Ionic Liquid-Based Materials, Biomedical Applications

Subjects: Materials Science, Biomaterials

Submitted by: Daniela Correia

Definition

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 pharmaceutics and medical strategies.

1. Introduction

ILs are commonly defined as salts composed of organic cations and organic/inorganic anions with low melting temperatures [1]. They can be synthesized with a large number of specific functionalities [1][2]. Some of the interesting physical-chemical properties of ILs include tailored viscosity [3][4], melting temperature [5], solubility, stability at high temperatures, and surface activity [6], 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 However, DESs have been replaced by ILs in the most recent studies [7][8][9].

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 [10][11][12][13]. This has led to their "green" nature being questioned over the past few years [14][15]. 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 [16]; nonetheless, it has been also reported [17] 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 [18]. 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 [19]. 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 [20][21][22], or pharmaceuticals [19][23], 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**).

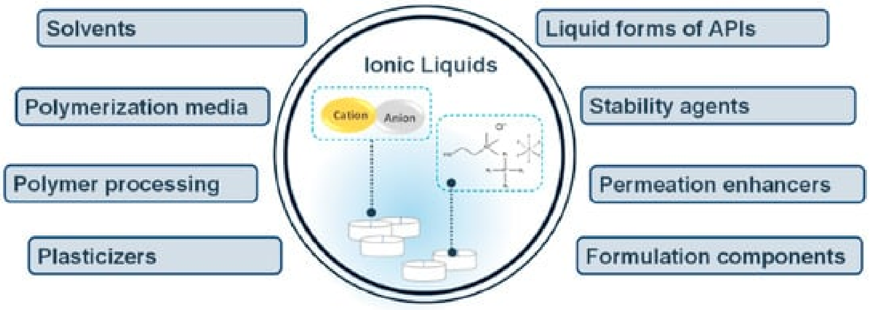

Figure 1. Applications of ILs in drug delivery systems design and development (APIs: active pharmaceuticals ingredients). Reprinted with permission from [24].

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]	Electrical and pH-sensitive drug delivery	[25]
	[Ch][DHP]		
Chitin	[C_2mim][Ac]	Topical release drug delivery	[26]
	[Bmim][HSO_4]	Sustained drug release application	[27]
	[Hmim][HSO_4]		
	[Chol][HSO_4]		
	Choline acrylate		
	Choline chloride-thiourea		
Cellulose/Chitosan/Keratin	[Bmim][Cl]	Bandage to treat chronic and ulcerous wounds	[28]
Cellulose/Fe_3O_4 NPs/Heparin	[Emim][Ac]	Magnetically responsive drug delivery	[29]
Locust bean gum	[Bmim][Cl]	Potential drug delivery system	[30]
	[Emim][Ac]		
	[C_2OHmim][Cl]		
Active pharmaceutical ingredient/grafted-PLLA	Choline chloride	Potential drug delivery system	[31]
	di(2-hydroxyethyl)dimethyl ammonium bromide		
Active pharmaceutical	2-hydroxyethyl triethyl ammonium bromide		
	2-hydroxyethyl tributyl ammonium bromide		

Materials	Ionic Liquids (ILs)	Biomedical Property	Ref.
ingredient/grafted-PLLA		Drug delivery system	[32]
	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.

References

1. Daniela Maria Correia; Liliana Fernandes; Pedro Martins; Clara García-Astrain; Carlos Miguel Costa; Javier Reguera; Senentxu Lanceros-Méndez; Ionic Liquid–Polymer Composites: A New Platform for Multifunctional Applications. *Advanced Functional Materials* **2020**, *30*, 1909736, 10.1002/adfm.201909736.
2. Carolina Cruz; Alina Ciach; Phase Transitions and Electrochemical Properties of Ionic Liquids and Ionic Liquid—Solvent Mixtures. *Molecules* **2021**, *26*, 3668, 10.3390/molecules26123668.
3. I.M. Marrucho; Luis Branco; Luis Paulo Rebelo; Ionic Liquids in Pharmaceutical Applications. *Annual Review of Chemical and Biomolecular Engineering* **2014**, *5*, 527-546, 10.1146/annurev-chembioeng-060713-040024.
4. Guangren Yu; Dachuan Zhao; Lu Wen; Shendu Yang; Xiaochun Chen; Viscosity of ionic liquids: Database, observation, and quantitative structure-property relationship analysis. *AIChE Journal* **2011**, *58*, 2885-2899, 10.1002/aic.12786.
5. Fangyou Yan; Shuqian Xia; Qiang Wang; Zhen Yang; Peisheng Ma; Predicting the melting points of ionic liquids by the Quantitative Structure Property Relationship method using a topological index. *The Journal of Chemical Thermodynamics* **2013**, *62*, 196-200, 10.1016/j.jct.2013.03.016.
6. Haibo Zhang; Xiaohai Zhou; Jinfeng Dong; Gaoyong Zhang; Cunxin Wang; A novel family of green ionic liquids with surface activities. *Science China Chemistry* **2007**, *50*, 238-242, 10.1007/s11426-007-0024-x.
7. Fatemeh Soltanmohammadi; Abolghasem Jouyban; Ali Shayanfar; New aspects of deep eutectic solvents: extraction, pharmaceutical applications, as catalyst and gas capture. *Chemical Papers* **2020**, *75*, 439-453, 10.1007/s11696-020-01316-w.
8. Shahram Emami; Ali Shayanfar; Deep eutectic solvents for pharmaceutical formulation and drug delivery applications. *Pharmaceutical Development and Technology* **2020**, *25*, 779-796, 10.1080/10837450.2020.1735414.
9. Mohamad Hamdi Zainal-Abidin; Maan Hayyan; Won Fen Wong; Hydrophobic deep eutectic solvents: Current progress and future directions. *Journal of Industrial and Engineering Chemistry* **2021**, *97*, 142-162, 10.1016/j.jiec.2021.03.011.
10. Marija Petkovic; Kenneth R. Seddon; Luis Paulo N. Rebelo; Cristina Silva Pereira; ChemInform Abstract: Ionic Liquids: A Pathway to Environmental Acceptability. *ChemInform* **2011**, *42*, 1383-1403, 10.1002/chin.201127270.
11. Deborah Coleman; Nicholas Gathergood; Biodegradation studies of ionic liquids. *Chemical Society Reviews* **2010**, *39*, 600-637, 10.1039/b817717c.
12. Richard P. Swatloski; John Holbrey; Robin D. Rogers; Ionic liquids are not always green: hydrolysis of 1-butyl-3-methylimidazolium hexafluorophosphate. *Green Chemistry* **2003**, *5*, 361-363, 10.1039/b304400a.
13. Marianne Matzke; Stefan Stolte; Karen Thiele; Tanja Juffernholz; Jürgen Arning; Johannes Ranke; Urs Welz-Biermann; Bernd Jastorff; The influence of anion species on the toxicity of 1-alkyl-3-methylimidazolium ionic liquids observed in an (eco)toxicological test battery. *Green Chemistry* **2007**, *9*, 1198-1207, 10.1039/b705795d.
14. Dongbin Zhao; Yongcheng Liao; Ziding Zhang; Toxicity of Ionic Liquids. *CLEAN - Soil, Air, Water* **2007**, *35*, 42-48, 10.1002/clen.200600015.
15. Thi Phuong Thuy Pham; Chul-Woong Cho; Yeoung-Sang Yun; Environmental fate and toxicity of ionic liquids: A review. *Water Research* **2010**, *44*, 352-372, 10.1016/j.watres.2009.09.030.
16. J. I. Santos; A. M. M. Gonçalves; J. L. Pereira; B. F. H. T. Figueiredo; Francisca Silva; Joao Coutinho; S. P. M. Ventura; Fernando J. M. Gonçalves; Environmental safety of cholinium-based ionic liquids: assessing structure–ecotoxicity relationships. *Green Chemistry* **2015**, *17*, 4657-4668, 10.1039/c5gc01129a.
17. Xue-Dan Hou; Qiu-Ping Liu; Thomas Smith; Ning Li; Min-Hua Zong; Evaluation of Toxicity and Biodegradability of Cholinium Amino Acids Ionic Liquids. *PLOS ONE* **2013**, *8*, e59145, 10.1371/journal.pone.0059145.

18. Balu Gadilohar; Ganapati Shankarling; Choline based ionic liquids and their applications in organic transformation. *Journal of Molecular Liquids* **2017**, *227*, 234-261, 10.1016/j.molliq.2016.11.136.
19. Jing Chen; Fengwei Xie; Xiaoxi Li; Ling Chen; Ionic liquids for the preparation of biopolymer materials for drug/gene delivery: a review. *Green Chem.* **2018**, *20*, 4169-4200, 10.1039/c8gc01120f.
20. Julia L. Shamshina; Oleksandra Zavgorodnya; Robin D. Rogers; Advances in Processing Chitin as a Promising Biomaterial from Ionic Liquids. *Blue Biotechnology* **2018**, *168*, 177-198, 10.1007/10_2018_63.
21. Simone S. Silva; João F. Mano; Rui L. Reis; Ionic liquids in the processing and chemical modification of chitin and chitosan for biomedical applications. *Green Chemistry* **2016**, *19*, 1208-1220, 10.1039/c6gc02827f.
22. Hamayoun Mahmood; Muhammad Moniruzzaman; Suzana Yusup; Tom Welton; Ionic liquids assisted processing of renewable resources for the fabrication of biodegradable composite materials. *Green Chemistry* **2017**, *19*, 2051-2075, 10.1039/c7gc00318h.
23. Noorul Adawiyah; Muhammad Moniruzzaman; Siti Hawatulaila; Masahiro Goto; Ionic liquids as a potential tool for drug delivery systems. *MedChemComm* **2016**, *7*, 1881-1897, 10.1039/c6md00358c.
24. Julia L Shamshina; Patrick S Barber; Robin D Rogers; Ionic liquids in drug delivery. *Expert Opinion on Drug Delivery* **2013**, *10*, 1367-1381, 10.1517/17425247.2013.808185.
25. A. M. A. Dias; A. R. Cortez; M. M. Barsan; J. B. Santos; C. M. A. Brett; H. C. de Sousa; Development of Greener Multi-Responsive Chitosan Biomaterials Doped with Biocompatible Ammonium Ionic Liquids. *ACS Sustainable Chemistry & Engineering* **2013**, *1*, 1480-1492, 10.1021/sc4002577.
26. Catherine King; Julia L. Shamshina; Gabriela Gurau; Paula Berton; Nur Farahnadiah Abdul Faruk Khan; Robin D. Rogers; A platform for more sustainable chitin films from an ionic liquid process. *Green Chemistry* **2016**, *19*, 117-126, 10.1039/c6gc02201d.
27. Chandrakant Mukesh; Dibyendu Mondal; Mukesh Sharma; Kamalesh Prasad; Choline chloride–thiourea, a deep eutectic solvent for the production of chitin nanofibers. *Carbohydrate Polymers* **2014**, *103*, 466-471, 10.1016/j.carbpol.2013.12.082.
28. Chieu D. Tran; Tamutsiwa M. Mututuvari; Cellulose, Chitosan, and Keratin Composite Materials. Controlled Drug Release. *Langmuir* **2015**, *31*, 1516-1526, 10.1021/la5034367.
29. Lijuan Hou; W. M. Ranodhi N. Udangawa; Anirudh Pochiraju; Wenjun Dong; Yingying Zheng; Robert J. Linhardt; Trevor J. Simmons; Synthesis of Heparin-Immobilized, Magnetically Addressable Cellulose Nanofibers for Biomedical Applications. *ACS Biomaterials Science & Engineering* **2016**, *2*, 1905-1913, 10.1021/acsbiomaterials.6b00273.
30. Márcia G. Ventura; Ana Inês Paninho; Ana V. M. Nunes; Isabel M. Fonseca; Luís C. Branco; Biocompatible locust bean gum mesoporous matrices prepared by ionic liquids and a scCO2 sustainable system. *RSC Advances* **2015**, *5*, 107700-107706, 10.1039/c5ra17314k.
31. Mohammed Halayqa; Maciej Zawadzki; Urszula Domańska; Andrzej Plichta; API-ammonium ionic liquid – Polymer compounds as a potential tool for delivery systems. *Journal of Molecular Liquids* **2017**, *248*, 972-980, 10.1016/j.molliq.2017.10.136.
32. Mohammed Halayqa; Maciej Zawadzki; Urszula Domańska; Andrzej Plichta; Polymer – Ionic liquid – Pharmaceutical conjugates as drug delivery systems. *Journal of Molecular Structure* **2018**, *1180*, 573-584, 10.1016/j.molstruc.2018.12.023.
33. Mehrdad Mahkam; Abdolrahim Abbaszad Rafi; Leila Mohammadzadeh Gheshlaghi; Preparation of novel pH-sensitive nanocomposites based on ionic-liquid modified montmorillonite for colon specific drug delivery system. *Polymer Composites* **2014**, *37*, 182-187, 10.1002/pc.23169.
34. Daoben Hua; Jianlin Jiang; Liangju Kuang; Jing Jiang; Wan Zheng; Hongjun Liang; Smart Chitosan-Based Stimuli-Responsive Nanocarriers for the Controlled Delivery of Hydrophobic Pharmaceuticals. *Macromolecules* **2011**, *44*, 1298-1302, 10.1021/ma102568p.
35. Louise Carson; Peter K. W. Chau; Martyn J. Earle; Manuela A. Gilea; Brendan F. Gilmore; Sean P. Gorman; Maureen T. McCann; Kenneth R. Seddon; Antibiofilm activities of 1-alkyl-3-methylimidazolium chloride ionic liquids. *Green Chemistry* **2009**, *11*, 492-497, 10.1039/b821842k.
36. Alessandro Busetti; Deborah E. Crawford; Martyn J. Earle; Manuela A. Gilea; Brendan F. Gilmore; Sean P. Gorman; Garry Laverty; Andrew F. Lowry; Martin McLaughlin; Kenneth R. Seddon; et al. Antimicrobial and antibiofilm activities of 1-alkylquinolinium bromide ionic liquids. *Green Chemistry* **2010**, *12*, 420-425, 10.1039/b919872e.
37. Freemantle, Michael; An introduction to ionic liquids. *Choice Reviews Online* **2010**, *47*, 47-6874, 10.5860/choice.47-6874.
38. Brendan F. Gilmore; Gavin P. Andrews; Gabor Borberly; Martyn J. Earle; Manuela A. Gilea; Sean P. Gorman; Andrew F. Lowry; Martin McLaughlin; Kenneth R. Seddon; Enhanced antimicrobial activities of 1-alkyl-3-methyl imidazolium ionic liquids based on silver or copper containing anions. *New Journal of Chemistry* **2013**, *37*, 873-876, 10.1039/c3nj40759d.

Keywords

biomedical applications;ionic liquids;IL-polymer based materials