Journal of Comprehensive Pharmacy

Review ArticleAvailable Online at: www.jcponline.in

ISSN NO: 2349-5669

Ionic Liquids: Evident Application in Medicinal Chemistry

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ARTICLE INFO

Article history:

Received 10 March 2014

Accepted 20 March 2014

Available online 19 April 2014

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Abstract

In the present century an ever growing number of papers have been published describing the use of ionic liquids on organic synthesis. In general these works have shown evident advantages of this couple respect to conventional synthetic procedures for generation fast, efficient and environmental friendly synthetic methodologies. The industrial synthesis of pharmaceutical compounds often involves the use of organic solvents. Unfortunately, these reaction media are responsible for organic contaminations in the final product. In recent years, ionic liquids (ILs) have become the "green alternatives" of volatile organic solvents. Thus, the applications of ILs instead of conventional reagents offer a new opportunity to solve problems of environmentally harmful solvents. This mini-review discusses a new application of ILs in laboratory-scale Pharmaceutical synthesis.

Keywords: Active Pharmaceutical Ingredient, Green Chemistry, Ionic Liquid.

INTRODUCTION

An ionic liquid (IL) is a salt in the liquid state. In some contexts, the term has been restricted to salts whose melting point is below some arbitrary temperature, such as 100 °C (212 °F). While ordinary liquids such as water and gasoline are predominantly made of electrically neutral molecules. Ionic liquids are largely made of ions and short-lived ion pairs. These substances are variously called liquid electrolytes, ionic melts, ionic fluids, fused salts, liquid salts, or ionic glasses. The ionic bond is usually stronger than the Vander Waals forces between the molecules of ordinary liquids. For that reason, common salts tend to melt at higher temperatures than other solid molecules. Some salts are liquid at or below room temperature. Examples include compounds based on the 1-Ethyl-3-methylimidazolium (EMIM) cation and include: EMIM: Cl, EMIM dicyanamide, (C₂H₅)(CH₃)C₃H₃N₂N(CN)₂⁻ that melts at -21 °C (-6 °F); and 1-butyl-3, 5-dimethylpyridinium bromide which becomes a glass below -24 °C (-11 °F) [1]. Low-temperature ionic liquids can be compared to ionic solutions, liquids that contain both ions and neutral molecules, and in particular

to the so-called deep eutectic solvents, mixtures of ionic and non-ionic solid substances which have much lower melting points than the pure compounds. Certain mixtures of nitrate salts can have melting points below 100 °C [2]. The term "ionic liquid" in the general sense was used as early as 1943 [3].

The chemical structure of 1-butyl-3-methylimidazolium hexafluoro phosphate ([BMIM] PF₆), a commonly encountered ionic liquid.

COMPOSITION IN IONIC LIQUIDS

There are a number of different cation and anion combinations that may result in salts having low melting points; examples of some of the different cation structures and anion pairs that may result in an ionic liquid are [4]:

Most commonly used anions:

Most common alkyl chains: Ethyl, Butyl, Hexyl, Octyl, Decyl

Most commonly used cations:

To make an ionic liquid, researchers can select from dozens of small anions, such as hexafluorophosphate ($[\text{PF}_6^-]$) and tetrafluoroborate ($[\text{BF}_4^-]$), and hundreds of thousands of large cations, such as 1-hexyl-3-methylimidazolium or 1-butyl-3-methylimidazolium. Ionic liquids are thus "designer solvents". Chemists are free to pick and choose among the ions to make a liquid that suits a particular need, such as dissolving certain chemicals in a reaction or extracting specific molecules from a solution [5]. To date, commercial offerings of salts explicitly described as ionic liquids are largely imidazolium based [6,7].

Ionic liquids in pharmaceutical industry:

Industrial synthesis of pharmaceutical compounds often involves the use of organic solvents mainly for reasons of cost effective procedure and ease of handling. Unfortunately, these reaction media are responsible for organic contamination of the final product and are therefore referred to as 'residual solvents' or 'organic volatile impurities'. The acceptable limits for

contaminants resulting from the entire drug product manufacturing process have been specified in pharmacopoeias and the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use [8]. The ICH guideline distinguishes four classes of residual solvents in drug substances: solvents to be avoided, solvents to be limited, solvents with low toxic potential and solvents without adequate toxicological data. From the toxicological point of view, genotoxic impurities (GTIs) are the most dangerous contaminants for human health. Exposure to even low levels of such impurities present in the final active pharmaceutical ingredient (API) may induce genetic mutations and may potentially cause cancer in humans [9,10]. However, regardless of the solvent class, it is important to explore the possible opportunities to reduce or avoid the use of harmful solvents in the manufacturing process of pharmaceuticals. The use of ionic liquids (ILs) as non-conventional media in chemical synthesis is increasing attention because of their physical and chemical properties. Their growing application in organic chemistry stems from their favourable physicochemical properties, such as the lack of vapour pressure, good thermal and chemical stability and very good dissolution properties of both organic and inorganic compounds. ILs are generally organic salts composed of various organic or inorganic cations and anions with a melting point at or near room temperature. They are therefore liquid at room temperature and are known by many synonyms, such as room temperature ionic liquids (RTILs), liquid organic salts, low temperature molten salts or ambient-temperature molten salts [11]. They are also referred to as neoteric solvents, meaning new types of solvent or materials that are finding new application as solvents. ILs, being 'designer solvents', are convenient to use because of their combined cationic and anionic properties, which can be independently modified [12]. The ability to modify their properties, e.g. viscosity, density, solvent miscibility and melting point, results in their flexibility in the design of new functional materials [13,14 & 15]. ILs are also called 'environmentally friendly' and have been suggested as ideal replacements for volatile organic solvents. The application of 'green' solvents, such as ionic liquids, in the pharmaceutical industry is currently being extensively investigated at the laboratory scale [16].

Preparation of ionic liquids

There are three basic methods for the preparation of ionic liquids:

1. Metathesis of a halide salt with, for instance, a silver, group 1 metal or ammonium salt of the desired anion; **H-OH**
2. acid-base neutralization reactions;

- The final method for the synthesis of ionic liquids is direct combination of a halide salt with a metal halide.

1. Metathesis reactions

Many alkyl ammonium halides are commercially available or they can be prepared simply by the reaction of the appropriate halogen or alkane and amine. Preparation of the pyridinium and imidazolium halides can be achieved similarly [17]. For volatile halogen of alkanes, the low boiling points lead to preparations requiring either a sealed tube, such as in the synthesis of [emim] Cl (where [emim]⁺ is the 1-ethyl-3-methylimidazolium cation), or an elaborate reaction still Fig.1. Hence, the use of salts with longer chain substituents, such as [bmim] Cl (where [bmim]⁺ is the 1-butyl-3-methylimidazolium cation), that can be prepared in conventional glassware by heating under reflux has become popular. In 1992 the first of the new ionic liquids, [emim] [BF₄], was prepared via metathesis of [emim] I with Ag [BF₄] in methanol. This salt also has a melting point of 12 °C and may be prepared considerably more cheaply using [NH₄] [BF₄] in acetone Fig.2.

Fig1: sealed tube

Fig 2: conventional glassware

Fig 3: Conical Flask

This ease of preparation, together with its relative moisture stability and its immiscibility with a number of organic solvents is leading to its increasing use in biphasic catalysis Fig.3. The preparation of [emim] [PF₆] shortly followed; this time it was prepared by reaction of [emim] Cl with HPF₆. This salt has a melting point of 60 °C, which makes it slightly less attractive than the [BF₄]⁻ salt, if room temperature working is desired. Since then, thiocyanate, nonafluoro butane sulfonate, bis ((tri fluoro

methyl) sulfonyl) imide, tris ((tri fluoro methyl) sulfonyl) methide, tri fluoro acetate, and hepta fluoro butanoate salts have all been prepared by metathesis reactions. These metathesis reactions are good candidates for those preparing new ionic liquids for the first time. However, they can leave the ionic liquids contaminated with a small amount of halide ions that may react with solute materials.

2. Acid-base neutralization reactions

Mono alkyl ammonium nitrate salts are best prepared by the neutralization of aqueous solutions of the amine with nitric acid. The ionic liquids are isolated by removing excess water in vacuo. In a similar reaction, tetra alkyl ammonium sulfonates have been prepared by mixing equimolar amounts of the sulfonic acid and the tetra alkyl ammonium hydroxide. Again, excess water was removed in vacuo. To ensure the purity of the ionic liquids, they were dissolved in either acetonitrile or tetra hydro furan and treated with activated charcoal for at least 24 h, and finally the organic solvent was removed in vacuo.

3. Final Method

The final method for the synthesis of ionic liquids is direct combination of a halide salt with a metal halide. This is how the halogenoaluminate (III) and the chlorocuprate (I) ionic liquids are prepared. The chlorocuprate (I) ionic liquids are particularly sensitive to oxygen and have not found widespread use in synthesis

Properties

Such properties include:

- high thermal stability,
- high electrical conductivity,
- large electrochemical window,
- highly viscous and frequently exhibit low vapor pressure
- low combustibility
- Many classes of chemical reactions, such as Diels-Alder reactions and Friedel-Crafts reactions, can be performed using ionic liquids as solvents
- ionic liquids can serve as solvents for biocatalysis [18].
- ionic liquids can be distilled under vacuum conditions at temperatures near 300 °C [19].
- low nucleophilicity and capability of providing weakly coordinating or non-coordinating environment,
- Very good solvents properties for a wide variety of organic, inorganic and organometallic compounds: in some cases, the solubility of certain solutes in RTILs can be several orders of magnitude higher than that in traditional solvents.

Moreover, by fine-tuning the structure, these properties can be tailor-designed to satisfy the specific application requirements.

Table 1: Comparison of organic solvents with ionic liquids

Property	Organic solvents	Ionic liquids
Number of solvents	>1000	>1,000,000
Applicability	Single function	Multifunction
Catalytic ability	Rare	Common and tunable
Chirality	Rare	Common and tunable
Vapor pressure	Obeys the clausius-clapeyron equation	Negligible vapor pressure under normal conditions
Flammability	Usually flammable	Usually nonflammable
Polarity	Conventional polarity concepts apply	Polarity concept questionable
Tune ability	Limited range of solvents available	Virtually unlimited range means “designer solvent”
Cost	Normal cheap	Typical between 2 and 100 times the cost of organic solvents
Recyclability	Green imperative	Economic imperative
Viscosity	0.2-100	22-40,000
Density	0.6-1.7	0.8-3.3
Refractive index	1.3-1.6	1.5-2.2

As a result, ionic liquids are very popular materials and they enjoy a plethora of applications in various domains of physical sciences

Stability

In most of these applications, the stability of ionic liquids, at least at a certain extent, is crucial for optimum process performance. Several studies have indicated that, although not 100% inert, certain ionic liquids incorporating 1,3-dialkyl imidazolium cations are generally more resistant than traditional solvents under certain harsh process conditions, such as those occurring in oxidation, photolysis and radiation processes [20].

Color

High quality ionic liquids incorporating [bmim]⁺ cation and a variety of anions, such as [PF₆]⁻, [BF₄]⁻, [CF₃SO₃]⁻, [CF₃CO₂]⁻ and [(CF₃SO₂)₂N]⁻ have been reported to be colorless, even though they are not 100% pure. The color of less pure ionic liquids generally ranges from yellowish to orange. The formation of the color has been attributed to the use of raw materials with color or excessive heating during the synthesis of imidazolium salt. A number of precautions for synthesis of colorless ionic liquids have been described, and a procedure for removal of color from impure ionic liquids

using acidic alumina and activated charcoal has also been proposed [20]

Hygroscopicity

The water content has an influence on the viscosity of the ionic liquids. Viscosity measurement indicates that ionic liquids became less viscous with increasing water content. Hydrolysis problems can also occur [20].

Hydrophobicity

The degree of polarity can be varied by adapting the length of the 1-alkyl chain (in 1, 3-substituted imidazolium cations), and the counter ion. Long-chain IL salts have attracted some interest due to their liquid-crystalline (LC) properties. The anion chemistry has a large influence on the properties of IL. Though little variation in properties might be expected between same-cation salts of these species, the actual differences can be dramatic: for example, [bmim] PF₆ is immiscible with water, whereas [bmim] BF₄ is water-soluble [21].

Advantages

Chemical industry

The first major industrial IL application was the BASIL (Biphasic Acid Scavenging utilizing Ionic Liquids) process by BASF, in which 1-alkylimidazole scavenged

the acid from an existing process. This then results in the formation of an IL which can easily be removed from the reaction mixture. This increased the space/time yield of the reaction by a factor of 80,000 [22]. Eastman operated an IL-based plant for the synthesis of 2, 5-dihydrofuran from 1996 to 2004 [23].

The dimersol process is a traditional way to dimerize short chain alkenes into branched alkenes of higher molecular weight. Y. Chauvin and H. Olivier-Bourbigou developed an IL-based add-on to this process called the difasol process. Ionikylation is an IL based process developed by Petro china for the alkylation of four-carbon olefins with isobutane. Their 65,000 tons per year plant is claimed to be the biggest industrial application of ionic liquids to date [24].

Pharmaceuticals

ILs have many desirable properties of interest to the pharmaceutical Industry Recognizing that approximately 50% of commercial pharmaceuticals are organic salts, ionic liquid forms of a number of pharmaceuticals have been investigated. Combining a pharmaceutically active cation with a pharmaceutically active anion leads to a Dual Active ionic liquid in which the actions of two drugs are combined. Reactions in ILs are often faster and easier to carry out than those in conventional organic solvents and usually require no special apparatus or methodologies. It should, however, be emphasised that the thermodynamics and kinetics of the reactions carried out in ILs are different from those carried out in conventional solvents.

In recent years, ILs has attracted an increasing attention as reaction media in enzymatic processes because of the very high enzymatic activity and stability in these 'green' solvents. Generally, there are three ways in which ILs can be involved in the bio catalytic process: (i) as pure solvents in monophasic systems, various water-immiscible ILs (e.g. 1-ethyl-3-methylimidazolium hexafluorophosphate ([bmim] [PF6]), (ii) as water-miscible ILs in monophasic systems—co-solvents in aqueous systems (e.g. Nethylpyridinium trifluoroacetate), or (iii) as pure ILs in non-aqueous biphasic systems (used as liquid or solid enzyme immobilisation supports).[25-27] However, 1,3-dialkylimidazolium- and *N*-alkylpyridinium-based ILs have also been considered in biocatalysis. The properties of imidazolium-based ILs properties make it possible to use the solvents as a direct replacement for conventional solvents in multiphase bioprocess operations [28].

ILs in the Synthesis of Antiviral, Antileishmanial and Antiparasitic Drugs

The search for novel antiviral nucleoside analogues has resulted in the design of ILs which provides high solubility to nucleosides and has been found to be an efficient reaction medium giving high yields under

ambient conditions [29-30]. All the ILs made it possible to obtain TFT with high purity and a 10-fold decrease in solvent consumption compared to the standard reaction media, pyridine/DMAP or acetonitrile/Et3N/DMAP.

Shaabani studied drugs based on acyclic nucleoside analogues, which have a potential antiviral activity and reported an efficient and 'environmentally friendly' approach for the synthesis of 3-amino-imidazo [1, 2] pyridines with high antiviral activity using the 1-butyl-3-methylimidazolium bromide ([bmim] [Br]) ionic liquid. Replacing the commonly used organic solvents by the readily available imidazolium bromide improves the synthesis of the side-chain-modified imidazo [1, 2] pyridinic derivative [31,32].

ILs in Synthesis of Anticancer Drugs

ILs has also been used in the synthesis of drugs with a promising antitumor potential. Zaidlewicz used ionic liquids [bmim] [X] (bmim= 1-butyl-3-methylimidazole, X=BF4, PF6) in the synthesis of *L*-4-boronophenylalanine (*L*-BPA), a clinically approved drug in boron neutron capture therapy (BNCT). [33] BNCT is based on boron-containing compounds that target tumour tissue using a suitable boron carrier. Cross-coupling with pinacolborane with the use of protected *p*-iodophenylalanine was performed in an BF4 ionic liquid as part of the search for new alternative protocols of efficient synthesis of boron compounds that might offer therapeutic advantage. The use of "non-volatile" solvents enabled the synthesis of BPA and its analogues with a good yield (82–89%) after 20 min. There is also a report of another synthesis of compounds with antitumor activities that used ILs as the reaction medium. Kurata developed a novel, efficient bio catalytic procedure providing various caffeic acid phenethyl ester (CAPE) analogues exerting potential antiproliferative effects on human tumour cells by using *Candida antarctica* lipase B (Novozyme 435) in 1-butyl-3- methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][NTf2]) as the solvent [34]. A comparable conversion yield was obtained for CAPE analogues produced with the use of ([bmim] [NTf2]) and CAPE synthesised in isooctane (yield of 91.65%).

ILs in the Synthesis of Non-steroid Anti-inflammatory Drug (NSAIDs):

The application of ILs offers an alternative in the synthesis of the entire conventional non-steroid anti-inflammatory drug (NSAIDs). The synthesis of pravadoline has already been performed in an ionic liquid by combined Friedel-Crafts reaction and nucleophilic displacement reaction. Numerous imidazolium-based ILs have been tested to improve the efficiency of the reaction. The best yield (99%) of alkylation of 2-methylindole with 1-(*N*-morpholino)-2-chloroethane has been achieved in 1-butyl-2,3-dimethylimidazolium hexafluorophosphate ([bmim][PF6]), while the best yield

of Friedel-Crafts acylation of the product from the nucleophilic displacement reaction has been obtained in [bmim][PF₆] at 150°C. It is interesting to note that no catalyst or strictly anhydrous conditions are required when using the ILs as the reaction media [35].

The synthesis of another NSAID, (*S*)-naproxen, can be performed in the presence of *in situ* or performed Ru-BINAP catalyst precursors immobilised in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate IL phase with similar optical yields in comparison with the homogeneous reaction. One of the advantages of the ILs involves the possibility of using and recycling a homogenous transition-metal catalyst without significant changes in activity or selectivity [36]. A further study on optimisation and extension to other chiral pharmaceutical compounds is ongoing.

Ibuprofen, commercially available as a racemate, is one of the most popular NSAIDs. However, the (*S*)-(+)-enantiomer has been proved to be 160 times more active than the (*R*)-(–)-enantiomer [37]. Numerous alternative biosyntheses with the use of ILs have therefore been designed to obtain a more enantioselective product compared to the conventional solvent systems. *Candida rugosa* lipase was shown to possess a comparable or higher activity and enantioselectivity in some ILs compared to those in isooctane [38]. It was concluded that [bmim] [PF₆] could be applied to substitute the conventional organic solvent. Contesini *et al.*, [39] described the effect of commercially available lipases and two native lipases from *Aspergillus niger* and *Aspergillus terreus* on the kinetic resolution of (*R*, *S*)-ibuprofen in systems containing [bmim] [PF₆] and [bmim] [BF₄]. The results indicated that the commercial *Candida rugosa* and native *Aspergillus niger* lipases exhibited the highest enantioselectivity and esterification activity in a two-phase system containing isooctane and [bmim] [PF₆] (1:1) compared with a system in pure isooctane.

ILs in the Synthesis of Antidepressant Drugs

(*S*)-3-chloro-1-phenyl-1-propanone ((*S*)-CPPO) obtained from enantiopure (*S*)-3-chloro-1-phenyl-1-propanol (3-CPP), is often used as a substrate in the synthesis of the most popular drugs employed in the treatment of depressive disorders (fluoxetine, tomoxetine). Enantioselective enzymatic reduction using a variety of reductases and dehydrogenases enables asymmetric synthesis of pure chiral compounds. However, the problem in this system is the low solubility of 3-CPP in the aqueous phase resulting in a low yield of (*S*)-CPPO. The entire cell-ionic liquid biphasic system enables the synthesis of water-insoluble chiral compounds. A system based on recombinant *Escherichia coli* cells co-expressing reductase and glucose dehydrogenase in a biphasic medium was used for the synthesis of (*S*)-CPPO. A variety of ILs were tested in aqueous two-phase

systems to increase the solubility of 3-CPP. Finally, ([bmim] [NTf₂]) was selected as the optimal modifier which dramatically increased the concentration of the substrate and the yield of the target compound ((*S*)-CPPO) with an enantiomeric excess of >99%. [40]

Cellulose processing

At a volume of some 700 billion tons, cellulose is the earth's most widespread natural organic chemical and, thus, highly important as a renewable resource. But even out of nature's annual 40 billion tons output, only approx. 5% is used as feedstock for further processing. More intensive exploitation of cellulose, as a renewable feedstock, is aided by the development of suitable solvents for mechanical and chemical processing. ILs has been shown to be highly effective at solvating cellulose to technically useful concentrations [41].

This may allow for development of new processes and intensification of existing ones substituting existing cellulose solvents for ILs. Making viscose-based fibers from dissolving pulp currently involves the use, and subsequent disposal, of great volumes of various chemical auxiliaries, esp. Carbon disulfide (CS₂).

Major volumes of wastewater need to be disposed of. Following in the footsteps of the Lyocell process, which uses hydrated N-Methylmorpholine N-oxide, as a novel non-aqueous solvent for the dissolution of the pulp, it has been suggested that IL can greatly simplify these processes, serving as solvents that are potentially recyclable. The "Institut für Textilchemie und Chemiefasern" (ITCF) in Denkendorf and BASF are jointly investigating the properties of fibers spun from solutions of cellulose dissolved in IL in a pilot plant [42]. The dissolution of cellulose-based materials like tissue paper waste, generated in chemical industries and at research laboratories, in room temperature IL 1-butyl-3-methylimidazolium chloride, bmimCl and the recovery of valuable compounds by electrodeposition from this cellulose matrix was studied [43].

Fundamental Research

Ionic Liquids on single-crystal surfaces in ultra-high vacuum are used as model systems for electrode, electrolyte interfaces

Algae processing

Algae is perhaps the most widespread organism on Earth, occupying most niches on the planet. Algae perform photosynthesis and produce high-energy molecules such as lipids and sugars, that can be converted to useful chemicals such as biodiesel, ethanol and other biofuels. To accomplish this, however, algae must be harvested and its constituents extracted from within the cell in an economically viable industrial process. ILs have been shown to be effective at destroying the cell wall and releasing cell contents using a fraction of the energy, and

potentially the cost, of current harvesting and extraction processes.

Dispersants

ILs can act as dispersing agents in paints to enhance finish, appearance and drying properties [44].

ILs are used for dispersing nonmaterial's at IOLITEC.

Gas handling

ILs have several properties that make them useful in gas storage and handling applications, including low vapor pressure, stability at high temperatures, and solvation for a wide variety of compounds and gases. They also have weakly coordinating anions and cations which are able to stabilize polar transition states. Many ionic liquids can be reused with minimal loss of activity. The company Air Products uses ILs instead of pressurized cylinders as a transport medium for reactive gases such as trifluoroborane, phosphine and arsine. The gases are dissolved in the liquids at or below atmospheric pressure and are easily withdrawn from the containers by applying a vacuum. Gas manufacturer Linde exploits the low solubility of hydrogen in ILs to compress the gas up to 450 bar in filling stations by using an ionic liquid piston compressor [45], which has only 8 moving parts (down from about 500 in a conventional piston pump). IL 1-butyl-3-methylimidazolium chloride has been used for separating hydrogen from ammonia borane [46], ILs and amines can be used to capture carbon dioxide CO₂ and purify natural gas [47].

Nuclear fuel reprocessing

IL 1-butyl-3-methylimidazolium chloride has been investigated as a non-aqueous electrolyte media for the recovery of uranium and other metals from spent nuclear fuel and other sources. [48-50] Protonated betaine bis (tri fluoro methane sulfonyl) imide has been investigated as a solvent for uranium oxides. Ionic liquids, N-butyl-N-methyl pyrrolidinium bis(tri fluoro methyl sulfonyl) imide and N-methyl-N-propyl piperidinium bis(tri fluoro methyl sulfonyl) imide, have been investigated for the electro deposition of Europium and Uranium metals respectively [51].

Solar thermal energy

ILs have potential as a heat transfer and storage medium in solar thermal energy systems. Concentrating solar thermal facilities such as parabolic troughs and solar power towers focus the sun's energy onto a receiver which can generate temperatures of around 600 °C (1,112 °F). This heat can then generate electricity in a steam or other cycle. For buffering during cloudy periods or to enable generation overnight, energy can be stored by heating an intermediate fluid. Although nitrate salts have been the medium of choice since the early 1980s, they freeze at 220 °C (428 °F) and thus require heating to prevent solidification. Ionic liquids such as Cmim 4[BF₄]

have more favorable liquid-phase temperature ranges (-75 to 459 °C) and could therefore be excellent liquid thermal storage media and heat transfer fluids [52].

Food and bioproducts

IL 1-butyl-3-methylimidazolium chloride completely dissolves freeze dried banana pulp and with an additional 15% DMSO, lends itself to Carbon-13 NMR analysis. In this way the entire banana complex of starch, sucrose, glucose, and fructose can be monitored as a function of banana ripening. ILs can extract specific compounds from plants for pharmaceutical, nutritional and cosmetic applications, such as the anti malarial drug artemisinin from the plant *Artemisia annua* [53].

Waste recycling

ILs can aid the recycling of synthetic goods, plastics and metals. They offer the specificity required to separate similar compounds from each other, such as separating polymers in plastic waste streams. This has been achieved using lower temperature extraction processes than current approaches and could help avoid incinerating plastics or dumping them in landfill.

Batteries

Researchers have identified ILs that can replace water as the electrolyte in metal-air batteries. ILs have great appeal because they evaporate at much lower rates than water, increasing battery life by drying slower. Further, ILs have an electrochemical window of up to six volts (versus 1.23 for water) supporting more energy-dense metals. Energy densities from 900-1600 watt-hours per kilogram appear possible. A Metal-air battery draws oxygen through a porous ambient "air" electrode (-cathode) and produces water, hydrogen peroxide, or hydroxide anions depending on the nature oxygen reduction catalyst and electrolyte. These compounds store the electrons released by the oxidation of the anode [54].

Applications: [55]

Table 2: Ionic Liquids in Organic Synthesis

Hydrogenation	Wittig
Hydroformylation	Alcohol oxidation
Alkoxy carbonylation	Friedlander reaction
Cross coupling	Nitration of phenols
Allylic substitution	Dimer-/Oligomer-/Polymerization
Friedel-Crafts alkylation	Chiral solvent for asymmetric synthesis
Diels-Alder	Kinetic resolution
Epoxidation/Epoxide opening	Cyanosilylation of aldehydes
Ring closing metathesis	Bromination of aromatics/alkynes
Knoevenagel condensation.	Cyclopropanation
Baylis-Hillman	Biocatalysis

Fig 2: Applications of Ionic Liquids in Future

CONCLUSION

ILs are salt composed of organic anions and organic or inorganic cations, which have low melting point. Their physical & chemical properties can be adjusted by the variation of the ions. The fine adjusting of properties is possible by the variation of the length and branching of the alkyl groups incorporated into the cations. Ionic liquids have interesting advantages; they are Non-flammable and have extremely low vapour pressure. These properties are significant when addressing the health and safety concerns associated with many solvents applications. Negligible vapour pressure and solvent evaporation is elevated. Reducing the need for respiratory protection and exhaust systems. They have liquid range more than 400K. While many solvents will freeze or boil across such a large temperature range, ionic liquids maintain their value and fluidity. This wide range of Thermal stability allows for tremendous kinetic control of chemical processes. The wide temperature range is also helpful in temperature dependent separation processes. Ionic liquids have higher density than the water and miscible with substances having very wide range of polarities and can simultaneously dissolve organic and inorganic substances. These features of RTILs offer numerous opportunities for modification of existing and further development of new processes. In such cases, such processes would be impossible with conventional solvents because of their limited liquid range or visibility.

As a replacement of classical organic solvents; the application of ILs offers a new and environmentally benign approach towards modern, synthetic chemistry. IL Technology has been successfully applied in several classical organic chemical reactions such as

Hydrogenation, Hydroformulation, Condensation, Oxidation etc. Recently ionic liquids have been successfully employed as dual reagent (solvents + catalytic activity) for a variety of reactions, but their use as catalyst under solvent free conditions still need to be given more attention.

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Cite this Article as: Sekar VK, Kotramangalam K, Alluru M, Manikantan J. Ionic Liquids: evident Application in Medicinal Chemistry. *J Compr Phar* 2014;1(1):1-10