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» Ionic liquids based active pharmaceutical ingredients

Sekhon BS.

Ars Pharmaceutica

Ionic liquids based active pharmaceutical ingredients

Bhupinder Singh Sekhon
PCTE Institute of Pharmacy, near Baddowal Cantt (India).

Special Paper
Artículo Especial

Correspondence/Correspondencia:
Bhupinder Singh Sekhon
PCTE Institute of Pharmacy, near Baddowal Cantt, Ludhiana-142 021, India.
E-mail:sekhon224@yahoo.com

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RESUMEN

Objetivos: la formación de sales de principios activos farmacéuticos mejora su solubilidad, procesado a nivel industrial, aspectos de seguridad y en ocasiones las propiedades biológicas. El objetivo de la presente revisión es considerar los líquidos iónicos basados en principios activos como una herramienta versatil y alternativa en la industria farmacéutica.

Material y Métodos: Los líquidos iónicos son sales cuaternarias con punto de fusión por debajo de 100ºC. Los efectos secundarios negativos asociados a un determinado principio activo pueden ser tratados si se administra como líquido iónico, en el cual el contraión neutraliza los efectos negativos no deseados. Otro enfoque plantea que los resultados de la sinergia sean mejor en tratamientos terapéuticos combinados con la utilización de líquidos iónicos como principio activo en lugar de aquellos en los que se emplean aditivos. Recientemente, se ha manifestado un mayor enfasis en el uso de liquidos iónicos como transportadores de la actividad biológica deseada. En este contextos, las propiedades de los líquidos iónicos pueden modificarse con la elección juiciosa de cation(es) y anio(es).

Resultados y Conclusiones: Los líquidos iónicos farmacéuticos pueden proporcionar una herramienta en el desarrollo, diseño y distribución de fármacos. Las sales de líquidos iónicos como principios activos eliminan los problemas asociados a estado sólido y presentan propiedades fisicas y biológicas sinergicas.

PALABRAS CLAVES: Líquidos iónicos, principios activos farmacéuticos, antimicrobianos

ABSTRACT

Aims: Salt formation of active pharmaceutical ingredients (APIs) improve their aqueous solubility, processing at industrial level, safety aspects and sometimes biological properties. The aim of the present review is to consider ionic liquids (ILs) based active pharmaceutical ingredients (APIs) as an alternative versatile tool in the pharmaceutical industry.

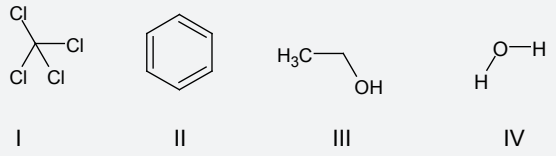
Materials and Methods: ILs are the quaternary salts having melting point below 100 ºC. The negative side effects of a given API can be treated by delivering it as an ionic liquid in which the counterion neutralizes the unwanted side effects. Ionic liquid form such as APIs pair for dual treatment therapies with synergistic rather than additive results is another approach. Recently, a major emphasis has been placed on ionic liquids as bearers of desired biological activity. In this context, the properties of the Ionic liquids can be tuned by judicious choice of cation(s) and anion(s).

Results: Recent developments have shown that Ionic liquids have potential biological applications in drug delivery, particularly as APIs. Some examples of ionic liquids produced as APIs are described from literature which has at least one pharmaceutical active ion with improved biological activity over the precursor ions. The use of ionogels in sensing platforms clearly has several advantages over current technologies. ILs have considerable potential to provide advances in liquid formulation of protein pharmaceuticals.

Conclusions: Pharmaceutical ionic liquids could provide another tool in drug development, design and delivery. Ionic liquid salts as APIs eliminate problems associated with the solid-state and exhibit synergistic physical and biological properties.

KEYWORDS: Ionic liquids, Active pharmaceutical ingredients, Antimicrobial.

Figure 1. Molecular solvents: I) carbon tetrachloride, II) benzene, III) ethanol and IV) water.

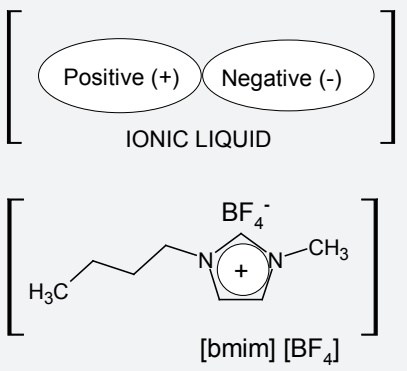


INTRODUCTION

Molecular solvents are composed of neutral species such as carbon tetrachloride, benzene, ethanol and water (Figure 1). An ionic liquid (IL) is a non-volatile organic salt (Figure 2a, 2b) that comprises discrete organic cation associated with anions, that can be either inorganic or organic (cation and/or anion quite large) with melting point preferably below 100° C. Ionic liquids (ILs) exhibit unusual solvent properties owing to the very strong ion–ion interactions and are of special interest with unique applications as tunable and environmentally benign solvents with negligible vapour pressures, high chemical and thermal stability (up to 300-400°C), viscosity normally < 100 cP, polarity moderate, molar conductivity< 10 Scm^2 mol^{-1}, immiscibility with many organic solvents, high fire resistance and wide liquid temperature range (often > 200°C) and electrochemical windows (> 2V, even 4.5 V, except for Brønsted acidic systems) [1-3]. The low melting points are related to the frustration of crystalline network formation, basically caused by the geometric characteristics of the constituent ions and their charge diffuse nature [4]. In recent years, ILs including task-specific ionic liquid[5], supported ionic liquid catalysis, basic and chiral ionic liquids have been exploited and explored in numerous fields among the physical, chemical and pharmaceutical sciences [6].

Ionic liquids are liquid at room temperature due to the shape of their ions. The ability to adjust the physiochemical and biological properties of ILs by changing their anion/cation combination is a real benefit and is applicable to diverse areas. In ILs, the strategy is to use large, nonsymmetrical ions, and the fact that lower is the lattice energy, lower is the melting point. Various cations and anions (building blocks) used in ionic liquids are given in Table 1[3]. Most common representative structures of ILs cations and ILs anions are shown in Figure 3 and Figure 4.

Figure 2. a) Ionic liquid representation; b) The tetrafluoroborate(BF4-)saltof1-butyl-3-methylimidazolium cation (bmim).



CLASSIFICATION OF ILS

(a) First generation ILs have unique tuneable intrinsic physical and chemical properties (density, viscosity, conductivity, solubility, and high thermal and chemical stability) e.g. mixtures of aluminium chloride and N-butylpyridinium chloride in different molar ratios (tetrachloroaluminate).

(b) Specific targeted behaviour (2nd generation ILs) such as dialkylimidazolium with neutral weakly coordinating anions such as $[BF_4]^-$ and $[PF_6]^-$), [non-haloaluminate] offered the potential to tune some of these physical and chemical properties, allowing the formation of "task-

Table 1. The building blocks of ILs.

Cations	Anions
Imidazoliums (disubstituted imidazoliums, trisubstituted imidazoliums, functionalized imidazoliums, protonated imidazoliums); Pyridiniums (unsubstituted pyridiniums, substituted pyridiniums, functionalized pyridiniums); Ammoniums (symmetrical ammoniums, unsymmetrical ammoniums, functionalized ammoniums, protonated ammoniums, cholines); Phosphoniums (symmetrical phosphoniums, unsymmetrical phosphoniums); Sulfonium; Piperidinium; Pyrrolidiniums; Pyrazoliums; Pyridazinium, Pyrazinium, Triazolium, Thiazolium, Oxazolium, Guanidiniums; Zwitterions; Ionic liquid cellulose solutions	{$[MX_n]^-$; M = Al, Ga, Fe, Cu, Zn; X = Cl, Br},$[Al_2Cl_7]^-$, $[Al_3Cl_{10}]^-$, $[Al(Et)Cl_3]^-$, $[Al_2(Et)_2Cl_5]^-$, $[Al(OCH_2CF_3)_4]^-$, Cl^-, Br^-, I^-, $[F(HF)_n]^-$, $[N_3]^-$, $[SCN]^-$, $[OCN]^-$, $[N(CN)_2]^-$, $[C(CN)_3]^-$, $[B(CN)_4]^-$, $[BF_4]^-$, $[B(oxalato)_2]^-$, $B(C_6H_{44}\text{-}CF_3)_4]^-$, $[PF_6]^-$, $[P(C_2F_5)_3F_3]^-$, $[SbF_6]^-$, $[NO_3]^-$, $[NO_2]^-$, $[ROSO_3]^-$, $[(RO)_2PO_2]^-$, $[MeCO_2]^-$, $[CF_3CO_2]^-$, [lactate]$^-$, [amino acidate]$^-$, [p-$MeC_6H_4SO_3]^-$, $[CF_3SO_3]^-$, $[(CF_3SO_2)_2N^-]$, $[{}^-O\text{-}(SO_2R)]$,$[{}^-N\text{-}(SO_2R)_2]$, $[{}^-C(SO_2R)_3]$, $[(CF_3SO_2)_3C^-]$, p-$MeC_6H_4SO_3$ tosylate

Figure 3. a) Commonly used cations for ionic liquids: I-Imidazolium; II-Pyridinium; III-Tetraalkylammonium; IVTetraalkylphosphonium; b) Commonly used anions for ionic liquids: V- Tetrafluoroborate (BH_4^-); VI-Hexafluorophosphate(PF_6^-); VII-bis(trifluoromethylsulfonyl)amide(NTf_2^-); VIII-methanesulfonate ($CH_3SO_3^-$); IX-p-tolunesulphonate($C_7H_7\ SO_3^-$); X-trifluoromethanesulfonate ($CF_3SO_3^-$).

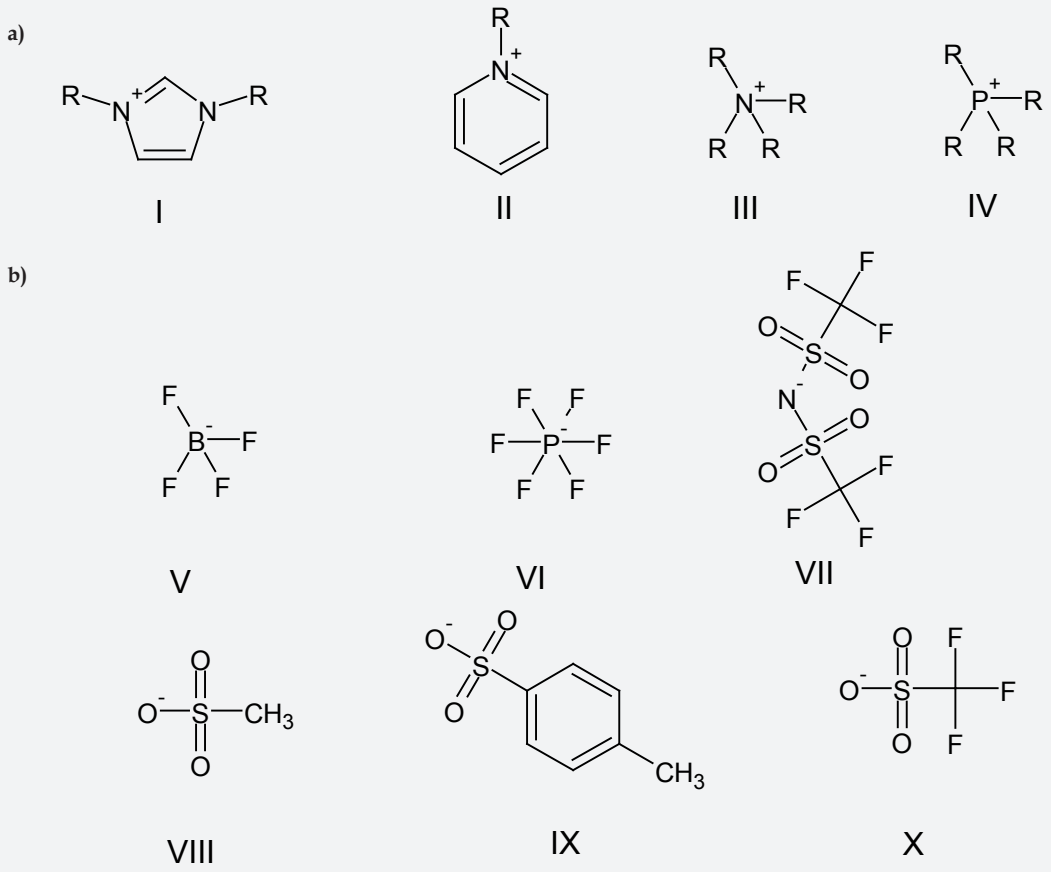


Figure 4. Lidocaine docusate.

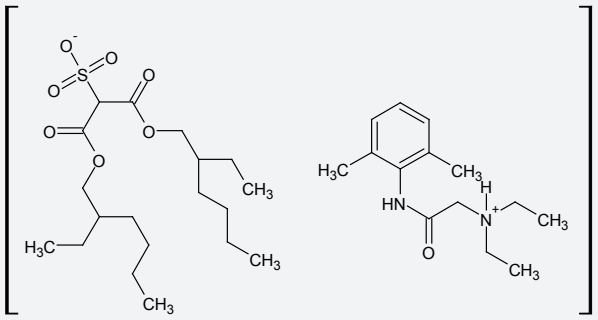
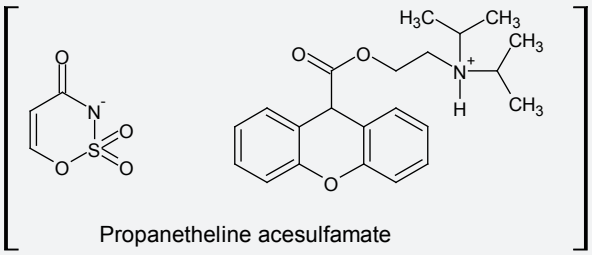


Figure 5. Propanetheline acesulfamate



specific ionic liquids" [7,8].

(c) The third generation (task-specific ILs and chiral ILs) of ILs involve active pharmaceutical ingredients (API), which are being used to achieve specific desirable biological features. The present review article deals with various aspects of IL-APIs with a particular focus on efforts to overcome current hurdles encountered by APIs [9].

IONIC LIQUIDS AS APIS

Pharmaceutical industry focus is the development of salts of the targeted active compounds in order to fulfil the desired requirements of solubility, bioavailability and stability. The arrival of ionic liquids into the pharmaceutical world offers another design option in addition to co-crystals, amorphous forms, and polymer embedded pharmaceuticals. The physiochemical properties of the ionic liquid salts tuned

Figure 6. Ranitidine docusate

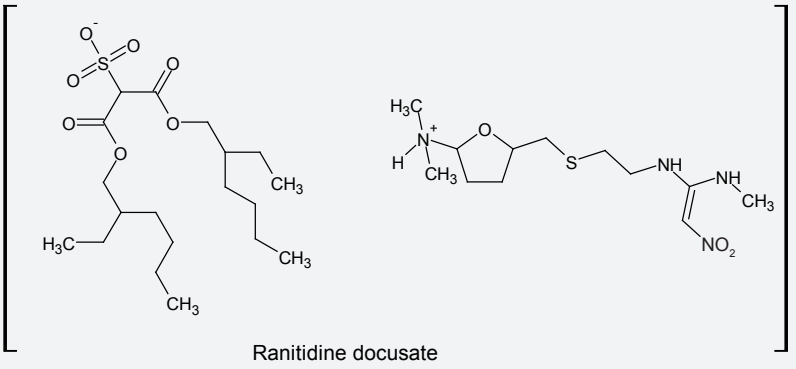
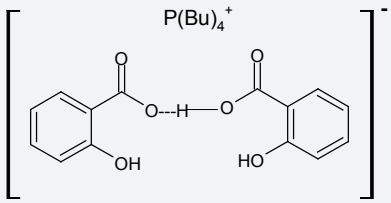


Figure 7. Oligomeric ions formed from [P(Bu)4]+ [salicylate] and salicylic acid.



by judicious choice of cation(s) and anion(s) makes them truly designer solvents. ILs made up of asymmetric ions of varying shapes and sizes possess disorganised structure that makes them liquid. They comprise solely of usually organic cations and polyatomic anions [large asymmetric ions, diffuse charges, weak inter-ionic interactions]. At least one ion has a delocalized charge and one component is organic, which prevents the formation of stable crystal lattice. The typical ions used in ionic liquids show only moderate polarization charge densities and this is due to the delocalization of the molecular charge. In the ions like the imidazolium, pyridiniuim ($C_5H_6N^+$), or nitrate and many others, the charge is delocalized via conjugation and hyperconjugation. Other, mostly high symmetrical ions, like ammonium and phosphonium cations or anions like $[PF_6]^-$, $[BF_4]^-$ delocalize the charge over their ligand surface. In general, ILs consists of a salt where one or both the ions are large, and have a low degree of symmetry**.** These factors tend to reduce the lattice energy of the crystalline form of the salt and hence lower the melting point [10, 11]. 'The idea of incorporating pharmaceuticals into ionic liquids is attractive and inspiring. Pharmaceutical ionic liquids could provide another tool in drug development, design and delivery. ILs behaviour is different in the body than simple halide containing salts. ILs can serve as pharmaceuticals, in which these liquid salts eliminate problems associated with the solid-state and display to synergistic physical and biological properties [10].

The susceptibility to polymorphism of solid salts can be reduced by designing ionic liquids pharmaceuticals, and/ or a pair of two active ions for dual treatment therapies with synergistic rather than additive results is the expected target of future research [3]. The counter ions could be used to add a second function to the ionic liquid drug such as anti-bacterial or anti-microbial behaviour. As many of the common ionic liquid cations bearing long alkyl chains are known to penetrate the skin and the cell membranes, therefore, one could imagine easy application of drugs through the skin [11]. Ionic liquids provide an alternative to certain solvents in select reactions used to synthesize intermediates and active pharmaceutical ingredients with a focus to overcome many problems currently encountered by APIs, as well as to offer innovative solutions in new treatment and delivery options [10].

Many nucleoside related compounds are prominent drugs and have been widely applied for cancer and viral chemotherapy. IL methodology has been successfully employed to synthesize a host of nucleoside analogues which are used as anti viral drugs [12]. Researchers have made an ionic liquid (Lidocaine docusate, Fig. 4) based on the common local anaesthetic, lidocaine hydrochloride by changing the anion from hydrochloride to docusate (dioctylsulfosuccinate). They found that the ionic liquid form of the drug delivered longer lasting pain relief compared to lidocaine hydrochloride, suggesting an active and beneficial slow-release mechanism of drug delivery [13]. A non-crystallizable ionic liquid [3-(dimethylaminocarbo nyloxy)-1- methyl pyridinium saccharinate] was formed when the bromide in 3-(dimethylaminocarbonyloxy)-1-methyl pyridinium bromide (acetylcholinesterase inhibitor) was replaced by saccharinate ion. IL-APIs can provide many advantages over solid or crystalline forms of drugs. For example, IL propantheline acesulphamate (Fig. 5) avoid polymorphism as compared to ranitidine hydrochloride (Fig. 6).

Scientists have reported that a pharmaceutically active cation combination with a pharmaceutically active anion produced a dual active ionic liquid in which the actions of two drugs were pooled [14]. Researchers reported a preparation of some pharmaceutically active ionic liquids by simple mixing of $[P(Bu)_4]^+$ [salicylate] with [salicylic acid] forming oligomeric ions (Fig. 7) [15].

Pharmaceutically active ionic liquids represent a thermodynamically stable phase, thereby, avoiding the troublesome issues surrounding polymorphism and "polymorphic transformation" of APIs. Applications of ILs as disinfectants, antibacterials, personal health care products and drug delivery were reported. Further,

ILs are up to 250 times better at killing 'difficult to treat' biofilms. A number of classes of ILs exhibited excellent antimicrobial and anti-biofilm activity [16]. The choline dihydrogenphosphate IL has potential as a stabilizing excipient or solvent for protein therapeutics [17]. Based on APIs, a series of protic pharmaceutical ionic liquids (salts) having extended hydrogen bonded clusters have been synthesised and characterized [18].

Researchers reported the controlled self-assembly of histidine acid phosphatase (HAP) enzyme in the IL 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF4], leading to the formation of HAP nanocapsules as template for synthesis of platinum nanospheres. Such HAP nanocontainers loaded with an anticancer drug curcumin were reported. Further, these workers demonstrated *in vitro* drug release and synergistic anticancer effect of these systems on three different cell lines viz. hepatocellular carcinoma (HepG2), breast cancer (MCF-7) and human acute monocytes (THP-1)[19].

IONOGELS AS DRUG RELEASING SYSTEM

Ionogels have been reported a new class of hybrid materials, in which the properties of the ILs are hybridized with those of another component, which may be organic (low molecular weight gelator, (bio) polymer), inorganic (e.g. carbon nanotubes, silica etc.) or hybrid organic-inorganic (e.g. polymer and inorganic fillers). There are two ways to achieve functionalization of ionogels: i) by incorporation of organic functions in the solid matrix, and ii) by encapsulation of molecular species (from metal complexes to enzymes) in the immobilized IL phase. Such studies have the potential to design drug release systems [20]. Ionogels containing imidazolium ibuprofenate have been shown to be an efficient drug releasing system with kinetics controlled by the nature of the silica wall [21]. Carbon-based ionogels tune the properties of the ionic liquid via carbon-ionic liquid interaction in this context, the two ionic liquids (ILs), 1-ethyl-3-methylimidazolium dicyanamide [Emim][DCA] and 1-ethyl-3-methylimidazolium triflate [Emim][TfO], in (meso)porous carbonaceous hosts showed significant changes in the thermal behaviour [22]. The use of ionogels in sensing platforms clearly has several advantages over current technologies. ILs trapped in silica nanoporous gels are promising materials for applications in electrochemistry and drug delivery (when one of the component of the ionic liquid is replaced by a drug) [23,24].

OTHER PHARMACEUTICAL ASPECTS

Pharmaceutically active ILs being more soluble and stable than solid drugs are superior at getting across cell membranes. Pharmaceutically active ILs have been immobilised onto solid supports to enable liquid drugs to be administered in solid form. Researchers combined known APIs into new dual functioning liquid salts in two ways. The first approach combining an acidic API with a basic API simply by grinding or mixing them together produced a salt in which the proton transfer occurred from the acid to the base. IL-API immobilized onto mesoporous silica were found stable, easily handled solids, with fast and complete release from the carrier material when placed into an aqueous environment . In this context, a cationic API and an anionic API exchanged the inert counterions to produce a new salt [25]. ILs appealing solvent properties such as miscibility with water or organic solvents enable these to act as 'ionic liquid like pharmaceutical salts' and their importance and application in drug development has been reported [26]. Peptide synthesis in ionic media and particularly construction of cyclopeptides, enantioselective oxidations leading to chiral sulfoxides were reported as a route to drugs such as modafinil [27]. An overview of the recent advances made in the field of ionic liquids in peptide chemistry and peptide analytics has been reported [28]. "Supported Ionic Liquid Phase" (SILP) strategy has remarkable advantage in the loading of ILs that are necessarily leached in order to carry out their functions, as is the case of ILs of APIs. Researchers have found that IL-APIs are readily loaded and leached from silica, giving to the material a few advantages including the ability to deliver these liquid salt drugs in solid form as free flowing powders [29].

IL [1-ally-3-ethylimidazolium tetrafluoroborate ($AEImBF_4$)] has been used for designing polymorphs of the active pharmaceutical ingredient adefovir dipivoxil. Because of the influence of IL on the formation of the intermolecular interaction of AD in the solution, new anhydrous (N-II) and hemihydrate (N-I) crystals of AD were produced. The N-I crystals underwent three polymorphic changes: N-I → amorphous → form-V → liquid, while the N-II crystals undergo two polymorphic changes: N-II → form-V → liquid [30]. Chiral ionic liquids are also used for pharmaceutical applications [31]. Ionic liquid-in-oil microemulsions have been adopted to increase the solubility of insoluble or sparingly soluble drugs to enhance their topical and transdermal delivery [32].

Protein-based therapeutic drugs have demonstrated significant efficacy in controlling and curing disease. ILs have considerable potential to provide advances in liquid formulation of protein pharmaceuticals. ILs has also been formulated from naturally occurring biomolecules [salts, sugars, amino acids] and many of which have already been approved as excipients for drug formulation.

Biocompatibility has been established for a number of these bio-inspired ionic liquids, including salts based on the choline cation. These results suggested that biocompatibility and protein stabilization characteristics can be rationally designed into ionic liquids and clinical application of such ionic liquids have been reported [33]. Alkylated imidazolium ionic liquids salts, as non-aqueous solvents, permit desirable reactions to occur for drug delivery purposes. In this context, structures similar to the extracellular matrix gel were obtained on drying with supercritical CO_2. This is also feasible even when the chitosan is cross-linked, or in combination with metal oxides of interest in orthopedics [34]. Crystalline proteins may offer superior properties for drug delivery compared to standard protein formulations such as aqueous solutions or amorphous precipitated lyophilisates. Substituted alkylammonium-based ILs as additives for the advanced crystallization of lysozyme and lipase resulted in less crystal polymorphism and precipitation was consistently avoided, even at larger concentrations of the conventional crystallization agent [35]. Reports are available in literature to develop novel anti-cancer agents using metal-free imidazolium salts. IBN-1 and IBN-9 significantly inhibited the cell proliferation and arrested Hepatocellular carcinoma cells in the G1-phase [36]. The toxicity and ecotoxicity of imidazolium salts yield valuable informations for their use as pharmaceuticals as well as their impact on the environment [37].

CONCLUSIONS AND PERSPECTIVES

ILs are the quaternary salts having melting point below 100 ^{o}C. In general, they are typically constituted of organic cations (imidazolium, pyridinium, sulfonium, phosphonium, etc.) and inorganic anions. Scientists are exploring a strategy to produce ILs containing at least one pharmaceutical active ion with improved biological activity over the precursor ions. Such ILs pharmaceuticals have the potential to eliminate problems associated with the solid-state crystalline pharmaceuticals by exhibiting synergistic physical and biological properties. Chiral and achiral ILs obtained from natural molecules such as sugars and amino acids should be exploited in this direction.

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