram-positive aerobic bacterium and *Staphylococcus aureus*, which is an anaerobic bacterium; *E. coli,* which is an anaerobic Gram-negative bacteria and *P. fluorescens*, which is an anaerobic Gram-negative bacteria were tested and the results confirmed the increase in toxicity; however, each of these bacteria received a different effect amount. For example, all ionic liquids were inhibitor of *B. subtilis. E. coli,* and *P. fluorescens* were dramatically affected or

S. aureus, *Coccus,* and *S. cerevisiae*, which is yeast, received the least impact. One way that researchers have been working to add toxicity and antibacterial to ionic liquids is to change the alkyl chain length or replace it with different groups. The results of methyl group substitution experiments around the pyridinium ring in anionic series Bromi and Dicyanamide ($(CN_2)_2$)-indicate the increased toxicity of these substances for *V. ficheri* bacteria. The toxicity of cation pyridinium also increases with the addition of methyl branches, for example,1-butyl-3,5-dimethyl pyridinium is more toxic than 1-butyl-3-methyl pyridinium and this substance is more toxic than 1-butyl pyridinium (Docherty and Kulpa Jr 2005; Pernak et al. 2004). ILs replacing butyl shows intense antimicrobial effects especially on more complex organisms such as *Daphnia magna*. Among the alternative groups around the pyridinium ring, the most effective colony formation inhibition was related to [Ompyr][Br] and the ionic liquids of the group Hexyl showed the least inhibitory effects. The antimicrobial effects of octyl substituents also depend on the microorganism studied. [Bpyr][Cl] substance attacks lipid glands in cytoplasmic membrane and destroys them by creating superoxide radicals (Docherty and Kulpa Jr 2005).

One of the mostly used cations in creating ionic liquids is imidazolium cation. Antibacterial effects of ionic liquids containing imidazolium alike pyridinium cation are directed by alkyl branches and cation hydrophobicity and with increase in c-1 Alkyl chain length this process also increases. For instance, the more alkyl chain length of the groups replacing *c-1* in 1-alkyl-3-methyl imidazolium increases, the more hydrophobic it gets, and shows more toxicity than *V. ficheri* bacteria. Almost, all ILs including imidazolium-based cations are inhibitors of the three bacteria, namely *P. fluorescens*, *E. coli*, and *B. subtilis*. Among the ionic liquids containing imidazolium, [Omim][Br] substance has the most effective inhibition of colony formation against bacteria *Coccus*, *yeast*, *Daphnia magna* (Docherty and Kulpa Jr 2005). In order to investigate the ionic liquids from different aspects, the ILs given in Table 3, are studied. IL1-4 have similar Alkyl chain lengths but their cations are different. Commonly for an easier and more straightforward description of antibacterial effects, an indicative substance named "Minimum inhibitory concentration" (MIC) is defined. The lower this value, the lower the amount of ionic liquid needed to kill the bacteria, thus the probability of IL being harmful to human body or cause toxication would decrease. Among these, IL1 had minimum MIC value against bacteria *S. epidermidis*, *E. faecalis,* and *S. aureus*. Antimicrobial property of IL1-IL4 against bacteria *E. coli*, *Enterococcus faecalis*, *S. epidermidis*, *Pseudomonas aeruginosa,* and *Staphylococcus aureus* is as follows: IL1 > IL3 > IL2 > IL4.

IL1-IL3 are able to inhibit the bacteria colony formation. Even for *S. aureus*, colony formation inhibition is also remarkable in half MIC. IL5 is similar to IL1 with the only difference that one diol was placed on its nitrogen. Comparison of their antimicrobial activity indicates that antimicrobial activity of IL5 decreased with respect to IL1 except for *P. aeruginosa* and this result indicates that hydroxy groups are impairing antimicrobial activity. The results have shown that the presence of some specific groups like amids, esters, carboxyls, and hydroxyls in the cation chain leads to reduction in the toxicity of ILs and increases their degradability (Florio et al.

Table 3 Chemical structure of ILs 1–15

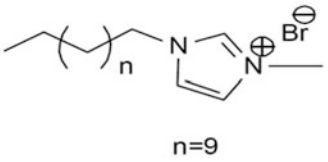
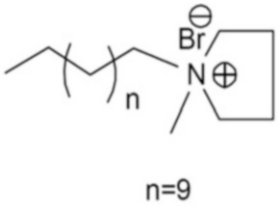
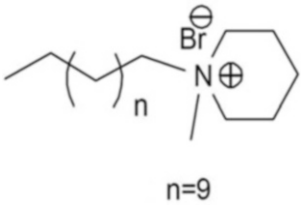
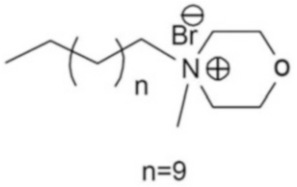
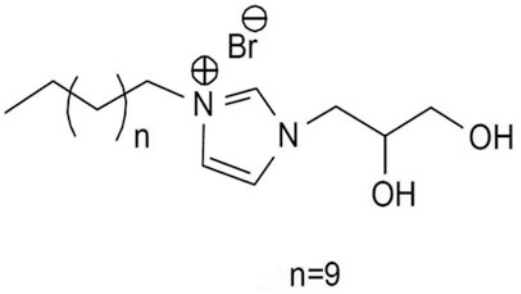
Ionic liquid	Structure
IL1	
IL2	
IL3	
IL4	
IL5	

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Table 3 (continued)

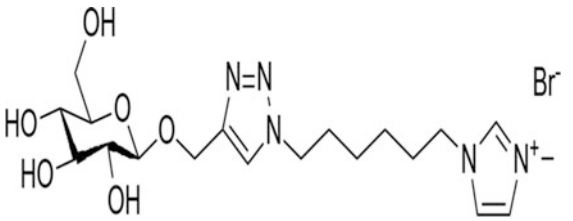
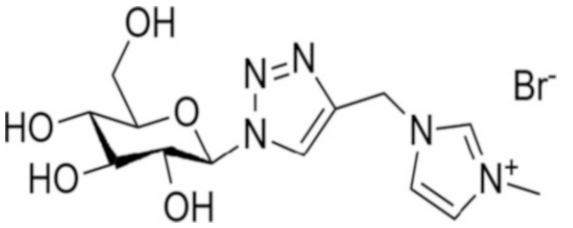
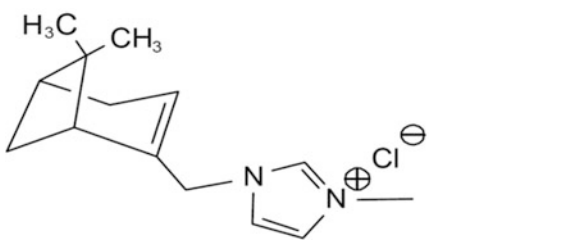
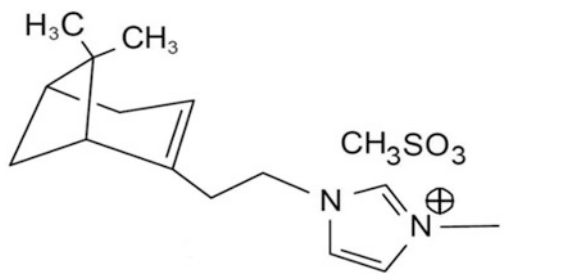
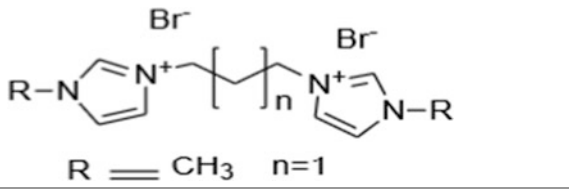
Ionic liquid	Structure
IL6	
IL7	
IL8	
IL9	
IL10	

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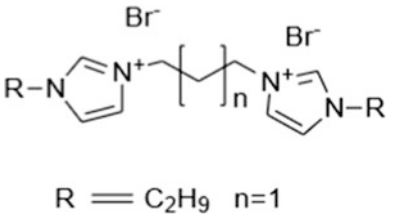
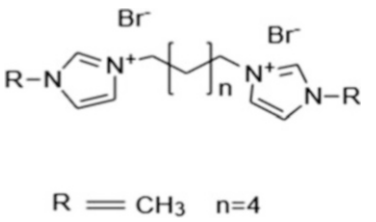
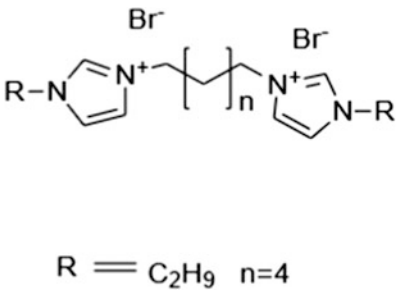
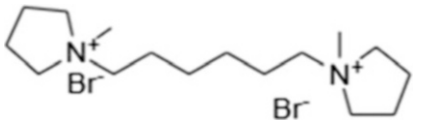
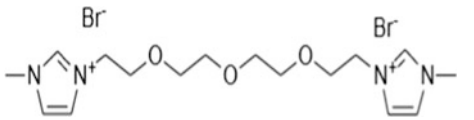
Table 3 (continued)

Ionic liquid	Structure
IL11	
IL12	
IL13	
IL14	
IL15	

Modified after Florio et al. (2019)

2019). IL6-7 that includes Triazole links showed a sharp reduction in antimicrobial strength. IL9 compared with IL8 has about twice as much higher antibacterial potential except against *S. aureus* and that is while, IL9 has an extra methyl group than IL8. To check for the presence of excess cation IL10-15 was made. Among these six cationic ionic liquids, IL13 has the longest alkyl chain. The results of the researchers' experiments (Florio et al. 2019) have shown that IL13 has the highest antimicrobial activity among the anti-cationic liquid groups, especially against

Table 4 Minimum inhibitory concentration of ionic liquids 1–15

Ionic liquid	MIC value for				
	Escherichia coli	*Staphylococcus epidermidis*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Enterococcus faecalis*
1	20 μg/mL	2.5 μg/mL	2.5 μg/mL	160 μg/mL	5 μg/mL
2	80 μg/mL	10 μg/mL	10 μg/mL	312.5 μg/mL	20 μg/mL
3	40 μg/mL	5 μg/mL	5 μg/mL	312.5 μg/mL	10 μg/mL
4	156.2 μg/mL	20 μg/mL	20 μg/mL	312.5 μg/mL	40 μg/mL
5	80 μg/mL	10 μg/mL	10 μg/mL	160 μg/mL	20 μg/mL
6	>5 mg/mL	>5 g/L	>5 g/L	>5 mg/mL	5 g/L
7	>5 mg/mL	5 g/L	>5 g/L	>5 mg/mL	>5 g/L
8	1.25 mg/mL	312.5 μg/mL	625 μg/mL	2.5 mg/mL	1.25 g/L
9	625 μg/mL	160 μg/mL	160 μg/mL	1.25 mg/mL	625 μg/mL
10	10 mg/mL	>10 g/L	>10 mg/mL	>10 mg/mL	>10 mg/mL
11	>10 mg/mL	5 g/L	>10 g/L	>10 mg/mL	10 mg/mL
12	>10 mg/mL	10 g/L	10 g/L	>10 mg/mL	>10 mg/mL
13	2.5 mg/mL	2.5 g/L	5 g/L	>10 mg/mL	10 mg/mL
14	>10 mg/mL	10 g/L	>10 g/L	>10 mg/mL	>10 mg/mL
15	>10 mg/mL	>10 g/L	>10 g/L	>10 mg/mL	>10 mg/mL

Modified after Florio et al. (2019)

S. epidemidis, *E. coli,* and *S. aureus* bacteria. IL1 and IL5 were compared to each other in order to study the effect of antimicrobial activity on alkyl chain length, which are the same in terms of cation and anion but IL5 is taller in terms of chain length. The results showed that antimicrobial activity of IL5 is far less than IL1. This suggests that the alkyl chain (C_nH_{2n+1}) length is partly effective on antimicrobial activity. In general, ionic liquids with the alkyl chain length of twelve to fourteen carbon atoms indicated the highest antimicrobial activity. However, the antibacterial activity in chains above 16 carbon atoms and lower than 10 carbon atoms was significantly reduced (Florio et al. 2019). MIC is defined for some ionic liquids in Table 4, which is described in the following. In general, the activity of ionic liquids against Gram-negative bacteria in particular *P. aeruginosa* is less than other bacteria. As one can see in Table 4, this process also holds about MIC values. The outer membrane of Gram-negative bacterium could be one reason for it.

2.1.1 Polymeric Ionic Liquids

Polymeric ionic liquids (PILs) which deal with polyelectrolytes are a class of polymers that are formed by ionic liquid monomers and they are synthesized from solid salt monomers. These liquids are better than their IL sample in some properties such as hydrophobicity (Mecerreyes 2011). These polymers can be used to create antibacterial surfaces. PILs of antimicrobial typically relying on cationic groups like: (a) 1,2-thiazolium, (b) quaternary ammonium, (c) phosphonium,

(d) pyrrolidinium, (e) imidazolium, (f) guanidinium, (g) pyridinium, (h) 1,2,4-thiazolium, and so on. They are synthesized fundamentally with three ways: (1) polymerization of ionic liquid monomers directly, (2) synthetic precursor polymers are actually modified chemically through a quaternization reaction, (3) by grafting after ILs polymerization through effective ligation reactions (Muñoz-Bonilla and Fernández-García 2018). An ion exchange step is often required in these strategies. Although the main method of reducing Poly (ionic liquid) s is the radical polymerization of conventional ionic liquid monomers, in recent years polymerization control techniques have become important because they allow the accurate design and precise control of the structures of macromolecule. In some cases, PILs could be chemically modified by polymers that were formerly polymerized, making it difficult to create some structures or chemicals with directly IL monomers' polymerization (Muñoz-Bonilla and Fernández-García 2018). Plenty of PILs is produced and tested like antimicrobial compounds, including the cationic section of the moving anions and the polymer backbone (Muñoz-Bonilla and Fernández-García 2018). However, few studies have assessed active and cationic counter ions with anionic PILs (Muñoz-Bonilla and Fernández-García 2018). Figure 2 clearly illustrates the comparison of different PILs performance against *E. coli* and *S. aureus*, *C. albicans*, *MRSA* bacteria (Xu et al. 2017).

One of the most important characteristics of an antibacterial substance is the ability killing the bacteria colony. PILs containing Zinc was able to completely eliminate the bacteria colonies of *E. coli*, *S. aureus*, *C. albicans,* and *MRSA* after 4 h. There are two factors contributing to this result (Xu et al. 2017): (1) Electrostatic interaction of Zinc with teichoic acids available in the membranes of microorganism. (2) Resulted Zn^{2+} can produce active oxygen in the cell, thereby prolonging the growth delay phase and inhibiting the synthesis of cell wall and ultimately growth and death of germs. In addition, an ideal antibacterial substance should have good biocompatibility, high efficiency, long-term activities, easy combination, and low cost (Guo et al. 2012). The ionic substance made of imidazolium cation, styrene, and acrylonitrile is expected to have good antibacterial properties since poly (styrene-acrylonitrile) is a copolymer substance, which has high chemical resistance and is predicted to have the ability to form strong membrane. Because the hydrophobic region of membrane PIL units facilitate antimicrobial activity, while hydrophobic region provides high mechanical resistance (Guo et al. 2012; Viau et al. 2010). PIL-Br membrane showed effective antibacterial properties compared to two bacteria *E. coli* and *S. aureus*. Antimicrobial activity of this membrane was more than *S. aureus* compared to *E. coli*. These different antibacterial efficiencies could be related to the different structures of the cell membranes. *E. coli* is a Gram-negative bacterium. The cell wall of this bacterium is more sensitive to Gram-positive, anionic, and hydrophilic bacteria. Thus, it is assumed that higher antimicrobial activity is resulted from a stronger electrostatic interaction between imidazolium cation and anionic cell wall and the same interaction is why the membrane works better than *E. coli* (Guo et al. 2012). Among the polymeric membranes poly ionic liquid-Br (PIL-Br), poly ionic liquid-Pro (PIL-Pro), PIL-Trp, and poly ionic liquid-Trp (PIL- Trp) showed the highest antibacterial activity such that in duration of

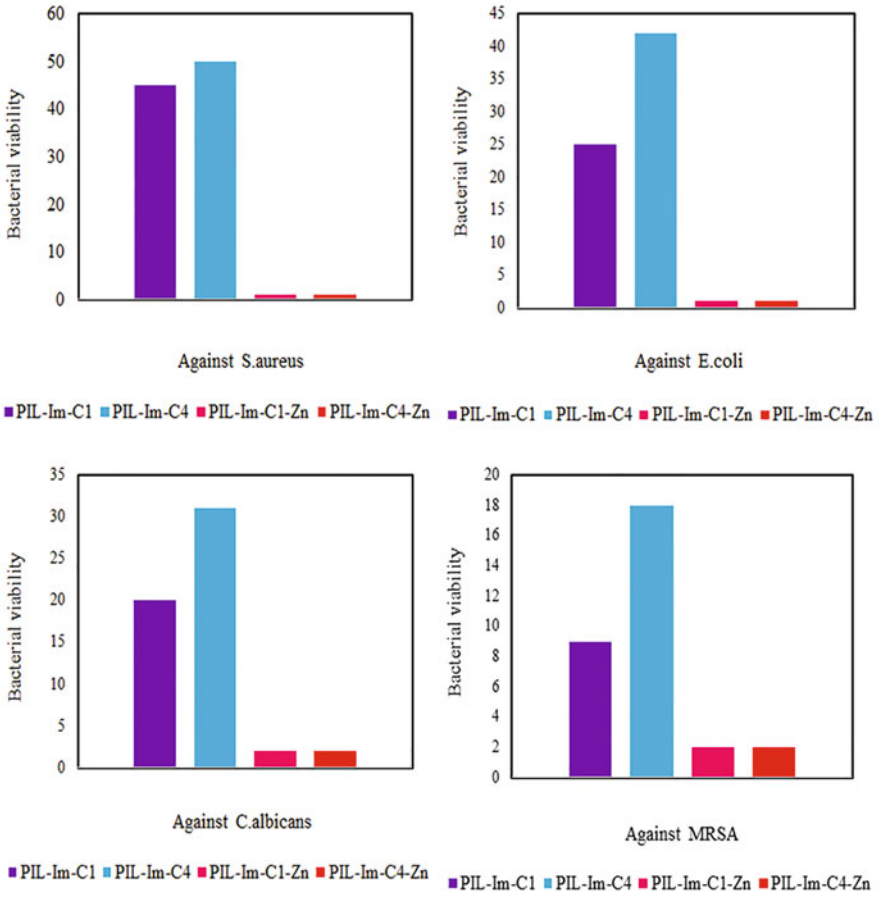


Fig. 2 Comparison of viability bacteria in the presence of IL-Im and PIL-Im. Modified after Xu et al. (2017)

1 hour, approximately 80–90 % of *E. coli* and *S. aureus* were killed. Furthermore, approximately 98% *S. aureus* and *E. coli* were killed and disappeared in four hours. The results of the hemolysis procedure for these polymeric ionic liquids showed that all membranes based on synthesized PIL are biocompatible with human cells. In addition, these polymeric membranes are easily recyclable without significant reduction in antimicrobial activity (Guo et al. 2012). Traditional dressing like cotton wool, bandages, and gauzes cause the wound to dry out while the wet wound bed promotes angiogenesis and when the wound heals, the epithelial cells in this environment are more active than in the dry environment. Hydrogels have a three dimensional network structure that adsorb a lot of water or biological fluids (Yu et al. 2020). PVA (Poly vinyl alcohol), a non-toxic polymer, is biodegradable and water-soluble and has hydrophobic nature. Hydrogels based on PVA have many useful properties, for example, high biocompatibility, biodegradability, good viability, and

adhesion performance (Yu et al. 2020). $B(OH)_4$ has interaction with two separate groups of cis-diol on PVA to create a hydrogel system. Hence, antibacterial hydrogels by combining antibiotics in PVA-$B(OH)_4$ hydrogels provide versatility and responsiveness. Introducing borate ester bonds leads to change in PVA/$B(OH)^-_4$ hydrogels rheological properties in the presence of $C_6H_{12}O_6$ since borate esters formed in the another competing presence saccharide molecule like $C_6H_{12}O_6$ are separated (Yu et al. 2020). In order to measure glucose ($C_6H_{12}O_6$) or their insulin secretion, these hydrogels can be adjusted depending on their glucose ($C_6H_{12}O_6$) response, system of PVA/C_4 MPBr/B $(OH)_4$ has furthermore responded to $C_6H_{12}O_6$. In addition, responsive behavior to pH from hydrogels were tested and considering the binding among the cis-diols and boric acid group, which is highly pH dependent and reversible, hydrogels PVA/C_4 MPBr/$B(OH)_4$ exhibits responsive properties to pH (Yu et al. 2020).

To evaluate antibacterial ILs activity, the results indicate that without addition of C_n MPBr, pure hydrogels PVA did not show any antibacterial property. But the prepared hydrogel demonstrated effective antimicrobial reaction against *S. aureus* and *E. coli*. It should be noted that the hydrogels containing IL with longer alkyl chains ($C_nH_{2n\ +\ 1}$) have more prominent antibacterial characteristics. Retention of moisture, self-healing, and behavior of being multiresponse together with antibacterial characteristics of hydrogels have made them ideal applicants as multifunctional dressings in order to heal the skin wounds (Yu et al. 2020). Since joints often move, a joint wound dressing which is ideal should make proper touch with the skin lacking preventing movement. Hydrogels that are generated from natural polymers have proper expandable properties and can applied to simulate the human skin tissue expansion capability. PVA/C_n MPBr/$B(OH)_4$ hydrogels tensile characteristics have been proven through tensile testing. In addition, hydrogels have good adhesion characteristics on human skin. Hence, these antimicrobial hydrogels have applications of potential for dressing substances to heal skin wounds (Yu et al. 2020; Soni et al. 2015). To investigate the antimicrobial effect on a set of chiral imidazolium ($C_3H_5N_2^+$) ILs containing amino acid, ester (R′COOR) and features of dipeptidyl, medicinal properties of chiral ionic liquids (CILs) as shown in Fig. 3 were against Methicillin-resistant *Staphylococcus aureus* (Coleman et al. 2012).

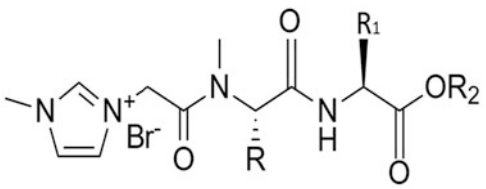


Fig. 3 Chemical structure of CIL1-4 (R=$CH_2(C_6H_5)$ and for CIL1: R_1=$CH(CH_3)_2$, R_2=C_2H_5, for CIL2: R_1=$CH_2CH(CH_3)_2$, R_2=CH_3, for CIL3: R_1=CH_3, R_2=CH_3, for CIL4: R_1=$CH_2(C_6H_5)$, R_2=C_2H_5). Modified after Coleman et al. (2012)

CIL1 showed inhibitory effect in small quantities of MIC. This CIL also has antifungal toxicity, low antibacterial toxicity with selectivity established for MRSA inhibition. CIL2, CIL3, and CIL4 also showed anti-bacterial behavior against bacteria. The relationship between these CIL structures and the results of their biological activities are remarkable. The presence of lipophilic and aromatic phenylalanine ($C_9H_{11}N_1O_2$) units in the dipeptidyl side chain of ILs led to properties of antibacterial being highlighted. CIL4 with a Phe-Phe sequence was more active. It was assumed that an antibacterial selective MRSA ionic liquid would have less toxicity in a toxicity experiment, than a proven antimicrobial biocidal (Coleman et al. 2012).

Among other choices for ionic liquid cations or maybe in some ways the best choice is quaternary ammonium or in short Qa. Researchers' results so far have been satisfying and promising for all the synthesized samples containing Qa. For example, PIL-Qa-C1 was tested on *MRSA* Gram-negative bacteria, which is a resistant bacterium and the effectiveness of the substance was proven as an antibacterial (Xu et al. 2017). IL-Qa-C4 showed good antibacterial properties on *E. coli*, *MRSA*, *S. aureus* bacteria and also *C. albicans* fungus, so that the properties of these materials have been much better compared to those of imidazolium cation. Antibacterial activity of IL-Qa-Br has also improved significantly compared to other cations (Jin et al. 2019). PILs, which have been synthesized from Qa cation and Zn anion like Poly Ionic Liquid-Quaternary ammonium-C4-Zinc (PIL-Qa-C4-Zn) and Poly Ionic Liquid-Quaternary ammonium-C1-Zinc (PIL-Qa-C1-Zn), have been reported to be biologically safe so that researchers are evaluating their application for operational medical use and are expected to be used in manufacturing wound dressing or antibacterial surfaces soon (Zhang et al. 2019; Zheng et al. 2017). Figure 4 compares of viability bacteria in the presence of ILs containing the Qa cation and polymeric ionic liquids containing Qa.

So far, in this chapter we have studied ionic liquids (ILs) from the perspective of their cations. But we know that an IL is formed of a cation and an anion. In order to get a better conclusion on their properties, we give a brief description of anions and researches conducted around them. The most common anions used in the ionic liquids synthesis are Hexafluorophosphate (PF^-_6) and Tetrafluoroborate (BF_4), which are hydrophobic, while Chloride (Cl^-), Bromide (Br^-), and Iodide (I^-) are hydrophilic. The mechanism of phosphate anions is that there is an electrostatic interaction among the phosphate (PO_4^{3-}) groups on the bacteria cell membrane and the ionic liquids positive charge, thus the cell membrane permeability increases and causes the cytoplasmic contents of the bacterium to leak and eventually death of the cell (Zhang et al. 2019; Fang et al. 2019; Florio et al. 2019). On the other hand, the hydrophobic part of the anion enters the lipid membrane of the bacterium and penetrates it (Zhang et al. 2019; Fang et al. 2019). Trp^- is another anion that a high antibacterial efficiency was reported for it compared with other anions of this substance (Xu et al. 2017).

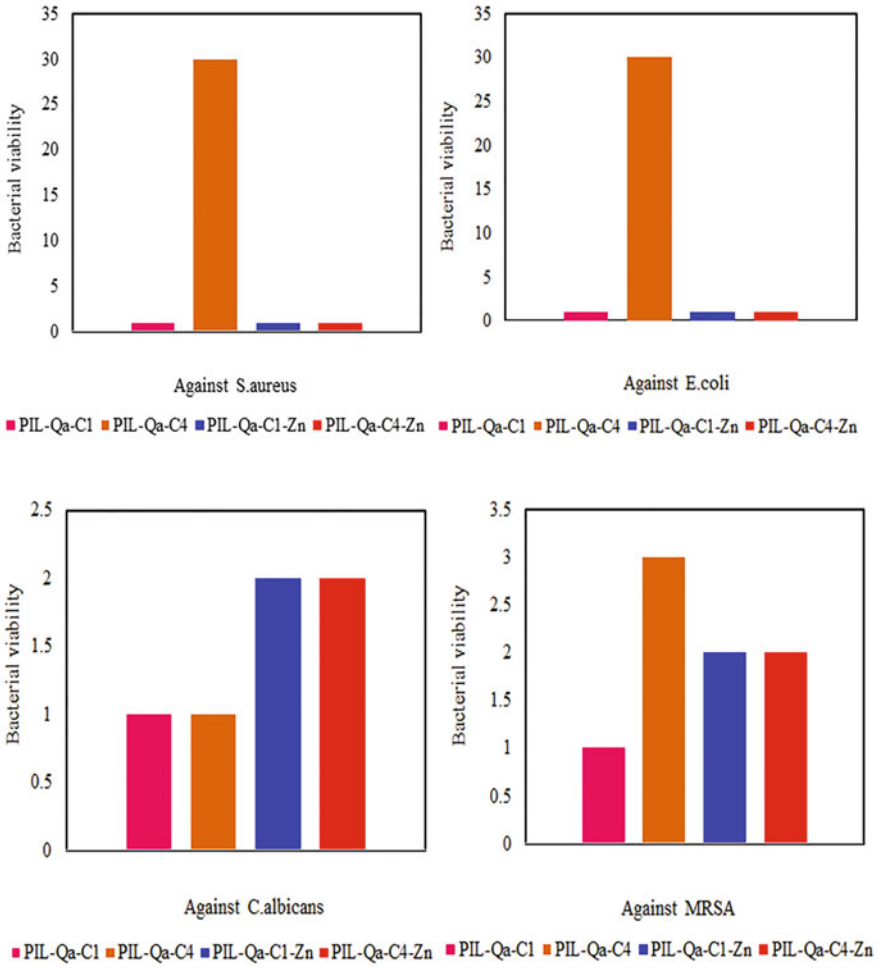


Fig. 4 Comparison of viability bacteria in the presence of IL-Qa and PIL-Qa. Modified after Xu et al. (2017)

In total, about those polymers based on cation, the PILs chemical structure containing hydrophobicity, molecular weight, and charge density should be completely intentional until achieving low toxicity and high antimicrobial efficiency (Muñoz-Bonilla and Fernández-García 2018). It has also to be recommended that ILs have been got attention like hopeful candidates for prohibiting biofilm development and counteracting pathogens. However, there have been few studies on their toxicity. Poly ionic liquids (PILs) are a combination of the antimicrobial ability of ILs and the ability of polymers processing, which have got much attention in antibacterial applications (Fang et al. 2019). Furthermore, one of the most important

factors affecting antibacterial activities to take into consideration is the counter ions (Muñoz-Bonilla and Fernández-García 2018).

Charge density and alkyl chain length affect the antibacterial properties of *N*-alkyl imidazolium-based PILs. A longer alkyl chain leads to an increase in the antibacterial activity of the PIL suspension, but for the PIL-based copolymer membranes, a longer alkyl chain leads to a decrease in the antibacterial activity of the PIL. However, higher charge density in both the PIL membrane and PIL suspension comforted the progress in antibacterial activity (Fang et al. 2019). When PIL nanoparticles are adsorbed by electrostatic interaction on the surface of the bacteria, the hydrophobic PIL alkyl chains enter into the hydrophobic bacteria membrane section, resulting in bacteria death and membrane separation. For instance, the activity of antibacterial poly [CnVIm] [Br^-] nanoparticles is powerfully associated to the alkyl chain length, i.e. C12 > C16 > C10 > C8 (Fang et al. 2019). This revealed that to improve the antibacterial effect the long alkyl side chains were required, while excess hydrophobic side chains played instead of an opposing role. Further, the anion interactions depend on the length of the alkyl chain. For instance, anion exchange from $Trp^-$to Br^- in the poly [CnVIm] [Br] nanoparticles, caused an increase in antibacterial properties for C8 and C12, but a decrease for C16. The relationship between structure and antibacterial effect plays an important role in the optimized modeling and the structure of the antibacterial property of medicine (Fang et al. 2019). The longer alkyl chains, the lower minimum inhibitory concentration values in ionic liquid monomers. Moreover, the imidazolium cations charge density is related to the ionic liquid monomers antibacterial activities (Zheng et al. 2017). The bis-imidazolium IL shows more activities of antibacterial than monoimidazolium analogs, which is characterized that if the charge density becomes greater, the minimum inhibitory concentrations of the ionic liquid monomers decrease. For example, the minimum inhibitory concentration values for compounds [OVIM][Br] (1-octyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide (IL-C6-Im-C8)) and [C_{12}VIm][Br] (1-dodecyl-3-vinylimidazolium bromide (IL-C12)), respectively, are much lower than those for compounds [EVim][Br] (1-ethyl-3-vinylimidazolium bromide (IL-C2)) and [PBVIm][Br] (1-butyl-3-vinylimidazolium bromide (IL-C4)), which justify the preceding explanation. It is assumed that the cationic compounds (or polymers) antibacterial mechanism makes the electrostatic interaction of cell wall phosphates with cationic portions. Cell death occurs when the hydrophobic portions of the polymers (or compounds) enter the lipid membrane of the bacteria, which destroys the membrane of the cell. In addition, it is obvious that stronger electrostatic interactions among groups of phosphate of the cell wall and cations increase the antibacterial efficiency (Zheng et al. 2017).

The investigation of polymeric membranes with their hard and flexible properties is essential among the antibacterial materials. Moreover, those membranes, which have major antibacterial properties, are essential for medical applications. Colony counting is one way of describing the poly ionic liquids membranes antibacterial properties. In fact, number of bacterial colonies on the culture plate indicates their antibacterial activity (Zheng et al. 2017). Accordingly, it is acquired that the activities of antibacterial of PIL membranes based on bis-imidazolium are higher

than that of monoimidazolium. However, length of carbon chain in antibacterial effects of PIL membranes is distinct from the factors of ionic liquid monomers and poly ionic liquids. As a mismatch might be because of various orientations of the carbon chains in the PIL membrane surfaces and IL monomers (or PIL) suspensions. Tending hydrophobic groups of carbon (C–) chains into hydrophobic wall of cell enhance the activities of antimicrobial. Nevertheless, the manufactured poly ionic liquid membranes antimicrobial properties depend on both the molecular surface structure and the chemical composition (Zheng et al. 2017). However, the poly ionic liquid membranes antimicrobial properties can be related to their molecular surface structure and chemical composition, so which, the groups end strongly influence the poly ionic liquid membrane surface that forms a fully different composition from the bulk. About the PIL membranes, the imidazolium-based cations as hydrophilic groups remain in the bulk part and the long carbon chains of hydrophobic groups tend to separate to the interface between polymer and membrane. However, after suspending the bacteria on the surface of the membrane, the cations based on imidazolium are likely to spread in H_2O and the interface of polymer, therefore significantly decrease the efficiency of antimicrobial. Hence, the longer carbon chains of PIL membranes treated with weaker antibacterial properties (Zheng et al. 2017).

In the biomedical analysis of ILs, the importance of APIs (active pharmaceutical ingredient) of RTIL (room-temperature ionic liquids) compounds, which were chosen, has been totalized with two significant issues regarding the RTILs potential as an adjuvant to drug formulation and plenty potential of RTILs applications in biomedicine (Benedetto and Ballone 2016). The available bioavailability or their slow release upon formation of RTIL micelles or vesicles in physiological solutions improves with the chemical-physical properties of RTILs. These investigations link the room-temperature ionic liquid pharmacology biochemical aspects to the biology of system, and also analyze how a metabolite, in this case the RTIL ions, becomes available to an organism. Most significantly, the RTILs based on the liquid phase might prohibit drug polymorphism problems, which illustrate the challenge to drug development (Benedetto and Ballone 2016).

The cell boundary is known to perform many proceedings, from sticking with layer and cell attachment in tissues to intercellular relations through conveyancing. For example, adhesion is because of variegation of proteins protruding from membranes of the cell, attaining into a layer, in other cells, or an environment like a gel (extracellular matrix) between cells. Every one of these components properties was affected with RTILs, possibly increasing cell adhesion or prohibiting them from adhering to the surface or each other (Benedetto and Ballone 2016). Therefore, its adhesion or absence affects the crawling of cells on their surfaces and rheology in tissues (Benedetto and Ballone 2016). All viewpoints are of medical and diagnostic significance and can supply wide RTILs applications. The new RTIL classes, magnetic ion liquids (MILs), contain organic compounds. $[FeCl_4]^-$, $[MnBr_3]^-$ and $[CoCl_3]^-$ are instances of MIL anions (Benedetto and Ballone 2016). A few studies of these systems have been published so far; none of them attached biological implications. One day, the exact nature of the magnetic conditions was unknown,

and due to the small anisotropy forces, it was unclear how the magnetic moment orientation affected the ions structures and dynamics in the phase of liquid at ambient temperature, though it was estimated that itinerant exchange interactions and low molecular symmetry might be effective (Benedetto and Ballone 2016). For example, in the long-domain magnetic sorting compounds (ferric-, ferro-, and antiferro-) none of them are above the temperature of a few Kelvin. Nevertheless, the properties and their dynamics responses are paramagnetic to higher ranges. This affects their interaction with biosystems. We need to improve the dependence of magnetic MIL anions to amplify this effect using biomaterials or the transition of magnetic function to cations in which properties of biomembranes are already apparent (Benedetto and Ballone 2016). Given the versatility of RTILs, both options should be available. Using magnetic resonance as a reaction, upon reaching this tuning, like MILs, can modify the cells interact with the surroundings via forces coming out of their boundaries. The possibility of this method is supported by the results of many studies achieving the same outcome by magnetic forces by driving nanoparticles to cells (Benedetto and Ballone 2016). The magnetic material is distributed throughout the system in the MIL method, or more absolutely, it penetrates the cell's biomembranes. As such, due to the magnetic forces pervasiveness, they may be topically less severe. The last important point in expanding the domain of the applications of RTIL to their theoretical extent is the derivation of a large number and different kinds of chemical features of these compounds. In addition, new applications are restricted to popular compounds and limit the opportunities introduced via RTILs (Benedetto and Ballone 2016).

2.2 Ionic Liquid as Drug Formulation Components

Drug delivery is one of the hot topics in pharmaceutical field and recently ILs have been able to play an effective role in drug delivery field. Drug efficiency depends on its bioavailability, solubility, and permeability, so that lower solubility can lead to lower drug absorption and dissolution rates and subsequently, higher doses must be consumed for attainment and effect of therapeutic (Savjani et al. 2012). To overcome the mentioned problem, many researchers have suggested that drug formulations should be improved. The critical approaches to better solubility of drug are comminution, dispersion or micellization, usage of alternative solvents or co-solvents, preparation of solvates and hydrates, reducing the drug particle size, applying solubilizing attachments, charged, and polar group and prodrugs. However, reducing the drug particle size is very popular approach to increase drug dissolution and solubility rate because of increasing surface area (Feeney et al. 2016). For instance, in applying solubilizing method, solubilized attachments are added to the molecule of drug and drug active part stays intact. Amides, hydroxyl and amines groups are popular solubilizing. Furthermore, prodrug is promising method to improve the bioavailability and solubility of drug. A prodrug can modify chemically a drug and by increasing lipophilicity, stability, solubility, and action period of

pharmaceutical molecule leads to improve drug delivery (Clas et al. 2014). Ionic liquids are potential substance for drug formulation. As mentioned, ILs are green solvent and environmentally friendly chemical components, which are an adequate candidate for toxic conventional solvents. Many drugs are water-soluble and many ILs have good solubility in water; therefore, leads to increase absorption, rate of dissolution, and hydrophobic drugs targeting ability. Hydrophilic drugs indicate well hydrophilic ILs solubility and drugs with hydrophobic properties choose solvents with hydrophobic features. However, the effect of the anion part of IL on drug solubility is complicated (Balk et al. 2015). In total, ILs may be employed as emulsifiers, copolymers, solvents, anti-solvents, and co-solvents for drug formulation. Table 5 gives examples of ILs application to increase drug emulsifying agents and solubility. From this table, the ionic liquids activity can be as anesthetics, antioxidants, antimicrobial and antiviral agents, anticancer drugs, nonsteroidal anti-inflammatory, and anticoagulants.

Researches have shown that in addition to solubility, anions are somewhat effective in toxicity, especially in applications where toxicity is even harmful in small quantities. Therefore, certain anions should be selected for special purposes such as medical and pharmaceutical (API-IL). Here are some examples to make the problem clearer. A team of researchers used the metathesis response to produce ionic liquids containing quaternary ammonium (NR_4^+) with long alkyl chain (C_nH_{2n+1}) length and Ampicillin (AMP) anion, which is an antibiotic for bacterial infections. Prepared IL was tested with significant pathogenic germs like *Staphylococcus aurous* resistant to Methicillin and the results showed satisfactory antibacterial properties. In short, all ionic liquids that contain Ampicillin are non-toxic to human except $P_{6,6,6,14}$. Figure 5 indicates $P_{6,6,6,14}$ (Ferraz et al. 2014). Table 6 gives the value of MIC for both Gram-negative and Gram-positive bacteria groups for ionic liquids containing AMP (Ferraz et al. 2014).

To compare the effect of Ampicillin anion, some ILs are collected in Table 3, the cations of which are the same as those of the substances in Table 7 and their anion is Cl^-. The reason for the choosing Cl^- is that some chlorine-containing ionic materials are now being used in some products such as mouthwashes and toothpastes. By comparing them we can find that except in a few cases, chloride ILs toxicity in dilute solution has the same effect as that of Ampicillin (Ferraz et al. 2014).

Ferrocene (FC) an organometallic compound is a blend of aromatic, organic, and orange powder and has a sandwich structure, which is highly regarded because of its characteristics such as low toxicity, relative lipophilicity, and high thermal stability in solution. In addition, it can be incorporated as a positive property of ionic liquids. Ionic liquids having FC groups showed more antibacterial activity than the same IL without FC group against different Gram-positive and Gram-negative bacteria species. The relationship between antimicrobial toxicity and environmental toxicity is complicated. Antimicrobial toxicity determines the toxicity of a strain, while to check the environmental toxicity, it has to be determined for the entire society of living. Biodegradation studies of CIL5 (see Fig. 6) and CIL2 show that these two ionic liquid have passed "CO_2 Headspace Test" and are biodegradable (Coleman et al. 2012). The carbon dioxide headspace test describes a technique to determine the test items biodegradability using measuring the carbon dioxide-evolution in

Table 5 Ionic liquid as solubility emulsifiers and enhancers in delivery of drug

Drug	Role	Ionic liquid	Reference
Acetaminophen	Analgesic	[C_4MIM][BF_4] [C_8MIM][BF_4] [C_4MIM][PF_6] [C_4MIM][Br] [C_6MIM][Br]	Mehrdad and Miri (2016), Egorova et al. (2017)
Albendazole	Antiparasitic agent	[C_4MIM][PF_6] [C_6MIM][PF_6] [C_8MIM][PF_6]	Egorova et al. (2017)
Acyclovir	Antiviral drug	[C1MIM][DMP]	Egorova et al. (2017)
Coumarin	Anticoagulant	[C_{10}MIM][NTf_2] [$(C6)_3C_{14}P$][Cl] [$(C_6)_3C_{14}P$][NTf_2]	Egorova et al. (2017)
Curcumin	Antioxidant Anti-inflammatory Antitumor agent	[C_4MIM][BF_4]	Egorova et al. (2017)
4-hydroxycoumarin	Anticoagulant	[EMIM][OTf]	Egorova et al. (2017)
Dehydroepiandrosterone	Steroid hormone	[C_4MIM][PF_6] [C_6MIM][PF_6] [C_8MIM][PF_6]	Egorova et al. (2017)
Danazol	Steroid drug	[C_6C_6OCOPy][NTf_2] [C_8MIM][PF_6] [BMIM][PF_6] [C_6C_6OCOPy][$N(CN)_2$] [BMIM][BF_4]	Williams et al. (2014) Egorova et al. (2017)
Diclofenac	NSAID[a]	[C_6MIM][Br] [C_{12}MIM][Br] [C_{14}MIM][Br]	Egorova et al. (2017) Singh et al. (2009)
Dexamethasone	Steroid drug	[BMIM][PF_6] [C_6MIM][PF_6] [C_8MIM][PF_6]	Egorova et al. (2017)

(continued)

Table 5 (continued)

Drug	Role	Ionic liquid	Reference
5-fluorouracil	Antitumor agent	[BMIM][Br] [C_4MIM] [PF_6]	Goindi et al. (2015)
Etodolac	NSAID	[C_4MIM] [PF_6]	Goindi et al. (2015)
Glibenclamide	Antidiabetic drug	[Cho][Trp]	Alawi et al. (2015)
Isoniazid	Antituberculosis agent	[C_{10}MIM] [TFO]	Egorova et al. (2017)
Ibuprofen	NSAID	[$(C_6)_3C_{14}$P] [Cl] [$(C_6)_3C_{14}$P] [NTf_2] [C_2MIM] [NTf_2]	Egorova et al. (2017) Weber et al. (2015)
Ibuprofen	NSAID	[C_{12}MIM][Cl] [C_{12}MIM] [Ibu]	Egorova et al. (2017)
4′-isobutylacetophenone	Precursor in ibuprofen synthesis	[$(C_6)_3C_{14}$P] [Cl] [$(C_6)_3C_{14}$P] [NTf_2]	Egorova et al. (2017)
Methotrexate	Anticancer Anti-autoimmune Disease agent	[C_1MIM] [DMP]	Egorova et al. (2017)
Lidocaine hydrochloride	Local anesthetic	[C_{12}MIM][Cl] [C_{14}MIM][Cl]	Egorova et al. (2017)
Penicillin V	Antibiotic	[C_6MIM] [PF_6] [C_8MIM] [PF_6] [BMIM][PF_6]	Egorova et al. (2017)
Nimesulide	NSAID	[EMIM][BF_4] [EMIM][OTf] [EMIM][Ms]	Egorova et al. (2017)
Rutaecarpine	Plant alkaloid	[C_{12}MIM][Br]	Egorova et al. (2017)
Progesterone	Steroid hormone	[C_6MIM] [PF_6] [C_8MIM] [PF_6] [BMIM][PF_6]	
Pyrazine-2-carboxamide	Antituberculosis agent	[$(C_{10})_2(C_1)_2$N] [NO_3] [C_{10}MIM] [OTf]	Egorova et al. (2017)

[a]Nonsteroidal anti-inflammatory drug

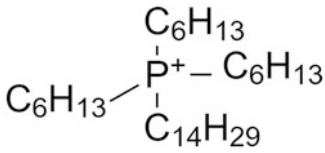


Fig. 5 Chemical structure of $[P_{6,6,6,14}]^+$. Modified after Ferraz et al. (2014)

sealed serum flasks by a headspace volume of about a third of the total flask volume. Since low toxicity in an ecotoxicity experiment does not make sure the biodegradation. Recalcitrant parent compounds durability or breakdown products should also be considered.

Cationic PILs in a wide range have been extended to applications of antimicrobial; however, those PILs based on imidazolium are the most extensively inspected (Muñoz-Bonilla and Fernández-García 2018). Thermal stability is one of the excellent properties of PIL that prepares a situation for non-crystalline polymers with low T_g (glass-transition temperature) amounts in comparability with the others like pyridinium and ammonium kinds of PILs, because of their easy syntheses (Muñoz-Bonilla and Fernández-García 2018). Further, derivatives of polymer and imidazolium salts have showed a wide range of activities of antimicrobial. A basic study of the correlation of the antibacterial structure-activity on IL monomers based on imidazolium, PILs, and membranes of PILs was published by Zheng et al. (2017). The characterization and imidazolium synthesis cation referring to antibacterial substances in Fig. 7 can be seen. A set of bis-imidazolium and mono ionic liquid monomers by different substitutions were synthesized and characterized by their antibacterial activities.

Following these different kinds of structure, the replacement carbon (C–) chain length at N3 positions was different, and also the activities and charge density were measured against both bacteria Gram-positive named *S. aureus* and Gram-negative named *E. coli*. Antibacterial properties of IL monomers and polymers change with concentration, they increase with minimal inhibitory concentration (MIC), because of increasing the alkyl chain length and higher charge density (Muñoz-Bonilla and Fernández-García 2018). As ILs based on pyrrolidinium have usually lower toxicity than imidazolium variants, studies are limited to antimicrobial drugs. A set of IL monomers based on pyrrolidinium was also developed by Zheng et al. (2017) that connected PILs through RAFT (reversible addition-fragmentation chain transfer) polymerization controlling (Muñoz-Bonilla and Fernández-García 2018). The results obtained for IL and PILs based on imidazolium revealed, the capability of antimicrobial against *S. aureus* and *E. coli* was enhanced with increasing the alkyl chain length. On the other hand, PILs indicate better antimicrobial activities because of lower MIC quantity than their corresponding IL monomers (Muñoz-Bonilla and Fernández-García 2018). In total, the values of MIC are lower in these IL structures based on pyrrolidinium than those in imidazolium-like structures. The low activity of PILs based on quaternary ammonium was reported in other studies (Muñoz-Bonilla and Fernández-García 2018). For example, the antimicrobial activity of some ionic liquid monomers and polymers stand on 2-(methacryloyloxy) ethyl]

Table 6 Minimum inhibitory concentration of ionic liquids containing AMP

Ionic liquid	MIC value for (mM)				
	Enterococcus faecalis	*Staphylococcus epidermidis*	*Staphylococcus aureus* ATCC 25923	*K. pneumoniae*	*Escherichia coli* ATCC 25922
[Na][Amp]	0.05	0.05	0.005	2.5	0.05
[TEA][Amp]	>5	>5	>5	>5	>5
[$P_{6,6,6,14}$][Amp]	0.05	0.05	0.05	5	2.5
[C_{16}Pyr][Amp]	0.005	0.005	0.005	0.05	0.5
[choline][Amp]	>5	>5	>5	>5	>5
[EMIM][Amp]	>5	>5	>5	>5	>5
[C_2OHMIM][Amp]	5	2.5	>5	>5	5

Modified after Ferraz et al. (2014)

Table 7 Minimum inhibitory concentration of ionic liquids containing Cl

Ionic liquid	MIC value for (mM)				
	Enterococcus faecalis	*Staphylococcus epidermidis*	*Staphylococcus aureus* ATCC 25923	*K. pneumoniae*	*Escherichia coli* ATCC 25922
[$P_{6,6,6,14}$][Cl]	>5	2.5	2.5	2.5	2.5
[C_{16}Pyr][Cl]	0.5	2.5	0.5	2.5	0.5
[choline][Cl]	>5	>5	2.5	>5	>5
[C_2OHMIM][Cl]	5	5	>5	>5	5

Modified after Ferraz et al. (2014)

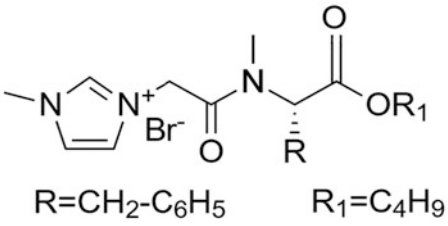


Fig. 6 Chemical structure of CIL5. Modified after Coleman et al. (2012)

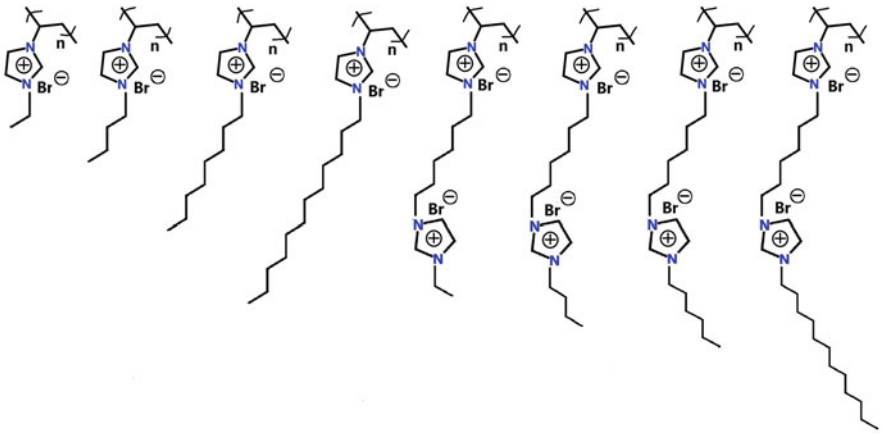


Fig. 7 Chemical structures of imidazolium type PILs. Reprinted with permission of Muñoz-Bonilla and Fernández-García (2018)

dimethyl heptyl ammonium cation and different ions was reported: bis (trifluoromethylsulfonyl)-imide, 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro undecanoate, decanesulfonate, heptadecafluoro octane sulfonate, nonafluoro-1-butane sulfonate, and dodecyl benzenesulfonate. This activity was examined against Gram-positive bacteria named *Micrococcus luteus (M. luteus)*, Gram-negative bacteria named *Stenotrophomonas maltophilia (S. maltophilia)*, *dematiaceous hyphomycetes Cladosporium* sp., and black yeast *Aureobasidium pullulans (A. pullulans)* (Muñoz-Bonilla and Fernández-García 2018). In this case, the IL monomers represented antimicrobial activity, while PILs did not indicate any significant activity. The cause of this low activity for PILs is the powerful electrostatic interaction among poly-cations and anion counterparts. This emphasized that the counter-ion decreases the activity of antimicrobial in these systems (Muñoz-Bonilla and Fernández-García 2018).

In total, anionic PILs, which contain sulfonate and carboxylate polymers with large organic counter ions, are much limiter than cationic PILs (Muñoz-Bonilla and Fernández-García 2018). In particular, most polymer systems for antimicrobial

applications are named cationic polyelectrolytes, since this process mechanism entails interactions of electrostatic with the membranes of bacterial cell based on negatively charged. Numerous systems are stand on poly ionic liquids including AMPS (2-acrylamido-2-methyl propane sulfonic acid) that is simply polymerized using radical polymerization. For instance, anionic poly ionic liquids with antimicrobial properties were produced from AMPS as quaternary salts. Besides, AMP-based polyanionic membranes were developed, for example, acrylonitrile, divinylbenzene, and anionic monomer by several cations, containing imidazolium, metal cations and ammonium. Finally, there are a few studies about anionic PILs so far, though these hopeful components for antimicrobial activity in which the moveable cationic counter ions can display a role of decisive (Muñoz-Bonilla and Fernández-García 2018). According to earlier reports, the counter ions have an important effect on the antimicrobial performance for the anionic and cationic poly ionic liquids. Counter ions are typically responsible for the antimicrobial activity in anionic PILs. For example, the cation effects on polyanionic membranes including anionic sulfate units (AMPS) by the activity of exchanging cation with imidazole and trimethylamine in the role of several metal cations and organic groups were measured using salt (K^+, Na^+, Zn^{2+}, Fe^{3+}, Cu^{2+}, and Ag^+). The polyionic membranes antimicrobials activities were evaluated versus *C. albicans*, *E. coli,* and *S. aureus* strains. Using Zn^{2+}, Fe^{3+}, Cu^{2+}, Ag^+ and the membranes activity was much more prominent than in the case of K^+ and Na^+ with imidazolium, the organic counter ions or quaternary ammonium. In the cationic poly ionic liquids stand on imidazolium groups, the metal ions effect on activities of antimicrobial was investigated (Muñoz-Bonilla and Fernández-García 2018). The counter ions were bromotrichloro ferrates, bromodichloro zincate, and anionic bromodichloro cuprate (Fig. 8). In comparison, the original bromide systems tolerated like a counter-ion and showed higher activity with metal ions, while PILs reacted poorly with iron ions (Muñoz-Bonilla and Fernández-García 2018).

2.3 Drug Synthesis Using Ionic Liquid

ILs are applied in many processes like fascinating usage in the drugs and pharmaceutical components synthesis. Ionic liquids are also used in heterocyclic molecules synthesis, like quinolones, thiazoles, oxazoles, furans, and imidazoles, which are employed in medicine and biology. Ionic liquids can influence the enzymes selectivity used in biotechnological processes. For instance, Monteiro et al. (1997) used a method to produce the nonsteroidal anti-inflammatory drug (NSAID) (S)-naproxen. They applied [BMIM][BF_4] as media. Some instances of advanced drugs molecules synthesis by IL media are given in Table 8.

Some of the most exciting and hopeful findings are the ILs usage for controlling the selectivity and stability of enzymes. Actually, usage of IL leads to increase enzymes activity and stabilization (Dang et al. 2007), permits (controls), proteins reversible folding or unfolding and decreases protein aggregation. Furthermore, ILs

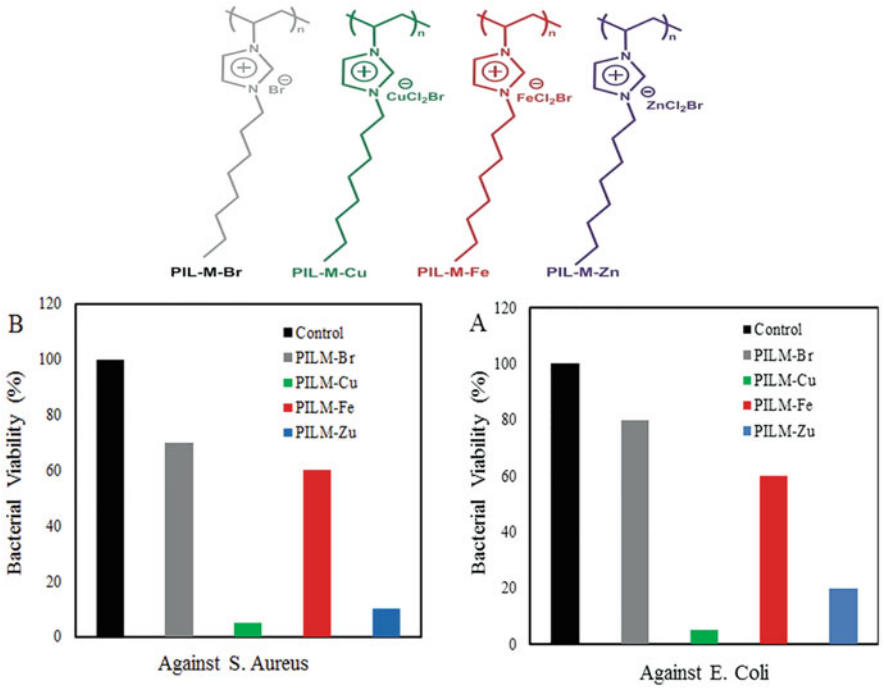


Fig. 8 Chemical structure of PILs containing different metal counter-anions; and bacterial viability of the corresponding membranes against (**a**) *S. aureus* and (**b**) *E. coli*. Modified after Muñoz-Bonilla and Fernández-García (2018)

are able to stabilize protein molecules by divided into structuring ions (Benedetto and Ballone 2016).

ILs are used in drug delivery systems preparation. In these systems IL roles are as solvent, functionalization agent, microporosity enhancers, catalyst and reaction media, additive for microsphere preparation, media for self-assembly of enzyme nanospheres, dispersing agent, and so on. A summary of ILs application in drug delivery systems is given in Table 9. A one can see from Table 9, imidazolium ILs are frequently employed as dispersion agents and media (Fileti and Chaban 2014; Wood et al. 2011; Weuster-Botz 2007; Pfruender et al. 2004).

2.3.1 Production of an Antibacterial Substance from ILs

The function and structure of the hydrophobic material are not affected by the unique assembly IL. However, ionic liquid shows the toxicity to ordinary cells. Afterward, the ionic liquid toxicity is a problem, which needs to resolve. One of the necessary constituents in the cell wall of both Gram-positive and Gram-negative bacteria is peptidoglycans, which was identified as an initial antibacterial target of antibiotics

Table 8 Application of ionic liquids in the drugs synthesis

Compound	Activity	Ionic liquid	Role of ionic liquid	Reference
(R,S)-ibuprofen	NSAID	[BMIM][PF_6] [C_8C1Py] [BF_4]	Enzymatic media	Egorova et al. (2017) Hongwei et al. (2005)
Iodoquinol and clioquinol	Antiprotozoal and antifungal drug	[C_4C_1Py] [ICl_2]	Iodinating reagent	Deshmukh et al. (2015)
Pravadoline	NSAID	[C_4MIM][PF_6]	Media	Egorova et al. (2017)
(R)-modafinil	Wakefulness-promoting agent	[EMIM][Br]	Enzymatic media	Egorova et al. (2017)
Stavudine	Anti-HIV[a] drug	[C_1OC_2MIM] [Ms] [C_4MIM] [TFa]	Media	Egorova et al. (2017)
Brivudine	Anti HSV[b] drug	[C_1OC_2MIM] [Ms] [BMIM] [TFa]	Media	Egorova et al. (2017)
Trifluridine	Anti HSV drug	[C_1OC_2MIM] [Ms] [BMIM] [TFa]	Media	Egorova et al. (2017)
(S)-naproxen	NSAID	[BMIM][BF_4]	Media	Egorova et al. (2017)
Tioconazole	Antifungal drug	[AlkMIM][Br]	Catalyst	Egorova et al. (2017)
Hydrocortisone	Steroid hormone	[EMIM][BF_4] [C_1MIM] [BF_4] [BMIM] [PF_6]	Catalyst	Egorova et al. (2017)
Hydrazinyl phthalazines	Antimalarial agents	[C_1C_1MIM] [C_1SO_4]	Dehydrating agent	Egorova et al. (2017)
Ciclesonide	Anti-asthmatic Anti-allergenic drug	Acidic ILs	Media, catalyst	Egorova et al. (2017)
α-Tocopherol succinate	Vitamin E ester	[C_5MIM] [NO_3]	Media, catalyst	Egorova et al. (2017)
Modafinil and its derivatives	Stimulant for sleep disorders treatment	[BMIM][PF_6]	Media	Egorova et al. (2017)
Isoxazolines	Antimicrobial agents precursor	[BMIM][BF_4]	Media	Chakraborty and Sharma (2013)
(S)-3-chloro-1-phenyl-1-propanol	Antimicrobial agents precursor	[BMIM] [NTf_2]	Ionic liquid phase Whole cell catalysis	Choi et al. (2011)
(R)-phenylacetylcarbinol	Precursor of (1R,2S) ephedrine	[BMIM][PF_6]	Ionic liquid phase	Kandar et al. (2015)

(continued)

Table 8 (continued)

Compound	Activity	Ionic liquid	Role of ionic liquid	Reference
	and (1S,2S) pseudoephedrine		Whole cell catalysis	
3-Phenylglycidol	Precursor of various drugs	[BMIM] [NTf_2]	Media	Egorova et al. (2017)
11α-hydroxy-16α 17-epoxyprogesterone	Intermediate in the steroidal drugs synthesis	[BMIM][PF_6]	Media for enzymatic enantioselective esterification	Egorova et al. (2017)
(R)-1-trimethylsilylethanol	Key synthon for various silicon-containing drugs	[BMIM][PF_6]	IL phase Whole-cell catalysis	Zhang et al. (2009)

[a]Human immunodeficiency virus
[b]Herpes simplex virus

(Wang et al. 2016). Therefore, targeting peptidoglycans can reduce ionic liquid side effects such as toxicity. Wang et al. (2016) in their study used chlorine e6 (Ce6) as an anion containing three COO^- and [C_{12}vim] cation that could bind to the cell wall. This new antibacterial had various properties, including reducing IL toxicity and removing the active cell wall barrier. Morphology and antimicrobial mechanism showed that increasing the concentration of Ce6 in the bacteria and Ce6-IL could remove the cell wall barrier. Ce6-IL eliminated pathogenic bacteria by direct and indirect contact methods according to the binary function of anion and cation. The in vivo experiments have shown that bacterial infection and wound healing could be controlled by Ce6-IL. The safety assessment results have revealed that Ce6-IL works with good biocompatibility. Consequently, there is a new antibacterial agent instead of antibiotics that is made of ionic liquids and photosensitizer to treat wound infection. The new antibacterial agent due to the presence of Ce6-IL has excellent biocompatibility and high antimicrobial activity (Wang et al. 2016). Patachia and Damian (2014) determined the appropriate situation for poly vinyl alcohol cryogels ions loading, to obtain both conductive and antimicrobial gels. ILs antibacterial behavior was in agreement with their positive charge from large organic cations, which makes breaking down the cell wall. The behavior of cryogels of poly vinyl alcohol through plunging in solutions of IL indicates that due to the desalination or desalination capacity, the nature of the IL anions affects the decay and swelling poly vinyl alcohol hydrogels process more than cations (Patachia and Damian 2014). How do cations show their effect on the swelling of hydrogels? The efficiency of cations depends on the time of contact between the ionic liquid and gel. However, due to the low cations diffusion coefficient of them, cations are less effective than anions. Research has shown that in the contact between chloride ionic liquids and poly vinyl alcohol gel throughout the first 70 min, a slightly gel collapse was observed, and had observed that a longer chain of hydrocarbon adhered to the imidazolium ring causes a more initial collapse in the gel. Osmotic pressure is an effective factor in the first moments of ionic liquid solutions contact with the gel.

Table 9 ILs application in the drug delivery systems preparation

Drug delivery system	Ionic liquid	Role of ionic liquid	Reference
Microporous poly(lactic acid) scaffolds	[BMIM][OTf] [BMIM][Cl] [BMIM][BF_4] [BMIM][SbF_6]	Microporosity enhancers	Dorj et al. (2014)
Polylactic acid, Polycaprolactone Membranes, microspheres	[$(C_8)_3$C1N][Cl] [BMIM][NTf_2] [BMIM][PF_6] [BMIM][BF_4] [BMIM][OTf] [BMIM][Cl] [BMIM][SbF_6]	Additive for microsphere preparation	Egorova et al. (2017) Shin and Kim (2012)
Cellulose-biopolymer composite hydrogel	[EMIM][OAc]	Solvent	Egorova et al. (2017)
Cellulose-graf t-poly (L-lactide)	[BMIM][Cl] [AlkMIM][Cl]	Solvent	Egorova et al. (2017) Guo et al. (2012)
Cellulose/SWCNT complex	[BMIM][Br]	Solvent	Egorova et al. (2017)
Cellulose-nanohydroxyapatite composite scaffolds	[BMIM][Cl]	Solvent	Tsioptsias and Panayiotou (2008)
Cellulose, keratin Chitosan composite materials	[BMIM][Cl]	Solvent	Tran and Mututuvari (2015)
Chitosan-based nanocarriers	[BMIM][Cl]	Solvent	Egorova et al. (2017)
Linoleic acid-grafted chitosan micelles	[BMIM][OAc]	Solvent	Egorova et al. (2017)
Benzylpyrazolyl coumarin scaffolds	[C_5MIM][Br]	Catalyst Reaction media	Egorova et al. (2017)
Fullerenes	[C_4MIM][BF_4]	Fullerene dispersion enhancer	Fileti and Chaban (2014)
Silica particles	[C_4MIM][BF_4]	Solvent	Egorova et al. (2017)
Starch nanoparticles	[C_8MIM][OAc] +[C_{16}MIM] [Br] [BMIM][PF_6] [C_{16}MIM][Br] [C_{16}MIM][Br] +[C_8MIM][NTf_2]	Microemulsion cross-linking reaction	Wang et al. (2016) Egorova et al. (2017)

This is why poly vinyl alcohol cryogels membranes were selected for immersion in molar isomeric ILs, which considers the osmotic pressure effect (Patachia and Damian 2014). Another factor affecting the adsorption of IL inside the gel is the IL contact volume. The low contact volume of the IL increases its uptake. The gel loading capacity depends on the amount of the PVA cryogel swelling is affected

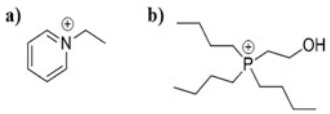


Fig. 9 Chemical structures of the IL as precursors: (**a**) 1-ethylpyridinium, (**b**) tributyl(2-hydroxyethyl) phosphonium. Modified after Choi et al. (2011)

using the concentration and nature of the contacted IL (Patachia and Damian 2014). Choi et al. (2011) studied the antimicrobial activity of two ionic liquids (Fig. 9), namely, 1-ethylpyridinium dactate (IL1) and tributyl (2-hydroxyethyl) phosphonium (IL2). They are effective plasticizers for PVC, and had antibiotic-forming and antimicrobial properties.

The cationic precursor of the bromide salt of the Epy^{+} did not show an important antimicrobial effect, despite having a structure usually used in a wide antimicrobials range and disinfectants (Choi et al. 2011). As previously mentioned, it is not from the cation; however, originates from the anion and is not limited to the length of alkyl chain in the ions (Choi et al. 2011). To study the incorporation of ionic liquids into polymers (encapsulating) as antibacterial agents, different interactions must be considered, for instance, those among anion and cation and their solubility that may repress the antimicrobial activity of a specific ionic liquid. The ionic liquid, in aqueous solution, may show antibacterial and anti-adherence activities; however, its encapsulation into a polymer results in a decrease in antibacterial activities (Choi et al. 2011).

2.3.2 ILs Applications in Pharmacy

Obviously, pharmacology will develop significantly in room-temperature ionic liquid-based research. This discussion is shortened to the pharmacology of room-temperature ionic liquid, which is straightly associated with their interactions with biomembranes (Benedetto and Ballone 2016). The pharmacology basis is based on the difference of properties and different cells membrane structure similar eukaryotic cells and bacteria or diseased and healthy cells like cells of cancer. These differences, together with the inherent versatility of RTILs, represent a choice in the biomembrane of RTIL interactions and finding the way to influencing the destiny of cells and final behavior. Eventually, it could be assumed that biomembranes based on phospholipid (see Fig. 10) encircle a variety of organs of cellular (ribosomes, chloroplast, mitochondria, vacuoles, nucleus, and so on).

The unique and structural composition of each membrane provides the basis for the room-temperature ionic liquids selective interaction with intracellular organelles. Thus, it can be concluded that RTIL's biological activity includes general cytotoxicity and widespread antibacterial activity against not only both Gram-positive and Gram-negative bacteria but also mycobacteria and fungi (Benedetto and Ballone 2016). These properties are common to all RTIL groups, among those based on

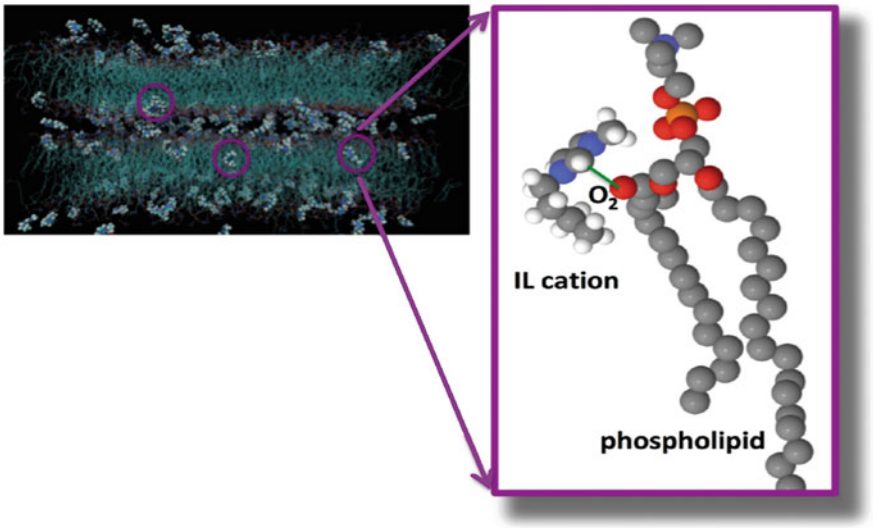


Fig. 10 Pictures from recent MD simulations. Simulation snapshot showing [C_4C1Im][PF_6] ions on POPC in water. Comparison of the density distribution of cations and anions in [C_4C1Im][Cl] and in [C_4C1Im][PF_6]. Reprinted with permission of Benedetto and Ballone (2016)

pyridinium, imidazolium, phosphonium, and ammonium. The experimental evidence indicates that the active mechanism of RTIL is not significant because the toxicity and activity of bactericides appear via collapsing of them (Benedetto and Ballone 2016). It should recommend that bacterial activities are not similar to common toxicity. For instance, pyridinium salts, especially, destroy bacteria without injuring mammalian cells. This is a fundamental property for any pharmaceutical application (Benedetto and Ballone 2016). Now using the quantitative structure-activity relationship (QSAR) model, the cytotoxicity and ability of bactericidal agents can be almost exclusively obtained. No general database of any property is retained. The antibacterial activity of RTILs and the cytotoxicity are not unexpected. Most of the known antibiotics are based on cation and prepared like a salt, due to medium-high and unidentified melting point they are not classified as RTI. The activities of antimicrobial based on peptides (a short chain of amino acids) forcefully depend on their electrostatic effect, which is the first interaction with the external bacteria's membrane. Beside, quaternary ammonium cations have known with their antimicrobial properties. In addition, the quaternary activity of phosphonium cations depends on the alkane chain length. Imagine this compound against Gram-negative bacteria with external wall completed of a peptidoglycan gel layer (Benedetto and Ballone 2016). In RTILs the bactericidal ability is attributed to one or both ions, in fact the pure RTILs antibacterial activity is usually maintained in aqueous solution because they are nominally dissociated. Therefore, the common role of cations is identified according to previous sections. The common structure of RTILs consists of a cationic core (quaternary, ammonium, imidazolium, and pyridinium) and one or

more polar branches, and this structure is common to active RTILs (Benedetto and Ballone 2016). Cations become determinants when pass through the membrane, like making stable complexes by core acids electrostatic signatures are often anionic. Other evidences are that known RTIL anions are involved in known antibacterial activity; however, new compounds shown to have the activity of both cations and anions (Benedetto and Ballone 2016). Actually, their capability of antielectrostatic is moderated using antielectrostatic interaction by the phospholipid bilayer surface. Astonishingly, this property displays positive connection with activity of antibacterial, at least for cholinium-based RTILs. However, there is not a similar correlation for other RTILs families, like those stand on phosphonium. Because of the chemical physics prejudice, the discussion focused on the interaction of room-temperature ionic liquid with the biomembranes lipid fraction. However, protein segment interaction maybe even more important in pharmaceutical applications and may show the bacteria resistance to compounds of RTIL, same as what is known for common resistance of antibiotic (Benedetto and Ballone 2016). A series of IL monomers based on imidazolium, poly ionic liquids and poly ionic liquid membranes were synthesized such as agents of antibacterial (Zheng et al. 2017). Among the factors investigated were the effect of the imidazolium cations charge density on the antibacterial activities against *E. coli* and *S. aureus* and the effects of chemical structures containing length of carbon chain on the N3 substituents. The higher charge density and the longer chain of alkyl length result in a decrease in minimum inhibitory concentrations and higher properties of antibacterial of both poly ionic liquids and ionic liquid monomers in suspension of bacteria. Use of the properties of antibacterial of small molecules and homopolymers is required to evaluate polymeric membranes, as is the contrast between PILs, IL monomers, and related PIL membranes. Zheng et al. (2017) compared six panels (Fig. 11) for the comparison of antibacterial activity of PIL membranes against *E. coli* and *S. aureus*. Significant

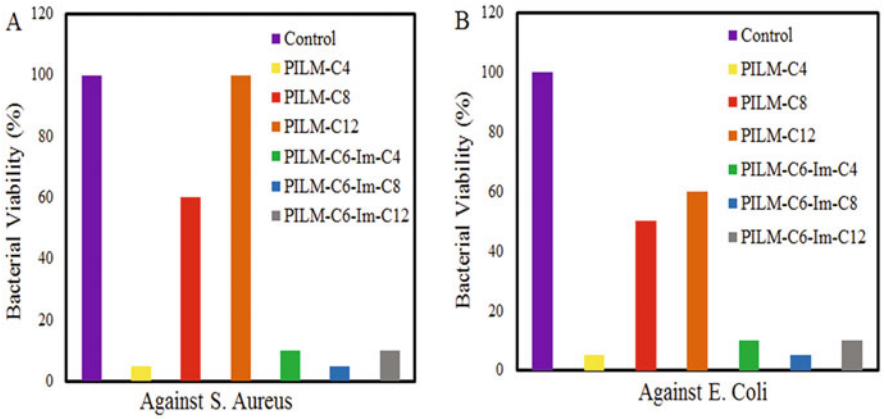


Fig. 11 Bacterial viabilities of (**a**) *S. aureus* and (**b**) *E. coli* after contacting with PIL membranes for 4 h, with PET membranes as controls (right two columns, an average of five samples). Modified after Zheng et al. (2017)

Table 10 IL antimicrobial activities monomers and poly ionic liquids measured as MIC

Samples	MIC (μmol mL^{-1})	
	S. aureus	*E. coli*
IL-C2	472.906	945.812
IL-C4	54.545	54.545
IL-C8	2.983	1.192
IL-C12	0.038	0.061
IL-C6-Im-C2	110.599	55.300
IL-C6-Im-C4	27.273	22.945
IL-C6-Im-C8	0.081	0.081
IL-C6-Im-C12	0.018	0.018
PIL-C2	110.345	110.345
PIL-C4	2.961	5.922
PIL-C8	1.491	1.192
PIL-C12	0.061	0.122
PIL-C6-Im-C2	33.180	33.180
PIL-C6-Im-C4	0.918	1.853
PIL-C6-Im-C8	0.081	0.041
PIL-C6-Im-C12	0.009	0.018

Modified after Zheng et al. (2017)

differences could be seen in the first 1 hour (see Table 10). The order of activity of antibacterial for synthesized poly ionic liquid membranes shows that poly ionic liquids membrane-C4 (1-butyl-3-vinylimidazolium bromide membrane) is more than poly ionic liquids membrane-C6-Im-C4 (1-butyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide membrane) and poly ionic liquids membrane-C6-Im-C8 (1-octyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide membrane) and eventually poly ionic liquids membrane-C12 (poly (1-dodecyl-3-vinylimidazolium bromide) membrane) is the least one against *S. aureus* and poly ionic liquids membrane-C4 is more than 1-octyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide membrane and 1-butyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide membrane and also poly (1-dodecyl-3-vinylimidazolium) bromide is the lowest one against *E. coli*.

3 Conclusions

Bacterial infection and viruses illnesses are main causes of deaths in last decades because of the antibiotics overuse and multi-drug-resistant pathogens increase. Effective antibacterial materials are crucial. Consequently, drug delivery field must be developed. Pharmaceutics preparations were reformed from powders to diffusion in polymers to nanoparticles and micelles. Ionic liquids are new type of green solvents with unique properties, which leads to encourage generating and developing of new drugs. Some of advantages of ILs employment are as follow:

- Using ILs is a cost-efficient way to create biological active compounds.
- ILs present formation of ion control in solution and biological fluids adjustment and water solvation properties to prepare an approach for solubility bioavailability alleviation and conventional drugs polymorphism limitations.
- ILs permit easy readily developed ionic cores incorporation in current molecules of drug, also novel drugs design and active molecules of biologically.
- ILs indicate adjustable organization of structural reflected at the micro- and nanoscale levels with approach to several kinds of biological activity.
- Application of ILs permits to optimize the price of pharmaceutical compounds analytics or production and development of biosynthetic processes.

As emphasized in the chapter, ionic liquids are predicted to discovery various applications in pharmaceutical field like biological activity, drug formulation, and drug synthesis.

It is still unclear what the reasons for antibacterial and inhibitory effects of ionic liquids are and it is not possible to accurately predict which ionic liquids affect which bacteria since there is no same laboratory result for all varieties of a single class of bacteria. Extensive researches have been done on the antibacterial effects of ionic liquids, including factors known so far: altering the alkyl chain length and adding methyl branches to their structure. In general, ILs with the alkyl chain length of twelve to fourteen carbon atoms indicated the highest activity of antimicrobial. Ionic liquids with FC groups showed more antibacterial activity than similar sample without FC group against different species of bacteria. But some groups such as hydroxyl groups, disrupt antimicrobial activity. Triazole bonds also greatly reduce the antimicrobial power of ionic liquids. Polymeric ionic liquids have higher antibacterial properties than ionic liquids. These polymers can be used to create antibacterial surfaces. Polymeric ionic liquids containing zinc are very effective in the removal of bacterial colonies. Most ionic liquids that have been tested except for a few cases such as PIL-Br have more effect on Gram-positive bacteria than Gram-negative bacteria. The Gram-negative bacteria outer membrane could be one of the reasons for this. ILs based on polyvinyl alcohol, which are often in the form of a hydrogel have antibacterial properties. Antibacterial hydrogel combined with antibiotics have versatility and responsiveness capability. Hydrogels made of natural polymers also have good tensile properties. The results of the hemolysis procedure for polymeric ionic liquids have shown that all membranes based on PIL synthesized with human cells are biocompatible. Quaternary ammonium cation perhaps could be known as the best choice for the synthesis of ionic liquids because researchers' results so far have been satisfying for all synthesized samples containing quaternary ammonium. Poly ionic liquids which are synthesized from Qa cations and Zn anion are biologically safe so that researchers consider them functional for medical purposes and so on they are expected to be used in order to create wound dressings or used in antibacterial surfaces. Researches have shown that anions, in addition to solubility, are partially effective in the toxicity of ionic liquids, especially in cases where toxicity is harmful even in small amounts. Therefore, since the anions are involved in the toxicity of ionic liquids, same as cations, they must be carefully

selected for specific purposes such as drug preparation. For example, most ionic liquids containing ampicillin are not toxic to human; ampicillin anion on the other hands is active against any bacteria because of an additional amino group. In general, polymer derivatives and imidazolium salts have a wide range of antimicrobial activities. As mentioned, the antibacterial ability of pure RTILs in aqueous solutions, it can be claimed that this ability is dependent on both ions. One of the factors affecting the antibacterial ability is the alkyl chain effect, increasing the alkyl chain length increases the antibacterial activity of the PIL suspension and decreases the activity of the PIL-based copolymer membrane. In addition, it was shown that small molecules antibacterial properties and homopolymers are applied to evaluate polymeric membranes. Another factor affecting the antibacterial activity of ionic liquid monomers and polymers is the concentration, subsequently the lower the minimal inhibitory concentration (MIC), the greater their antibacterial activity.

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