Ionic Liquids: Future Solvents and Reagents for Pharmaceuticals

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Keywords: Ionic Liquids, Sparingly Soluble Drugs, Active Pharmaceutical Ingredients (APIs), Transdermal Delivery, Antimicrobial Activity

The pharmaceutical industries are undoubtedly experiencing a series of challenges. One of these is the administration of solid form of many drugs due to many well known drawbacks including low solubility, polymorphic conversion and low bioavailability. Such problems are further aggravated when drug molecules or starting materials for synthesis of drugs are insoluble or sparingly soluble in aqueous media and most of pharmaceutical acceptable organic solvents. To overcome these problems, some times, highly polar organic solvents including pyridine, dimethylformamide (DMF) and N-methylpyrrolidone (NMP) which are not considered as environmental benign solvents have been used. These restrictions demand superior solvent systems and/or new drug forms that can be used as reaction media to avoid volatile organic solvents and/or as new forms of drugs. Much effort is being invested in such approaches to find new delivery technologies or development of new controlled-release dosage forms. In recent years, ionic liquids (ILs) that are salts of low melting point and consist only of ions have been increasingly exploited as solvents and/or (co)solvents and/or reagents in a wide range of pharmaceutical applications due to their tailor-made chemical, physical and biological properties. Studies have shown that ionic liquid-assisted drug carrier or active pharmaceutical ingredients (APIs) synthesized as IL form or many drug compounds produced using ILs as reaction media provide many unique and attractive properties compared to conventional counterparts. Furthermore, ILs could be employed as potential antimicrobial agents for various microorganisms. The aim of this article is to summarize the efforts placed on using ionic liquids in pharmaceutical applications.

Introduction

Room temperature ionic liquids (RTILs), an interesting class of tunable and designer solvents with the extremely low vapor pressure have been extensively used as a potential replacement for toxic, hazardous, flammable and highly volatile organic solvents (VOSs) (Welton, 1999; Rogers and Seddon, 2002). Ionic liquids (ILs) are composed entirely of ions (generally consisting of bulky asymmetric organic cations such as alkylimidazolium [R,R₂IM]⁺, alklypyridinium [RPy]⁺, tetraalkylammonium [NR₄]⁺ or tetraalkyl-phosphonium [PR₄]⁺ and anions (see Figure 1)), and are liquids at ambient or far below ambient temperatures. In fact, the asymmetry of the cation is believed to be responsible for the low melting temperatures. Based on the solubility of ILs in water, ILs can be divided into two categories: hydrophobic (water immiscible) and hydrophilic (water miscible). This water miscibility generally depends on the anions of ILs. ILs have many attractive physicochemical properties such as negligible vapor pressure, multiple solvation interactions with organic and inorganic compounds (Anderson et al., 2002), excellent chemical and thermal stability (Kosmulski et al., 2004), high ionic conductivity and a wide liquid temperature ranges which draw the growing interest in both industrial and academic research laboratories. Most importantly, the properties regarded as the viscosity, hydrophobicity, density and solubility of ILs can be tuned by selecting different combinations of cations and anions, to customize ILs for specific demands. During the last decade, the interest in the ILs has increased significantly because of their potential as solvents and/or (co)solvents and/or reagents in a wide range of applications, including chemical engineering (separation, extraction and membranes) (Visser et al., 2001; Anderson and Armstrong, 2005), chemistry
In order to meet these challenges, approaches ranging from biological modification of drug compounds to the tailoring the delivery techniques have been used with various degrees of success. One conventional way to address the poor solubility of drugs in order to increase their performance is to use excipients polar organic solvents, such as pyridine, N,N-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) (Yalkowaky, 1981). However, the use of such organic solvents has many drawbacks. They are often volatile, flammable and toxic. Pharmaceutical ingredients must be free from all such traces. Furthermore, when these solvents are used as reaction media for synthesis of drugs, they make difficulty in recovery and reuse steps. In addition, the production of large quantities of waste products and/or waste disposal has to be considered. Considering the properties of ILs, it is highly desirable for ILs to be potential solvents for overcoming the problems mentioned above.

In fact, due to their tailor-made properties, ILs can dissolve complex molecules including biologically active compounds such as protein, nucleosides and amino acids under milder conditions (Fujita et al., 2005, 2006; Kumar et al., 2007; Fukaya et al., 2008). We believe that ILs tunable properties may allow the possibility for tailoring pharmaceutical solvents or use them in the synthesis for new drug forms with specifically desired properties that are effectively limited when water or molecular organic solvents are used. Fortunately, the use of ILs in drug delivery technologies, ILs as APIs and ILs as media for drug synthesis has just started.

2. Toxicity and Biodegradability of ILs

Although ILs are considered as “green solvents”, their toxicological issue is still debatable. Regarding the use of ILs in pharmaceutics especially in medical application, most people think that the toxicological issue of ILs is the main challenge for its biological applications in drug delivery. In recent years, the cytotoxic, environmental, and microbial toxicity of the most common ILs have been studied extensively. The ability to finely adjust the biological properties of ILs by simply changing their anion/cation combination could be used to generate nontoxic ILs. Fortunately, in recent years, some reports have demonstrated that nontoxic ILs could be produced by selecting biocompatible organic cations and inorganic anions (Pernak et al., 2004a; Vidis et al., 2005; Wood and Stephens, 2010). The effect of [bmin][Cl] on marine algae, or enzymes like acetylcholinesterase indicate that the IL was not acutely toxic (EC50 = 13 μM) (Swatloski et al., 2004). More interestingly, some studies have shown low/negligible toxicity of some imidazolium based ILs towards Caco-2 cells (Jaitely et al., 2008) or female Wistar rats (LD50 = 1400 mg/Kg) (Pernak et al., 2001). However, there is a lack of in vivo investigation on IL biouptake. It should be noted here that many useful and necessary chemicals are toxic: many pharmaceutical excipients such as DMSO and nonionic surfactants (e.g., polysorbate 80) display similar toxicities to what was observed in many ILs.

However, special care should be paid in selection of IL because the toxicity of ILs depends significantly on

**Fig. 1** Commonly used ions of ionic liquids

<table>
<thead>
<tr>
<th>Cations</th>
<th>Anions</th>
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<tbody>
<tr>
<td>R1–N–R2</td>
<td>[Cl](^+)</td>
</tr>
<tr>
<td>R1–N–R2</td>
<td>[NO(_3)](^-)</td>
</tr>
<tr>
<td>R1–N–R2</td>
<td>[CH(_3)SOO](^-)</td>
</tr>
<tr>
<td>R1–N–R2</td>
<td>[BF(_4)](^-)</td>
</tr>
<tr>
<td>R1–N–R2</td>
<td>[CF(_3)CF(_2)COO](^-)</td>
</tr>
<tr>
<td>R1–N–R2</td>
<td>[PF(_6)](^-)</td>
</tr>
<tr>
<td>R1–N–R2</td>
<td>[(CF(_3)SOO)(_2)](^-)</td>
</tr>
<tr>
<td>Imidazolium</td>
<td></td>
</tr>
<tr>
<td>Pyridinium</td>
<td></td>
</tr>
<tr>
<td>Ammonium</td>
<td></td>
</tr>
<tr>
<td>Phosphonium</td>
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</table>
their cation and the alkyl side chain (Stolte et al., 2007). Generally, ILs synthesized with imidazolium cation are more toxic than phosphonium and ammonium based ILs (Jastorff et al., 2005). ILs with the benign cholinium cation were found to be highly biocompatible (Petkovic et al., 2010). For example, the cholinium alkanoates were less toxic than their corresponding sodium salts. On the other hand, the toxicity of ILs increases dramatically with the increase in the length of side chain. Additionally, it was found that the incorporation of ether groups into the ester side-chain significantly reduced the toxicity compared with alkyl ester derivatives (Morrisey et al., 2009). Hence, bulky cholinium, phosphonium or ammonium based ILs with the shorter side chains on the cation core would be safer/more useful ILs for pharmaceutical use.

To use ILs as solvents and/or reagents for drug formulations, ILs should preferentially exhibit good biodegradability with their low toxicity. Although toxicity evaluations of many ILs have been studied extensively, there are very few studies focused on biodegradation. Recently, much attention has been given to synthesis biodegradable ILs. Although ILs with a short alkyl chain appended in the cation have shown low toxicity, ILs containing short alkyl chains have proven resistant to biodegradation (Gathergood et al., 2004). Petkovic et al. (2010) have found that the biodegradation of ILs based on cholinium cation [NMe3(CH2CH2OH)]+ undergo complete biodegradation under aerobic conditions, with a range of linear alkanoate anions ([CnH2n+1CO2]-, n = 1–9) in P. corylophilum cultures. It was observed that ILs with longer linear chain anions such as butanoate, pentanoate, hexanoate and octanoate were fully biodegradable, whereas ILs with short linear chain anions (e.g., ethanoate and propanoate) were not fully degraded. Another way to synthesize biodegradable ILs is with pyridinium core (Ford et al., 2010). However, biodegradability is highly dependent on the side chains. Pyridinium ILs bearing ester groups in the 1- and 3-positions showed high levels of biodegradation under aerobic conditions and can be classified as ‘readily biodegradable’. In contrast, pyridinium ILs with linear alkyl chains showed significantly lower levels of biodegradability. Recently, a comprehensive tutorial review of biodegradable studies of ILs was published by Coleman and Gathergood (2010) in which they reported different routes for the preparation of ILs that are non-toxic as well as biodegradable.

3. Ionic Liquids in Pharmaceuticals

3.1 Solubility of drug compounds in ILs

A number of compounds having pharmacological activity have been found to be difficult to dissolve into aqueous solution and commonly used organic solvents. Although such compounds contain several polar groups in their molecular structure, they have been found to be difficult to dissolve into aqueous solution and commonly used organic solvents. Therefore, the solubility of some poorly water soluble drugs can be increased markedly in ILs individually or in their mixtures. They have shown that the solubility of some poorly water soluble drugs can be increased markedly in ILs individually or in their mixtures. However, the solubility depends on the types of ILs as well as the types of drug molecules (see Table 1).

Table 1 Solubility of acyclovir in some commonly used ILs at 25°C

<table>
<thead>
<tr>
<th>ILs/solvents</th>
<th>Solubility [wt%]</th>
</tr>
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<tbody>
<tr>
<td>[C4mim][CH3CH (OH)COO]</td>
<td>above 5%</td>
</tr>
<tr>
<td>[C2mim][(CF3SO2)2N]</td>
<td>insoluble</td>
</tr>
<tr>
<td>[C2mim][BF4]</td>
<td>insoluble</td>
</tr>
<tr>
<td>[C2mim][CH3COO]N]</td>
<td>insoluble</td>
</tr>
<tr>
<td>[C2mim][PF6]</td>
<td>insoluble</td>
</tr>
<tr>
<td>[C1mim][(CH3O)2PO2]</td>
<td>above 25%</td>
</tr>
<tr>
<td>[C3mim][(CH3O)2PO2]</td>
<td>above 15%</td>
</tr>
</tbody>
</table>

*The solubility of ACV in water and IPM are shown; †Data taken from Moniruzzaman et al. (2010c)"
The authors reported that such solubility was achieved due to the appreciable drug-solvent interactions through hydrogen bonds, van der Waal’s forces as well as π–π interactions between aromatic rings as reported previously (Holbrey et al., 2003). The authors have also plotted the ternary phase diagram of water-miscible IL/water immiscible IL/water which indicated that the water miscibility of poorly water-miscible ILs could be improved by the inclusion of water-miscible ILs (Mizuuchi et al., 2008). This ability to modulate ILs aqueous miscibility expands their usefulness as pharmaceutical solvents. The drug release profiles show that sucrose and dexametasone from water-immiscible RTILs reservoirs into water can be prolonged over 48 h. Interestingly, saturated solutions of [bmim][PF6] and [hmim][PF6] showed little toxicity towards Caco-2 cells (Jaitely et al., 2008).

### 3.2 Synthesis of drug compounds in ionic liquids media

Presently, pharmaceutical industries look forward to developing new technologies/methodologies in which the production of large quantities of waste products can be reduced. In most of the drug synthesis processes, organic solvents, particularly polar organic solvents, are employed. In such cases, the production of by-product with the desired products is very high (the weight ratio of by-product to desired products as 25–100 times is common in pharmaceutical industry). The organic solvents also produce many other problems as already mentioned previously. Hence, to find alternative approaches for the synthesis of drug compounds is essential.

In 2000, Earle et al., reported for the first time that ILs could be used as good reaction media for the synthesis of pharmaceutical compounds. They synthesized pharmaceutical pravadoline (see Figure 2) in IL [bmim][PF6] and [bdmim] [PF6] with 90–94% overall isolated yield in which the production of waste products was reduced significantly. The product was extracted from IL with toluene, which was distilled from the product and recycled. The IL also was recovered easily by simply washing with water and reused in the reactions after drying under vacuum. Following this study, the environmentally benign ILs started to be used in the synthesis of many useful drug compounds.

Nucleoside derivatives are effective antiviral drugs for the treatment of many viral infections, such as herpes simplex virus (HSV), human immunodeficiency (HIV), hepatitis B virus (HBC) and so on (Nasr et al., 1990; Mathe and Gosselin, 2006). They also have been used extensively as probes for diagnostic purposes and in antisense therapeutics. However, most of the nucleosides are insoluble in many organic solvents. This introduces a big problem in developing new methodologies to synthesis these nucleoside derivatives. Generally, aprotic solvents including pyridine, DMF and NMP, which are not considered as environmental benign solvents, are used in nucleoside chemistry and reportedly many problems are caused during synthesis processes. In recent years, ILs have been found to be excellent solvents for dissolution of nucleosides (Uzagare et al., 2003; Kumar et al., 2007;
Moniruzzaman et al., 2010c). This finding opens the door to using ILs as reaction media for synthesis of nucleoside analogs with many advantages over conventional solvents (Uzagare et al., 2003; Kumar and Malhotra, 2008, 2009; Zhang et al., 2009; Zang et al., 2011).

Uzagare et al. (2003) have reported on the acylation of 3’ and 5’-functional groups of sugars and NH2 of base of 2’-deoxynucleosides in IL [MOemim][OMs] with different acylating agents including acetic anhydride, benzoyl chloride and isobutyryl chloride (see Figure 3). They used 1-methylimidazole (NMI) as a base and 4-(dimethylamino) pyridine as a catalyst. The system obtained a good yield (over 90%) within a reaction time less than 2 h. Notably, the products were easily isolated from IL simply by extracting with ethyl acetate. More interestingly, IL was recovered from the reaction mixture and reused without loss of product yield. In a following study, Prasad et al. (2005) carried out the similar reactions using benzoyl cyanide as a benzoylation agent and DMAP as a catalyst in IL [MOemim][OMs] at 25–30°C. The results indicated the selective benzoylation of sugar hydroxyl groups over amine group of nucleobase and produced O-benzoylated nucleoside derivatives with high yield. Later, Kumar et al. (2007) have expanded reaction media to another IL [MOemim][TFA] for benzoylation of 2’-deoxy-nucleosides using benzoic anhydride as acylating agents at 50°C and reported good yield of the products.

Recently, Kumar and Malhotra (2008) reported on the synthesis of nucleoside-based antiviral drugs including stavudine (d4T), brivudine (BVDU) and trifluridine (TFT) using three types of ILs (e.g., [MOemim][OMs], [MOemim][TFA] and [bmim][TFA]) and compared the results with what was found using conventional organic solvents such as DMA. The ILs were found to be better solvents for all the nucleosides in terms of the solubility and the reaction rates as compared to conventional molecular solvents (for example see Figure 4). Generally, tedious reaction conditions as well as longer reaction times are required for the synthesis of these drugs when organic solvents are used as reaction media (Lipahutz et al., 1995). In addition, the lower reaction volume of IL-based reactions makes the workup procedure very simple (generally, 10–15 mL of molecular solvent are required for 1 mmol scale reaction whereas only 1.5 mL of ILs are needed for the same scale reactions). In fact, the high solubility of nucleoside substrates in ILs reduces the solvent requirement. The same group also reported on the synthesis 5-halo derivatives (e.g., 5-halouridines and 5-halo-2’-deoxouridinines) of both protected and unprotected uridine (U) and 2’-deoxyuridine (2’-dU) in several types of ILs using lithium halide as halogenating agents, ceric ammonium nitrate (CAN) as oxidizing agents (Kumar and Malhotra, 2009). IL [MOemim][OMs] was found to be the best solvent with the following optimized reaction conditions: 1.2 mol equivalent lithium iodide, 2.0 mol equivalent CAN and 80°C. ILs were recovered and reused for up to 4 cycles without any loss in yields.

Thiazolidinone and their derivatives have a wide range of biological activities such as antifungal, antihistaminic, antimicrobial activity and use in the treatment of inflammation. They are most conveniently made by the three-component condensation of a primary amine, an aldehyde and a mercapto acid (see Figure 5). Although...
various ways to synthesize thiazolidinones have been reported, there exist many limitations, such as using poisonous solvents, expensive catalysts, long reaction time and low or moderate yield. To address such drawbacks, Zhang et al. (2009) have developed a novel and an efficient procedure for the synthesis of a series of novel pyrimidine nucleoside-thiazolidin-4-one hybrids using ILs as a recyclable promoter and reaction media without use of any catalyst. The antiparasitic activities of some thiazolidins were also studied. They have studied the effect of the type of ILs on the condensation process for the synthesis of 2,3-distributed-1,3-thiazolinin-4-one derivatives and compared them with the results of conventional organic solvents (see Figure 5). Hydrophobic IL [bmim][PF6] gave better results over hydrophilic IL [bmim][BF4]. However, both ILs were found to be better solvents as compared to organic solvents except toluene. Another beneficial point is that IL could be recycled at least five times without an obvious loss in its efficiency.

3.3 Ionic liquid assisted nano-carrier for delivery of sparingly soluble drugs

In Section 3.1, we discussed that many sparingly soluble drugs can be solubilized in ILs. For an example, hydrophilic ILs having coordinating anions (e.g., [dmim][(MeO)2PO2], [emim][(MeO)2PO2] and [emim][oAc]) are very effective in dissolution of acyclovir (Moniruzzaman et al., 2010c), which is an effective antiviral for the treatment of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), varicella-zoster virus (VZV) and Epstein-Barr virus (EBV) (Schaeffer et al., 1978), is poorly soluble in water and most common organic solvents. We checked for any diffusion of ACV dissolved in ILs through the skin and found there was essentially zero possibly due to the hydrophobic barrier function of the skin, provided by the highly organized structure of the stratum corneum (Cevec, 2004). In addition, incorporation of a drug into a particulate carrier can protect it against degradation in vitro and in vivo, and the release can be controlled with specific targeting.

To meet these challenges, we have developed IL-in-oil (IL/o) MEs—self-assembling colloidal particles in which a small amount of IL is dispersed in a large amount of oil in the presence of a surfactant (see Figure 6) that load drug molecules in the IL core and the continuous oil phase can be used to obtain the desired features for topical or/and transdermal transport behavior (Moniruzzaman et al., 2010c, 2010d, 2010e). It is well known that MEs, which are homogeneous, transparent and thermo-dynamically stable dispersions of water and oil, stabilized by a surfactant or a blend of surfactants have emerged as prospective systems for drug delivery mainly due to their size, biocompatibility and straightforward preparation (Kogan and Garti, 2006; Gupta and Moulik, 2008). MEs with their supramolecular structure can increase not only the skin permeability, but also drug solubilization in the formulation and drug partitioning into the skin. Oil-soluble drugs can be formulated in o/w MEs whereas, water-soluble ones are better suited to w/o systems. Consequently, stable IL/o MEs could lead to effective drug carriers for IL soluble drugs.

The formulation of IL/o MEs was composed of a blend of nontoxic surfactants, polyoxy-ethylene sorbitan monoooleate (Tween-80) and sorbitan laurate (Span-20), isopropyl myristate (IPM) as an oil phase. It was found that hydrophilic ILs having coordinating anions can be solubilized in the core of Tween-80/Span-20/IPM micelles, whereas hydrophobic ILs containing nonco-ordinating anions (e.g., PF6−, (CF3SO2)2N−) are found to be very poorly soluble (Moniruzzaman et al., 2010d). Among hydrophilic ILs used, [dim][[(MeO)2PO2] was found to be very effective as a disperse phase in the bulk IPM stabilized by a mixture of Tween-80 and Span-20. This system yields spherical micelles 8 to 34 nm in diameter, which are similar to those found in typical reverse micelles with water core stabilized by common surfactants (Pileni, 1989). The solubility studies of three sparingly soluble drugs molecules (i.e., acyclovir, methotrexate and dantrolene sodium) (Figure 7) indicated a high degree of drug solubilization in IL/o MEs, whereas various IL free systems can solubilize very small amounts of drugs (Moniruzzaman et al., 2010d). It was speculated that the successful dissolution of such sparingly soluble drug molecules in the IL/o MEs may
be attributed to the formation of hydrogen bonds between the IL anions and the polar groups of drug molecules. The IL/o MEs with drug molecules showed very good physical stability with storage time at various temperatures (Moniruzzaman et al., 2010e). Drug release from the new system was evaluated in vitro using full thickness skin pieces of Yucatan hairless micropigs (YMPs). The skin permeability of ACV into the skin was increased by several orders of magnitude, when IL/o MEs were used. More significantly, application of IL/o system induced significant transdermal permeation of ACV, whereas other formulations showed essentially none (below our detection level) (see Table 3). The enhancement of ACV penetrations by using this new IL/o ME is thought to be due to the combination of factors including the high ACV solubility in IL disperse phase and the effect of lipophilic components.

To evaluate the relative safety of the IL/o MEs, the MTT cell viability assay was performed on the reconstructed human epidermal model Lab-Cyte™ EPIMODEL 12. The results demonstrated that a significant decrease in cell viability was observed when pure IL was used. However, ME containing 4 wt% IL showed over 80% in cell viability compared to control experiments (Moniruzzaman et al., 2010e). The same trend is consistent for many useful and necessary chemicals being used in the pharmaceutical industry. Although these cyto-toxicity results indicated that this newly developed IL/o MEs may be a safe TDD particularly for poorly soluble drugs, a more nontoxic IL is required to explore these systems.

### 3.4 Ionic liquids as active pharmaceutical ingredients (APIs)

Solid and crystalline forms of active pharmaceutical ingredients (APIs) have been traditionally used in drug formulations because of their improved properties with respect to solubility, purity, thermal stability and bioavailability. Such forms of drugs are also desirable for ease of handling and lower production and storage costs (Dutta and Grant, 2004). However, the solid form of many drugs has drawbacks that are mainly related to polymorphic conversion, low solubility, and low bioavailability for crystalline solids, and the tendency of amorphous forms to spontaneously crystallize (Hancock and Dalton, 1999). Considering these factors, researchers have paid attention to finding new physical drug forms, including salts, polymorphs, solvates, and co-crystals (Peterson et al., 2006).

In 2007, Rogers and co-workers have discovered that ILs could be used as active pharmaceutical ingredients (APIs) with new and unique properties compared to the solid pharmaceutical forms (Hough et al., 2007). They reported that hydrophobic RTIL [Lidocainium] [Docusate] (LD) prepared from lidocaine hydrochloride and sodium docusate showed modified solubility, increased thermal stability, and a significant enhancement in the efficacy of topical analgesia in two different models of mouse antinociception when compared to lidocaine hydrochloride. Following this interesting finding, researches on IL-based APIs have just begun (Hough and Rogers, 2007; Pamela et al., 2009; Bica et al., 2010; Stoimenovski et al., 2010). Figure 8 shows some of the reported IL-APIs with their physical properties.

IL-APIs can provide many advantages over solid or crystalline forms of drugs. IL-APIs can address the issue of polymorphism, a major problem in modern medicine.

### Table 3

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Topical Delivery [μg/cm²]</th>
<th>TDD [μg/cm²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>IPM b</td>
<td>0.18 ± 0.34</td>
<td>ND</td>
</tr>
<tr>
<td>Surfactants + IPM c</td>
<td>3.86 ± 1.65</td>
<td>ND</td>
</tr>
<tr>
<td>w/o ME d</td>
<td>4.57 ± 3.17</td>
<td>ND</td>
</tr>
<tr>
<td>IL/o ME e</td>
<td>10.78 ± 3.12</td>
<td>1.95 ± 1.30</td>
</tr>
<tr>
<td>ACV cream f</td>
<td>1.21 ± 0.10</td>
<td>ND</td>
</tr>
</tbody>
</table>

*a all formulations contained 5 mg/mL ACV and penetration time 24 h; b almost all ACV remained as suspended powders in formulations; c the weight fraction of surfactants was 20 wt% (Tween-80: Span-20 = 3:2 [w/w]; d w/o emulsion contained 4 wt% water; e the system containing 4 wt% IL; f ACV herpecia topical cream (equivalent to 5 mg ACV) used for penetration study. All data taken from Moniruzzaman et al. (2010e)
For example, propantheline bromide is an antimuscarinic drug that can be present in different polymorphs (Borka and Halebian, 1990). However, it can easily combine with acesulfamate potassium (a calorie-free artificial sweetener) to form IL propantheline acesulfamate that will not suffer from polymorphism (Stoimenovski et al., 2010). Similarly, IL-API ranitidine dosucate can avoid the polymorphism problem (Hough et al., 2007), although its starting material ranitidine hydrochloride has different polymorphs. Another advantage of IL-APIs is their controlled solubility. Since IL-APIs are composed of two biologically active ions (a cation and an anion),
their solubility can be controlled by choosing the appropriate ions. Generally, strongly hydrophilic ionic actives do not pass into the biological membranes due to their highly hydrophobic nature (Heinrich and Wermuth, 2008). In the case of IL-APIs, the combination of such an active ion with another more hydrophobic active ion produces a hydrophobic IL-salt exhibiting reduced water solubility. For example, the solubility of IL [LD] in water was 1.24 mM, whereas the solubility of Lidocaine hydrochloride and Sodium docusate was 2488 mM and 33.70 mM, respectively (Stoimenovski et al., 2010). More importantly, a number of delivery modes including topical and transdermal could be employed to deliver such hydrophobic liquid salts to the site of action more efficiently that dissolved crystalline APIs in a more concentrated and effective manner.

Very recently, Rogers and coworkers (Bica et al., 2010) have reported on an ionic liquid form of aspirin that could overcome the problems (e.g., poor solubility, bitter taste and large tablets required for the dosage) when solid aspirin is administered orally. Liquid aspirin was prepared by using simple ion exchange reactions between salts of the active component of aspirin (acetyl salicylate), or the chemically similar salicylic acid, and pharmaceutically active ammonium salts. The counter ions could be used to add a second function to the ionic liquid drug such as anti-bacterial or anti-microbial behavior. However, such ILs with aspirin show limited stability and slowly decompose into the corresponding salicylate ILs when exposed to moisture.

### 3.5 Ionic liquids as antimicrobial agents

In recent years, ILs have been increasingly exploited as potential antimicrobial agents possibly due to their toxicity, an important tunable characteristic. In fact, this property allows for appropriate design of ILs that could be used as new and improved antiseptics, disinfectants and anti-fouling reagents. To date, a number of publications have highlighted the antimicrobial activity of imidazolium, pyridinium and quaternary ammonium ILs against both environmental and clinically important micro-organism (Pernak et al., 2003, 2004b, 2004c; Pernak and Feder-Kubis, 2005; Docherty and Kulpa, 2005; Carson et al., 2009; Hough-Troutman et al., 2009; Busetti et al., 2010). For example, Pernak and co-workers evaluated the antimicrobial activity of a series of 3-alkoxyethyl-1-methylimidazolium ILs with different anions, (Pernak et al., 2003) 1,3-(dialkyloxymethyl)-substituted imidazolium ILs with different anions (Pernak et al., 2004b) and 1-alkylimidazolium and 1-alkoxymethyl-imidazolium prolic ILs with lactate anion (Pernak et al., 2004c) against clinically significant pathogens (rods, cocci and fungi). It was found that the antimicrobial activities of ILs are strongly dependent on the length of the substituent alkyl chain. Ionic liquids containing longer (≥10) carbon substituents showed very high antimicrobial activities. A similar trend was observed when antifungal and antibacterial activities of imidazolium based ILs with various anions was examined against bacteria and fungi (Luczak et al., 2010). However, changing the type of anion produced smaller effect on antimicrobial activities.

In another recent study, Carson et al. (2009) have reported on the antibiotic and antimicrobial activity of a series of 1-alkyl-3-methylimidazolium chloride ILs against a panel of pathogen microorganism, including MRSA (Methicillin-resistant Staphylococcus aureus) and other pathogens associated with hospital acquired infections. Clinically, microbial biofilms are extremely problematic and in general, such biofilms protect infectious microorganisms from antiseptics, disinfectants, and antibiotics. However, ILs can break down microbial biofilms easily to destroy microorganisms such as MRSA. It was found that antibiotic potency increased with the length of the alkyl chain. In a subsequent study, Busetti et al. (2010) have reported the antimicrobial and antibiotic activities of 1-alkylquinolinium bromide ILs [C,quin][Br] against a range of clinically relevant microorganisms, both planktonic and sessile (biofilm) cultures. It is well known that quinoline derivatives have been used extensively as antibacterial, antifungal and antimalarial agents (Larsen et al., 1996; Azad et al., 2007). All ILs exhibited excellent, broad spectrum antimicrobial activity expressed minimum inhibitory concentrations (MIC) and minimum bactericidal/fungicidal concentration (MBC). However, optimized antimicrobial activity was highly dependent on the length of alkyl substituents appended in the cation of ILs as shown in Table 4 for both Gram positive cocci and Gram negative rods and fungi (Carson et al., 2009; Busetti et al., 2010). These studies certainly indicate that using the tunability of ILs, antimicrobial agents for particular application or for specified microorganisms could be prepared.

### Conclusions

The results discussed in this review article clearly demonstrate that ionic liquids could be very effective solvents and/or agents in pharmaceuticals. The use of ILs as solvents for the synthesis of drugs, in particular, nucleoside-based antiviral drugs providing many advantages, such as milder reaction conditions, low solvent consumption, easy workup and less waste production. The high solubility of many sparingly soluble drugs in some ionic liquids could open up new functionalization methodology for effective delivery them that are not possible in conventional solvents. One of the most appealing features of ILs for pharmaceutical applications is their use as active pharmaceutical ingredients with some attractive properties. However, additional studies are required to obtain biologically and physically robust data to predict the proper design for pharmaceutically IL-APIs. The main drawback of using ILs is the significant uncertainty regarding the toxicity, biodegradability and potential impact of ILs on the environment.
However, in both of these areas significant steps have been made in the understanding and creation of cleaner routes to the preparation of ILs. We believe that green and biocompatible ILs will be available in the near future, which will stimulate the use of ILs in pharmaceutical applications.

### Table 4 MIC and MBC values of [C$_n$mim][Cl] (Carson et al., 2009) and [C$_a$quin][Br] (Bustti et al., 2010)

<table>
<thead>
<tr>
<th>Organism</th>
<th>$[C_n$mim][Cl]</th>
<th>$[C_a$quin][Br]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>$n$</td>
</tr>
<tr>
<td></td>
<td>6 8 10 12 14</td>
<td>8 10 12 14 16 18</td>
</tr>
<tr>
<td>$S$. aureus</td>
<td></td>
<td></td>
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<tr>
<td>MIC</td>
<td>&gt;1644 722 40 18 16</td>
<td>242 111.5 25.8 5.8 70.2 209.8</td>
</tr>
<tr>
<td>ATCC29213</td>
<td>&gt;1644 &gt;1444 643 36 66</td>
<td>884 111.5 51.6 5.8 70.2 419.5</td>
</tr>
<tr>
<td>MRSA</td>
<td>&gt;1644 1444 160 36 16</td>
<td>121.2 55.7 12.9 5.8 35.1 104.9</td>
</tr>
<tr>
<td>$S$. epidermidis</td>
<td>&gt;1644 1444 643 290 66</td>
<td>242 111.5 25.8 5.8 35.1 209.8</td>
</tr>
<tr>
<td>ATCC 12228</td>
<td>&gt;1644 1444 644 145 33</td>
<td>242 111.5 25.8 5.8 35.1 104.9</td>
</tr>
<tr>
<td>$S$. epidermidis</td>
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<td>242 55.7 25.8 5.8 35.1 209.8</td>
</tr>
<tr>
<td>ATCC 35984</td>
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<td>484 111.5 25.8 5.8 70.2 209.8</td>
</tr>
<tr>
<td>E. Coli</td>
<td>&gt;1644 1444 160 73 33</td>
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<tr>
<td>K. aerogenes</td>
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<tr>
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<tr>
<td>P. mirabilis</td>
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<td>60 55.7 12.9 5.8 35.1 104.9</td>
</tr>
<tr>
<td>NCTC 12442</td>
<td>&gt;1644 &gt;1444 1287 1161 530</td>
<td>242 111.5 25.8 5.8 70.2 209.8</td>
</tr>
</tbody>
</table>

Abbreviation

- A = adenosine
- ACV = acyclovir
- APIs = active pharmaceutical ingredients
- BVDU = brivudine
- C = cytidine
- CAN = ceric ammonium nitrate
- DMAP = 4-(dimethylamino)pyridine
- DMF = N,N-di-methylformamide
- DMSO = dimethyl sulfoxide
- d4T = stavudine
- G = guanosine
- ILs = ionic liquids
- IPM = isopropyl myristate
- MEs = microemulsions
- MBC = minimum bactericidal concentration
- MIC = minimum inhibitory concentrations
- MRSA = methicillin-resistant Staphylococcus aureus
- NaH = sodium hydride
- RT = room temperature
- RTILs = room temperature ionic liquids
- Span-20 = sorbitan laurate
- T = thymine
- TDD = transdermal drug delivery
- THF = tetrahydrofuran
- TTF = trifluoridine
- $T_g$ = glass transition
- $T_m$ = melting temperature
- Tween-80 = sorbitan monooleate
- U = uridine
- 2’-dU = 2’-deoxyuridine

IL/o = ionic liquid-in-oil
w/o = water-in-oil
o/w = oil-in-water

### Ionic liquids cations and anions

- [bmim] = 1-butyl-3-methyl imidazolium
- [bmim] = 1-buty1-3-methyl imidazolium
- [C$_a$quin] = 1-alkylquinolinium
- [C$_n$mim] = 1-alkyl-3-methyl imidazolium
- [dnim] = 1,3-dimethyl imidazolium
- [enim] = 1-ethyl-3-methyl imidazolium
- [hmim] = 1-hexyl-3-methyl imidazolium
- [onim] = 1-octyl-3-methyl imidazolium
- [LD] = [Lidocainium][Docusate]
- [MeOemim] = 1-methoxyethyl-3-methyl imidazolium
- [TFA] = trifluoroacetic acid
- [OMs] = methanesulonate
- [(MeO)$_2$PO$_2$] = dimethylphosphate
- [oAc] = acetate
- [TF$_2$N] = bis(trifluoromethanesulfonyl)imide

### Literature Cited

Bica, K., C. Rijksen, M. Nieuwenhuyzen and R. D. Rogers; “In Search
Pileni, M.; Structure and Reactivity in Reverse Micelles, Elsevier, Amsterdam, the Netherlands (1989)