

# Ionic Liquid-Based Materials, Biomedical Applications

Subjects: Materials Science, Biomaterials

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Ionic liquids (ILs) are being applied in a wide range of areas such as sensors and actuators. The increasing attention devoted to ILs is based on their unique properties and possible combination of different cations and anions, allowing the development of materials with specific functionalities and requirements for applications. In recent years, ILs have also been gaining attention in the biomedical field, where they allow important advances in novel pharmaceuticals and medical strategies.

Keywords: biomedical applications ; ionic liquids ; IL-polymer based materials

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## 1. Introduction

ILs are commonly defined as salts composed of organic cations and organic/inorganic anions with low melting temperatures <sup>[1]</sup>. They can be synthesized with a large number of specific functionalities <sup>[1][2]</sup>. Some of the interesting physical-chemical properties of ILs include tailored viscosity <sup>[3][4]</sup>, melting temperature <sup>[5]</sup>, solubility, stability at high temperatures, and surface activity <sup>[6]</sup>, which are important for developing specific materials for biomedical applications. It is noteworthy that deep eutectic solvents (DESs), formed by the mixture of a hydrogen bond acceptor and a donor, show similar properties to ILs and have been also used for biomedical applications. However, DESs have been replaced by ILs in the most recent studies <sup>[7][8][9]</sup>.

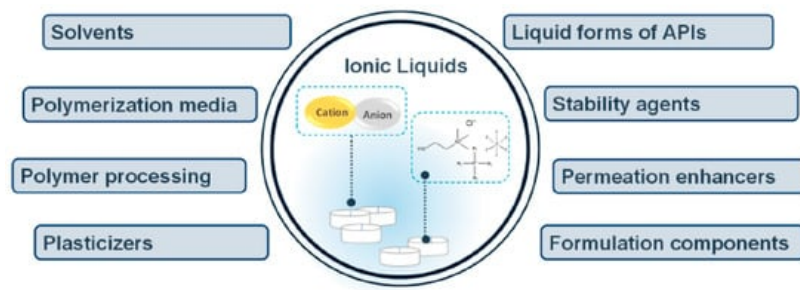
ILs are mainly derived from petroleum-based constituents such as imidazolium and pyridinium and can display toxicity and release hazardous decomposition products under certain conditions <sup>[10][11][12][13]</sup>. This has led to their “green” nature being questioned over the past few years <sup>[14][15]</sup>. Due to the strong socioeconomic impact of ILs and the doubts around their “green” nature, the synthesis of biocompatible ILs has gained special attention, expanding their applicability in different fields, particularly in the biomedical area.

The most effective strategy for the development of biocompatible compounds relies on the use of choline as the cationic moiety in the structure. It has been shown that the use of this component as cation allows the development of biocompatible ILs with biodegradability and very low toxicity <sup>[16]</sup>; nonetheless, it has been also reported <sup>[17]</sup> that more detailed toxicological tests with different organisms are necessary to truly determine the biocompatibility of the choline amino acid based ILs. The combination of cholinium cations with other compounds such as amino acids, artificial sweeteners, or carboxylic acids such as anions has been performed in recent years <sup>[18]</sup>. Besides the large attention devoted in cholinium based ILs and the intensive research in this field, some biocompatible alternatives to cholinium as cation for biocompatible ILs synthesis have received consideration.

The combination of ILs with different polymer-based materials has been also explored in recent years. For the preparation of biomaterials, ILs can play different roles by assisting or participating in the formation of the materials through polymer dissolution or polymer regeneration. IL/biopolymer hybrid materials are also emerging as biomaterials in biomedical applications <sup>[19]</sup>. Due to the large number of available combinations of ILs, and based on their intrinsic properties, they are being successfully implemented in a variety of applications in this field, such as biodegradable composite biomaterials <sup>[20][21][22]</sup>, or pharmaceuticals <sup>[19][23]</sup>, among others.

## 2. Biomedical Applications of Ionic Liquids-Based Materials

ILs have been commonly employed in the development of biomaterials, in particular in combination with natural and synthetic polymers for different biomedical areas, including drug delivery, cancer therapy, tissue engineering, antimicrobial and antifungal agents, and biosensing. As an example, in the area of drug delivery, ILs have been used either to develop delivery systems and pharmaceutical formulations or to functionalize biopolymers ( **Figure 1** ).



**Figure 1.** Applications of ILs in drug delivery systems design and development (APIs: active pharmaceuticals ingredients). Reprinted with permission from [24].

**Table 1** reports the main works using IL-based materials for drug delivery applications, presenting the used materials, the target application, as well as the main obtained results.

Materials	Ionic Liquids (ILs)	Biomedical Property	Ref.
Chitosan	[Ch][Cl] [Ch][DHP]	Electrical and pH-sensitive drug delivery	[25]
Chitin	[C <sub>2</sub> mim][Ac]	Topical release drug delivery	[26]
	[Bmim][HSO <sub>4</sub> ]	Sustained drug release application	[27]
	[Hmim][HSO <sub>4</sub> ]		
	[Chol][HSO <sub>4</sub> ]		
	Choline acrylate Choline chloride-thiourea		
Cellulose/Chitosan/Keratin	[Bmim][Cl]	Bandage to treat chronic and ulcerous wounds	[28]
Cellulose/Fe <sub>3</sub> O <sub>4</sub> NPs/Heparin	[Emim][Ac]	Magnetically responsive drug delivery	[29]
Locust bean gum	[Bmim][Cl]	Potential drug delivery system	[30]
	[Emim][Ac]		
	[C <sub>2</sub> OHmim][Cl]		
Active pharmaceutical ingredient/grafted-PLLA	Choline chloride di(2-hydroxyethyl)dimethyl ammonium bromide	Potential drug delivery system	[31]
Active pharmaceutical ingredient/grafted-PLLA	2-hydroxyethyl triethyl ammonium bromide	Drug delivery system	[32]
	2-hydroxyethyl tributyl ammonium bromide		
	di(2-hydroxyethyl)dibutyl ammonium bromide		
	tris(2-hydroxyethyl)butyl ammonium bromide		
pH-sensitive polymer/montmorillonite (MMT)	3-methyl-1-[2-(2-methyl-acryloxy)ethyl]imidazolium chloride	Colon Specific Drug Delivery System	[33]
Cellulose/PNIPAAm	[Bmim][Cl]	Temperature and pH-sensitive drug delivery	[34]

One of the most attractive characteristics of ILs is the fact that they can be dissolved in a wide range of solvents, including water, which makes them suitable for biomedical applications. Aqueous solutions of certain ILs have been indeed reported to possess potent antimicrobial activity [35][36]. Although dissolved ILs are not considered true ILs since they no longer consist exclusively of parent ions [37], this may indicate that the mechanism of action is due to one or both ions, both being able to possess inherent antimicrobial activity [38].

### 3. Main Conclusions and Future Trends

Due to their specific properties, ILs have been explored for a wide range of applications, of which biomedical applications are of particular interest and current activity. The large possible combinations of different cations and anions allow the development of a high and vast number of ILs with specific and tailored properties. Particularly for biomedical applications, the development of biocompatible and non-toxic ILs has been essential. Currently, the most commonly used ILs remain protein-derived amino-acids cations and anions and choline cations, but also other types are emerging in fields such as cancer treatment, biocides, or biosensing.

Besides the increasing interest devoted to ILs for different fields and application areas, the most common use of ILs is as green solvents for a wide range of polymers and other materials. Nevertheless, their combination with polymers matrixes to form IL/polymer-based hybrid materials is rapidly getting recognition in areas such as sensors, actuators, and tissue engineering where they have demonstrated an outstanding potential. Particularly for biomedical applications, and based on their different actuation possibilities, ILs are emerging as highly valuable candidates. Novel studies are demonstrating, for instance, the potential of ILs in drug delivery systems with photo-, temperature- or pH-sensitive drug release behavior. For tissue engineering, ILs have been employed as polymer solvents, and have been combined with polymers to develop a wide variety of responsive and functional materials, including films, fibers, spheres, membranes, and hydrogels. These early works make also evident that significant efforts to understand these systems are still necessary. For instance, the IL stability and release, in the case of drug delivery systems, needs to be better understood, while a lack of studies exists concerning the influence of the IL on the cell behavior of a larger variety of cells, namely their adhesion, proliferation, and differentiation. The effect of the ionic charges in the cells is also absent in many studies, reflecting the necessity of new works on the dynamics of the effect of the ILs ionic charges on cells.

The demonstration that certain ILs present less cytotoxicity against healthy cells than against cancer cells supports the potential of ILs to be used in the development of novel strategies for cancer therapies. Also highly related, the strong potential of ILs as antimicrobial and antifungal agents in biomedical applications, such as wound dressing, has been also demonstrated. In this field of applicability, advances are necessary to evaluate the cytotoxicity towards different cell lines determining the window of concentrations that are safe using. Finally, ILs have been also explored in the field of biomedical sensing and biosensing through the development of sensors able to recognize temperature and force variations, as well as to identify biomolecules, proteins, and pharmaceuticals, among others.

Despite the growing number of studies concerning the use of ILs in different areas of the biomedical field, strong efforts concerning the ILs toxicity, stability over time, and degradability as well the IL degradation products should be addressed deeply. Additionally, it is noteworthy that currently, a high number of studies report the use of ILs as solvents during preparation of materials, with still a limited number of studies existing on IL/polymer-based materials for biomedical applications. In this scope, the combination ILs with other materials allows them to confer interesting functional responses to the systems, including optical, catalytic, or shape memory. As an example, the exploration of the magnetic properties of ILs and magnetic ILs/polymer materials for tissue regeneration holds interesting potential. Different studies reports that the magnetic field can promote cell proliferation and differentiation mostly based on magnetic nanoparticles, which are toxic in certain concentrations. In this regard, magnetic ILs are of great interest due to the possibility of developing magnetic-particle-free magnetically responsive hybrid materials. Thus, IL and their tailorable properties as well as their rich synergetic effect in their combinations with polymers and related materials holds great promise as a next generation of smart and multifunctional materials for biomedical and biotechnological applications.

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