Ionogels for Biomedical Applications

Bojan Kopilovic, Francisca A. e Silva, Augusto Q. Pedro, João A. P. Coutinho, Mara G. Freire*

CICECO - Aveiro Institute of Materials, Chemistry Department, University of Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal

*Corresponding author: maragfreire@ua.pt

Abstract

Biomedicine seeks technological solutions to tackle major diseases, while bypassing the limitations of current treatment options. The pursuit of cost-effective and safer strategies has, among others, been focused on the design and development of novel engineered materials. Ionogels are a class of composite materials consisting of an ionic liquid (IL) immobilized by an inorganic or a polymer matrix. They have a significant structural diversity and can be tailored to address unmet needs of modern biomedicine. Based on a literature survey of the published data, this chapter aims to overview significant uses of ionogels in biomedical applications, namely in drug delivery, wound dressing, as bioelectronics and for sensing. Methods for the preparation of ionogels are described and their properties, particularly concerning biomedical suitability, are discussed. The main types of ionogels and associated ILs as well as their accomplishments and limitations are highlighted and, whenever possible, compared to other approaches. A critical assessment of ionogels application in biomedicine is provided by a SWOT analysis, thereby supporting the identification of future research directions and challenges.

Keywords: Ionogel, ionic liquid, drug delivery, wound dressing, electronics, sensing

1. Introduction

With the ageing of the global population and growing prevalence of diseases such as cancer, cardiovascular diseases, and diabetes [1, 2], the development of innovative approaches to improve diagnosis and treatment are in high demand. To address these needs, engineered materials based on basic molecular building blocks have been developed, with polymeric materials being one of the principals. Most of these have been inspired by the simplicity and efficiency with which nature builds complex self-assembled structures to carry out different biological processes [3, 4]. Along the years, a variety of functional polymers has been studied for biomedical applications, [3-5] with their use in micelles, gels, composites, fibers, particles, brush polymers, form memory polymers, among others [6-8]. The use of these novel materials in a biomedical perspective is quite recent. However, according to the

findings reported so far, some outlined in this chapter, these materials have high potential due to their advanced features, including stimulus sensitivity, swelling ability, antimicrobial activity, high biocompatibility, resistance to rheological stress, and even self-healing capability [4, 9-11].

The definition of a gel varies in the literature and there is still a terminological confusion [12-14]. Herein, a gel is considered as a rigid viscoelastic substance created by a main component, a solvent, and a minor component, a gelator [15]. The gelator forms a solid-like microfibrillar network that percolates the solvent and inhibits its flow due to capillary forces [16]. Many of the gel characteristics, such as thermal and chemical stability, shape, dimensions, surface chemistry, mechanical properties and porosity can be tailored to targeted functionalities to satisfy specifications of a particular biomedical application [17]. Among the various gels that can be prepared, those with different characteristics, such as softness, highly porous structure, relatively hydrophilic nature, enhanced biodegradability, and good biocompatibility, may be suitable for biomedical applications [4, 12]. In this field, novel stimuli-responsive gels and ionic liquid (IL)-containing gels (ionogels) have gained a growing interest [18–20].

Ionogels are an innovative class of soft materials that gained significant popularity in recent years [9], [21]. They are comprised of ILs, which are incorporated as a supramolecular, polymeric or confined network. Some of these gels, with a melting point above 140 °C [17], [22], were shown to be smart polymeric conducting materials, merging the chemical versatility of an IL with the morphological flexibility of a biopolymer [23]. If properly designed, ionogels may exhibit numerous advantages, including high ionic conductivity [17, 22], high thermal and electrochemical stability [17, 22], enhanced biocompatibility and low (cyto)toxicity [24]. Ion conductivity values tend to be close to the conductivity values of neat ILs, suggesting that the ion mobility of the ions contained in the IL is not impaired by the presence of the gelator or confinement substrate [25]. In addition, cyclic voltammetry of these gels revealed that they are electrochemically stable, underscoring their usefulness for electrochemical applications [22]. For instance, bactericidal activity of imidazolium-based ionogels against gram-positive bacteria has also been reported in a study with polymeric ILs, allowing eradication of 100% of selected microorganisms [21]. Other biological activities can be designed by the incorporation of proper ILs [26]. All the described characteristics unlock the potential of using ionogels in many domains [27], namely as sensors [28], membranes [29], actuators and solar cells [17], but also in biomedicine for drug delivery [30], wound dressing [27], sensing [28] and as tissue regeneration matrices [24].

Figure 1 shows the distribution of works reporting on the application of ionogels in electronics and biomedicine (A), together with the incidence on different classes of ILs in the preparation of ionogels (B). Based on the previously mentioned properties, it is not surprising that ionogels remain mostly applied in the electrochemical field for sensing [28], batteries

[31] and as solar cells [27], although they are being increasingly investigated within a biomedicine perspective (cf. Figure 1A) [11, 30, 32]. The majority of studies on ionogels resorts to imidazolium-based ILs (cf. Figure 1B), which are among the most studied and employed ILs across the related scientific and industrial communities [33–35]. For instance, imidazolium-based ILs bearing Cl^-, Br^-, $[BF_4]^-$, and $[NTf_2]^-$ anions were shown to have higher thermal stability, superior electrochemical performance and good durability, justifying their interest in electronics [36–38]. However, various imidazolium-based ILs are challenged by their poor biocompatibility and high toxicity, making the transition towards bio-based ILs urgent to leverage the potential of ionogels within biomedical applications [39–41].

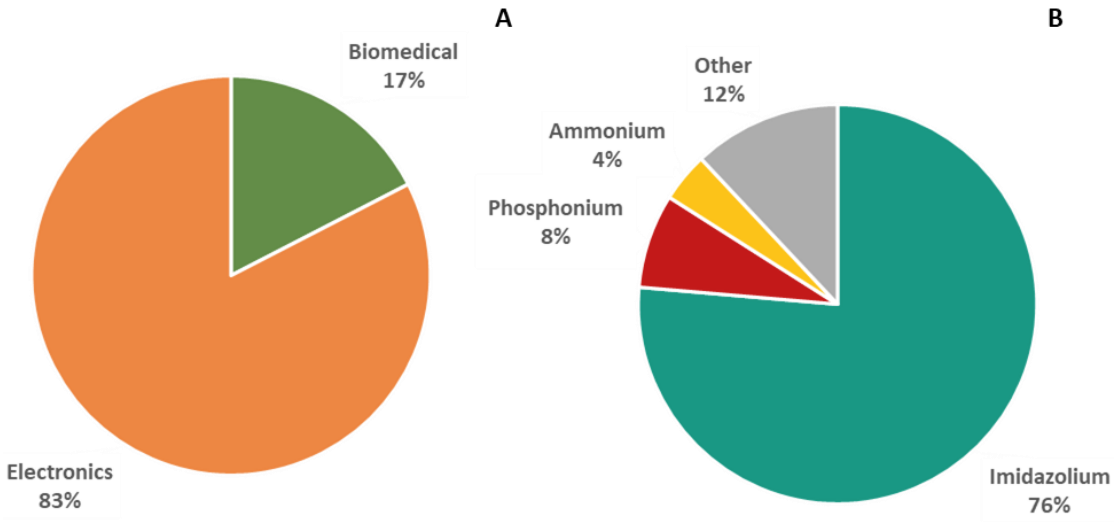

Figure 1. Distribution of works reporting on the use of ionogels for both electronics and biomedicine (A) and usage incidence of distinct ILs families for their preparation (B) in the past ten years (starting from 2010). Literature search was done in Web of Knowledge on February 11th, 2021, using the following keywords: ionogels, biomedicine, drug, cells, sensing and electronics.

This chapter aims to highlight the physical and chemical properties of ionogels that turn these materials relevant for biomedical applications, and to overview their most relevant applications in the biomedical field (Figure 2). Herein, the terms ionogel and gel are used interchangeably, resorting to ionogels or polymers comprising ILs.

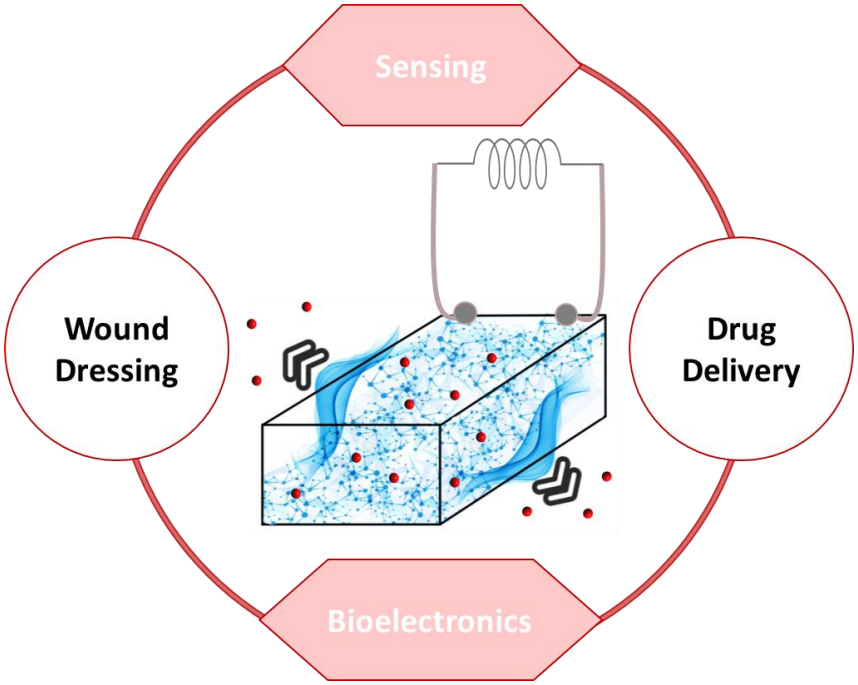

Figure 2. Outline of the information reviewed in this chapter related to the application of ionogels in biomedical applications.

2. Advances in biomedical applications by ionogels

ILs are a subject of high scientific interest since the mid-1990s, many being nowadays recognized as sustainable solvents and functional materials in many areas of science [42]. ILs are comprised of a large organic cation and an organic or inorganic anion. Due to the asymmetry and low charge density of their ions that prevents the formation of an ordered crystalline structure, ILs usually display melting points lower than common electrolytes, and by general definition below 100 °C. ILs' intrinsic properties can be easily modified by simply changing the combinations and/or substituent groups of the cation and the anion; such an ability to be finely-tuned and adapted to meet the needs of a given application justifies their designation of *designer solvents* [43, 44]. If correctly designed, ILs may present advantageous properties, such as negligible vapor pressure, high chemical and thermal stability, high ionic conductivity, non-flammability and high solvency/affinity for multiple compounds [45, 46].

As previously highlighted, a synergy is achieved in ionogels by combining the IL phase and the solid polymer phase: the liquid scattered or trapped within the solid retains the function and properties of the IL, yielding a gel with the desirable properties of both ILs (e.g. a range of tailored properties) and the solid (e.g., structural rigidity and practicality) [17]. Despite the intensive use of ionogels in electronics, the number of articles concerning ionogels for biomedical applications has been increasing throughout the last decade (Figure 3). It should

be additionally noticed that articles proposing new electronic platforms based on ionogels for biomedical application are also available [24, 32, 47]. This trend further highlights the potential of this kind of ionogels in healthcare. For instance, Yang *et al.* (2019) have recently developed a wearable IL-activated sensor, which provides effective monitoring of breathing, pulse wave, human joint motion, and plantar pressure [48]. This breathable, waterproof, washable sensor is envisaged for clothing purposes and it also has antibacterial properties [48].

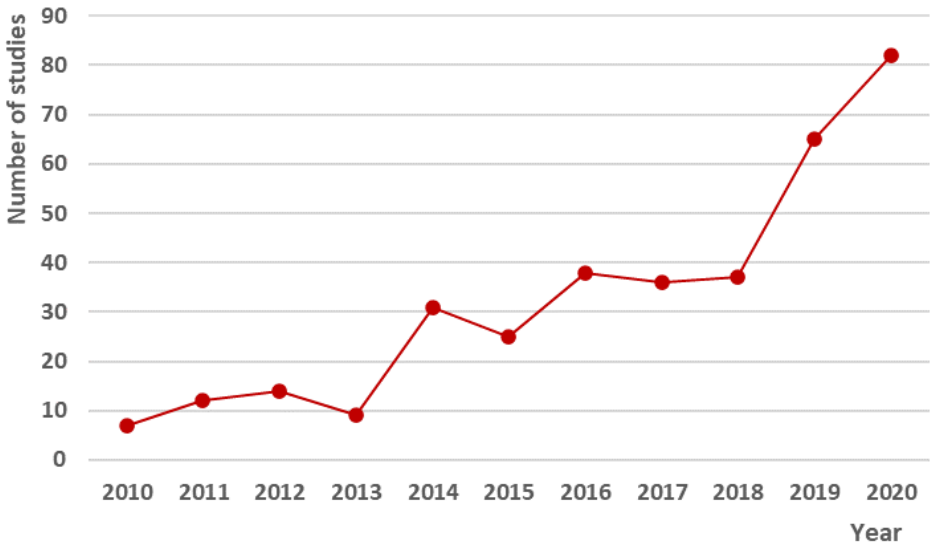

Figure 3. Number of studies reporting the use of ionogels in the last decade, starting from 2010. Data was obtained from the Web of Knowledge on February 11th, 2021, using the following keywords: ionogels, biomedicine, drug, cells, sensing and electronics.

Figure 4 showcases the incidence of several ILs' cations and anions in the preparation of ionogels for biomedical applications, together with their chemical structures. Table 1 provides these ILs' full names and corresponding abbreviations. In general, the ILs used are mostly comprised of imidazolium, but also of pyrrolidinium, quaternary ammonium, quaternary phosphonium and morpholinium cations, with several substituents/functionalizations. Regarding anions, halides (e.g., Cl^-, Br^-) are the most used, followed by carboxylates (e.g., $[C_1COO]^-$, $[Lac]^-$), and fluorinated (e.g., $[PF_6]^-$, $[NTf_2]^-$) ones, among others. These incidence patterns also consider electronic-related applications, notwithstanding a 15% decrease in the adoption of imidazolium-based ILs is noted in the biomedical field. Moreover, regarding the preparation of ionogels, those used for biomedical applications are mostly obtained by polymerization of either ILs containing a polymerizable group, or by building a polymer network within an IL.

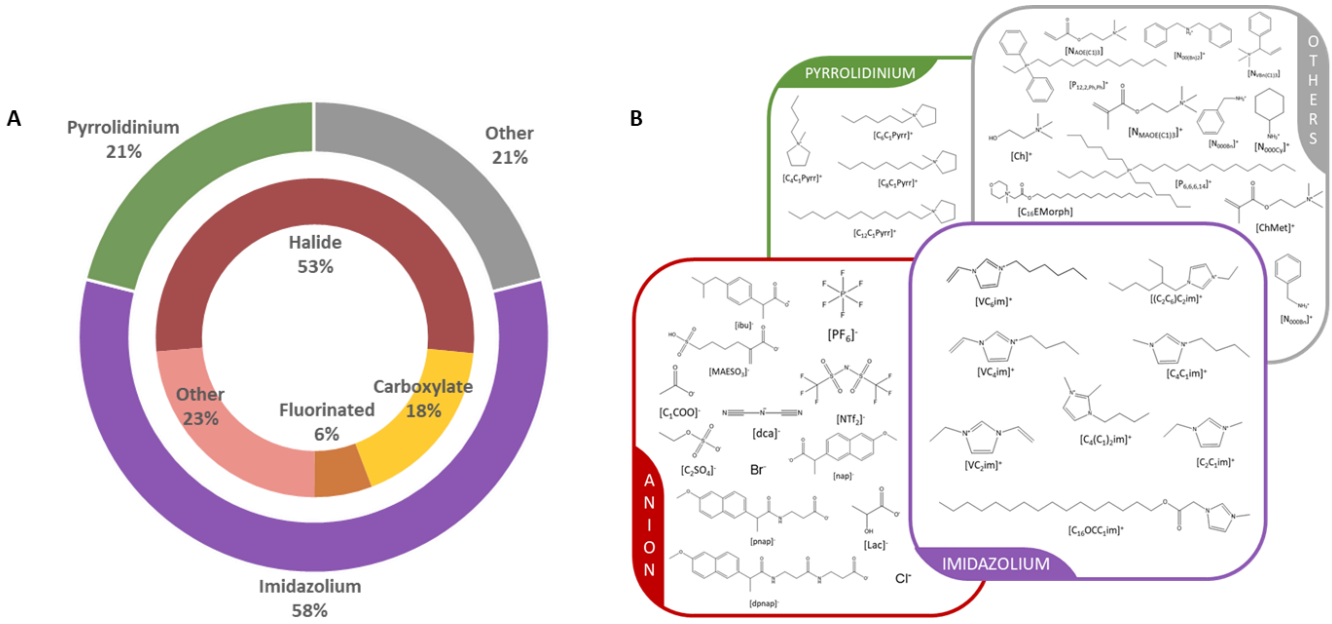

Figure 4. Distribution of ILs used for ionogels preparation discussed in this book chapter (A), Chemical structures of cations and anions mentioned herein (B).

Table 1. Name and abbreviations of the ILs considered in this book chapter.

IL	Abbreviation
(4-(2-(hexadecyloxy)-2-oxoethyl)-4-methylmorpholin-4-ium bromide	$[C_{16}EMorph]Br$
(vinylbenzyl)trimethylammonium chloride	$[N_{VBn(C1)3}]Cl$
[2-(acryloyloxy)ethyl]trimethylammonium chloride	$[N_{AOE(C1)3}]Cl$
[2-(methacryloyloxy)ethyl]trimethylammonium chloride	$[N_{MAOE(C1)3}]Cl$
1-(2-ethylhexyl)-3-ethylimidazolium hexafluorophosphate	$[(C_2C_6)C_2im][PF_6]$
1-butyl-1-methylpyrrolidinium bromide	$[C_4C_1Pyrr]Br$
1-butyl-2,3-dimethylimidazolium bis(trifluoromethanesulfonyl)imidate	$[C_4(C_1)_2im][NTf_2]$
1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imidate	$[C_4C_1im][NTf_2]$
1-butyl-3-methylimidazolium chloride	$[C_4C_1im]Cl$
1-butyl-3-methylimidazolium hexafluorophosphate	$[C_4C_1im][PF_6]$
1-dodecyl-1-methylpyrrolidinium bromide	$[C_{12}C_1Pyrr]Br$
1-ethyl-3-methylimidazolium acetate	$[C_2C_1im][C_1COO]$
1-ethyl-3-methylimidazolium dicyanamide	$[C_2C_1im][dca]$
1-ethyl-3-methylimidazolium ethylsulfate	$[C_2C_1im][C_2SO_4]$
1-hexyl-1-methylpyrrolidinium bromide	$[C_6C_1Pyrr]Br$
1-methyl-3-butylimidazolium ibuprofenate	$[C_4C_1im][ibu]$
1-octyl-1-methylpyrrolidinium bromide	$[C_8C_1Pyrr]Br$

1-vinyl-3-butyl-imidazolium acetate	$[VC_4im][C_1COO]$
1-vinyl-3-butyl-imidazolium bromide	$[VC_4im]Br$
1-vinyl-3-butyl-imidazolium chloride	$[VC_4im]Cl$
1-vinyl-3-ethyl-imidazolium acetate	$[VC_2im][C_1COO]$
1-vinyl-3-ethyl-imidazolium bromide	$[VC_2im]Br$
1-vinyl-3-ethylimidazolium dicynamide	$[VC_2im][dca]$
1-vinyl-3-hexylimidazolium bromide	$[VC_6im]Br$
2-cholinium methacrylate lactate	[ChMet][Lac]
3-methyl-1-(hexadecyloxycarbonylmethyl)imidazolium bromide	$[C_{16}OCC_1im]Br$
benzylammonium 2-(6-methoxynaphthalen-2-yl)propanoate	$[N_{000Bn}][nap]$
cholinium geranate	[Ch][Ge]
cyclohexylammonium 2-(6-methoxynaphthalen-2-yl)propanoate	$[N_{000Cy}][nap]$
dibenzylammonium 3-(2-(6-methoxynaphthalen-2-yl)propanamido)propanoate	$[N_{00(Bn)2}][pnap]$
benzylammonium 3-(3-(2-(6-methoxynaphthalen-2-yl)dipropanamido)propanoate	$[N_{000Bn}][dpnap]$
dibenzylammonium 3-(3-(2-(6-methoxynaphthalen-2-yl)dipropanamido)propanoate	$[N_{00(Bn)2}][dpnap]$
dodecylethyldiphenylphosphonium bis(trifluoromethanesulfonyl)imidate	$[P_{12,2,Ph,Ph}][NTf_2]$
trihexyl(tetradecyl)phosphonium dicyanamide	$[P_{6,6,6,14}][dca]$

2.1 Preparation and properties of ionogels

Advances during the past decades in biomedicine had a significant influence on the development of products derived from natural and synthetic sources, with biomimetic products as an evolving field [23, 49]. This prospect has led to the development of novel materials, including ionogels. An overview of the distribution of ionogel preparation routes for biomedical applications is shown with Figure 5.

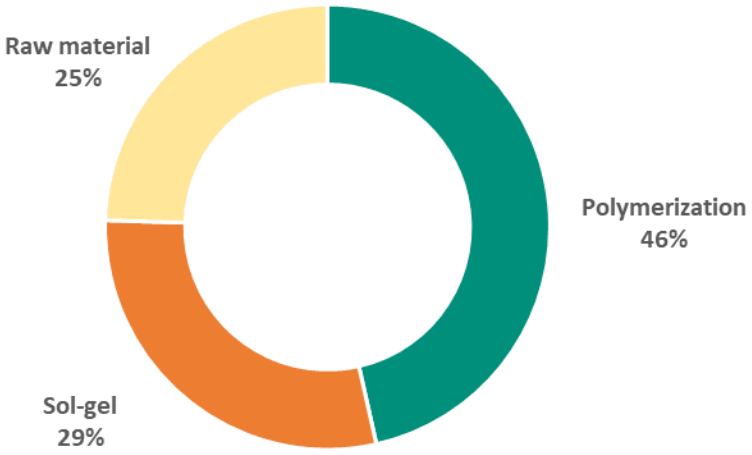

Figure 5. Distribution of the preparation routes of ionogels used in biomedicine that are discussed in this book chapter. Data search was done in Web of Knowledge on February 11th, 2021, using the following keywords: ionogels, biomedicine, drug, cells, sensing and electronics.

Depending on the nature of the solid-like network, the synthetic pathways of ionogels fall into three groups, which may be organic (using low molecular weight gelators or polymers), inorganic (frequently using oxide nanoparticles, carbon nanomaterials or sol-gel oxide networks), or hybrid organic-inorganic (typically polymers reinforced with inorganic fillers) as depicted in Figure 6 [17]. Herein, focus will be on every type of ionogel, except of oxide-based ionogels and without going into deeper detail about silica-based ionogels, since they were recently overviewed elsewhere [50, 51].

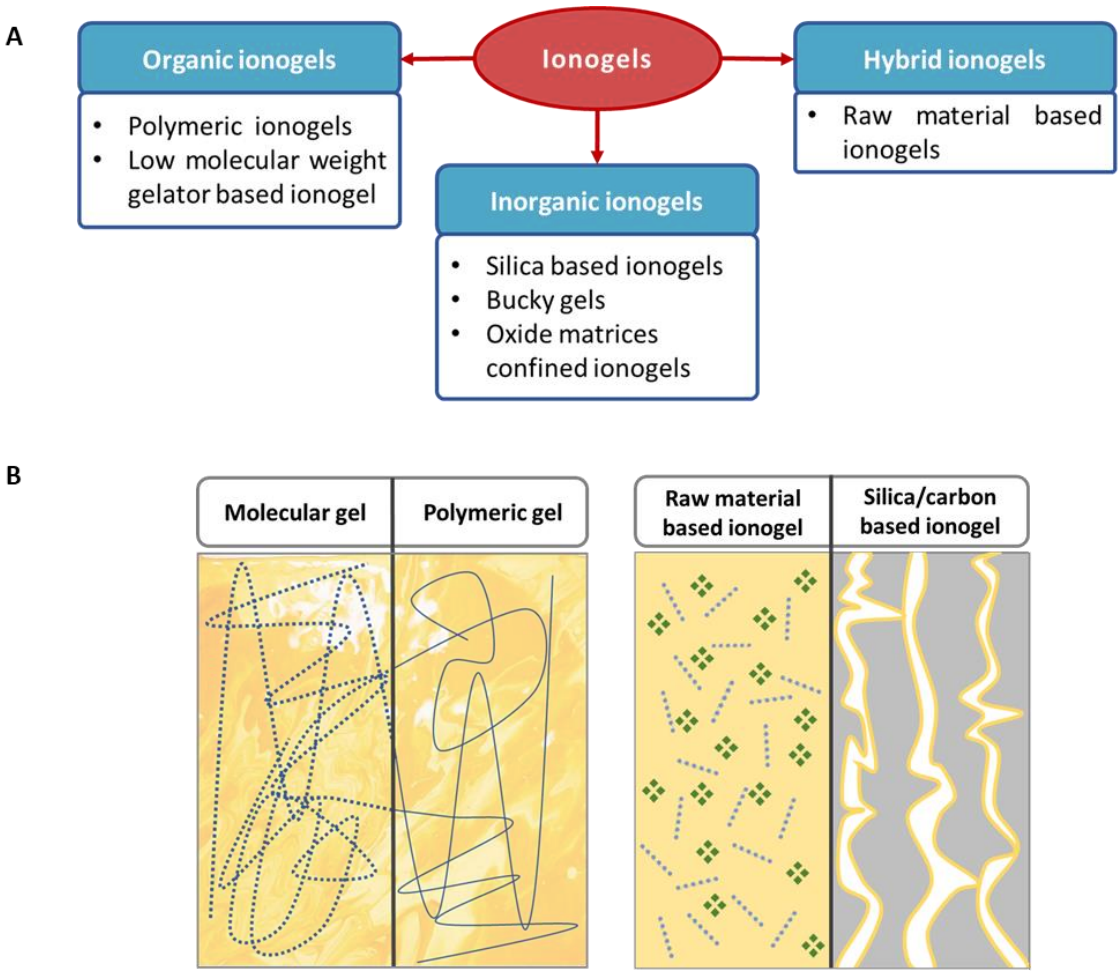

Figure 6. (a) General classification of ionogels, adapted from [59]. (b) Categorization of gels based on synthesis route, adapted from [60]; gels can either be comprised of polymeric (right of the vertical line) or molecular fibers (left of the vertical line) depicted on the left image; the illustration on the right shows to synthesis routes, the raw material based and the silica/carbon confinement-based route; the yellow color represents the IL.

It should be however highlighted that before using ionogels (or ILs) in medical purposes, their cyto/genotoxicities must be addressed. In fact, this represents a crucial step in the approval phase for medical and pharmaceutical products resorting to ILs and, hence, acts as an early exclusion factor in biomedical related applications. As mentioned before, rather than having an organic solvent or water as the solvent phase, ionogels are comprised of ILs within a polymeric structure mutually assembling a gel. Most studies in the field of polymeric ionogels have only focused on 1-alkyl-3-methylimidazolium-based ILs, rather than on ammonium, pyrrolidinium and other IL-based gels (Figure 4) [17, 25]. Significant progress has been made on cytotoxicity assays for ILs. Among the various cell lines that have been tested are human spontaneously immortalized human keratinocyte cell line (HaCaT) [54, 55], cervical carcinoma [56, 57], colon carcinoma cells (Caco-2) [55], [58], human hepatocellular carcinoma cells (HepG2) [59], human umbilical vein cell line (EA.hy926) [55]. Results reveal that the head groups are of moderate concern about their effect on lipophilicity and hence on IL cytotoxicity. In contrast to this, the alkyl side chain is the primary effect influencing cytotoxicity considering the structural nature of IL cations [56, 60]. It has been shown that most of the studied commercially available IL anions had no or minor cytotoxic effects when using these cell lines. In particular, cholinium-based ILs have been recognized as ILs that exhibiting the lowest cytotoxicity towards Caco-2, HepG2 and Ea.hy926 cell lines [55]. Overall, one of the most critical issues of using ILs is related to their cytotoxicity and biocompatibility. However, researchers thrive to develop ionogels using more biocompatible ILs, such as cholinium-based ones [24, 61]. In particular, cholinium-based ILs have been recognized as ILs that exhibiting the lowest cytotoxicity towards Caco-2, HepG2 and Ea.hy926 cell lines [55]. Overall, a deeper understanding of ionogels/ILs cytotoxicity is key to uncover their potential for broader implementation in biomedical applications.

2.1.1 Polymer-based ionogels

A common, efficient, and straightforward route of synthesizing ionogels is by radical polymerization of ILs monomers in another solvent [25]. One common feature for polymerizable ILs and ionogels formed using low molecular gelators, regardless of the type of solvent or gelator used, is the establishment of interconnected networked structures covering the entire volume of solvent during gelation [62, 63]. At this moment it is imperative to clarify that ILs can be polymerized (if they possess a polymerizable group in their chemical structure) and they can be solvents that fill in the cross-linked network of another polymer [25]. Polymerizable ILs are formed by dissolving the monomer and the corresponding amount of the crosslinker (usually a small quantity), adjusting the total concentration of the monomer [30]. Other compounds can subsequently be added to enhance the gels mechanical or self-healing properties, such as pharmaceuticals, metals, dextrose, glycerol, etc. [20, 64]. The reaction mixture occurs at a constant temperature, and sometimes at controlled humidity.

As an example [65], the radical polymerization of ILs comprising a vinyl group, e.g. [VC_2im]Br, with a crosslinker, results in a polyionic liquid gel, namely poly[VC_2im]Br. Commonly used crosslinkers include poly(vinyl alcohol) (PVA) [66], N,N,N',N'-tetramethylethylendiamine [9], glutaraldehyde [67], N,N0-methylenebis(acrylamide) [30] and 3-sulfopropylmethacrylate potassium [30]. The polymerization of several vinyl-alkyl-imidazolium ILs was already evaluated by disclosing the effect of the alkyl chain length and selected anion on the gelation process [18]. Overall, it was observed that both anion and alkyl chain length influenced the gelation process [18]. As an example, imidazolium-based ILs comprising I^- and $[Lac]^-$ did not form gels; on the other hand, similar ILs comprising $[PF_6]^-$ anion are not soluble in water, therefore no polymerization took place also in this case [68]. Furthermore, the polymerization of [VC_4im][C_1COO] in aqueous media could not be accomplished unlike that of [VC_2im][C_1COO], proving that longer alkyl chain lengths have a retarding effect on the polymerization process [18, 60]. The hydrophobicity also has an influence on polymerization, which was demonstrated by the unsuccessful polymerization of IL an with an octyl group in the side chain [18].

Supramolecular gels, or gels derived from small molecules, have been intensively studied. Small molecular weight gelators are known for being intrinsically diverse in chemical structures [62], and they can form hydrogels and organogels in solvents such as water and organic solvents, respectively [69], [70]. As a result of gelator self-assembly and aggregation by weak noncovalent interactions, such as H-bonding [71], hydrophobic interaction [72], π–π interaction [73], these gels are supramolecular in nature (i.e. supramolecular gels). The two pioneering works in this field were published nearly simultaneously in 2001, describing a glycolipid-derivative [68] and a cholesterol-derivative [63] as small-molecule IL gelators. The number of IL gelators has since then grown steadily, but not as significantly as the other two gelator types, hydrogelators and organogelators. Up to date the number of IL gelators does not exceed one hundred, while the corresponding number for organogelators must be beyond several hundreds [25]. Thereby, for researchers working in this area, relevant potential falls in the development of better IL gelators.

Ionogels have a significant advantage over hydrogels due to their negligible vapor pressure, which is a limiting factor in the case of water-based gels. Hydrogels gradually lose water during time, causing the material to become progressively brittle [74]. In addition to this, ionogels are more flexible and transparent than the equivalent hydrogels [74]. Given their suitable properties, polymeric ionogels are being used as drug loading devices [20], in disease monitoring and detection [75] and as dressing materials for wound healing [76], as it will be overviewed in section 2.2.

2.1.2 Sol-gel produced ionogels

The synthesis of ionogels was recently reported by sol-gel processing in ILs [77, 78], with two approaches found for the synthesis route: (i) the confinement of ILs within a matrix; and (ii) the ionogel formation through the conditioning of raw materials.

Dai *et al.* (2000) reported the pioneering work on sol-gel synthesis in an IL solvent, in 2000, where mesoporous silica with high surface area was prepared, from a mixture of tetramethoxysilane and formic acid in $[C_4C_1im][NTf_2]$. The IL, which had been removed at the end of the synthesis, was used as a template. Numerous sol-gel syntheses involving IL models have then been reported [17, 80, 81]. Confined ILs by the traditional sol-gel route are obtained after the removal of the liquid phase from the reaction mixture [82]. The solid matrix is commonly silica-based, although carbon-based matrices have also been reported [83]. After drying, the remaining porous solid loaded with a targeted compound is obtained. Traditionally, volatile solvents are being used for such purposes [78, 84]. However, the use of liquids without an apparent vapor pressure, such as ILs, delivers a stable solid-liquid system called ionogel [17]. It is also interesting to note that ILs are able to induce porosity in silica matrices [79,85]. Within this solid matrix, the confined IL fills a 3D-interconnected mesoporous structure creating a percolating network of ionic conduction. Although confined, the IL keeps the liquid-like dynamics [86]. This approach is, however, out of the scope of this chapter due to the number or relevant previous studies [50, 52, 87].

“Bucky” gels, or carbon nanotube (CNT)-based gels, are comprised of hexagonally organized sp2-hybridized carbon atoms of graphene layers, which have strong electronic and optical properties [17]. CNTs have excellent mechanical, electrical and thermal properties, but one major drawback is that they are difficult to process. A possible technique to improve solubility and processability is to absorb organic molecules on their surface [17]. Similarly as in the silica-based route, for the preparation “bucky” gels, Chernyshov *et al.* (2008) weighed graphite and one of three imidazolium- or the phosphonium-based IL in a precise ratio and further mixed intensively in tetrahydrofurane. After the evaporation of the solvent, viscous materials were obtained. Previously to this work, Fukushima (2003) noticed that single-walled carbon nanotubes when mixed with an imidazolium-based ionic IL formed gels after being ground. Phase transition and rheological properties indicated that the gels are formed by physical cross-linking of the bundles of nanotubes, mediated by local molecular IL ordering rather than by nanotubes' entanglement. The reported gels were thermally stable and did not show signs of shriveling [88, 89].

The breakthrough of using renewable sources led to an urge in developing sustainable materials. Accordingly, the recent field of ionogel synthesis via the conditioning of raw materials will be here briefly described. Renewable materials, such as biopolymers, can be utilized for many purposes and also for the synthesis of ionogels. Arvind Kumar and K. Srinivasa Rao (2014) reported the use of agarose and chitosan for ionogels formation. Agarose is an algal polysaccharide comprising repeatied D-galactose and 3,6-anhydro-L-

galactose units. It has excellent ability to form thermo-reversible gels in hot water [90]. The other component of the ionogel synthesis was chitosan, an extensively studied biodegradable, biocompatible, and antimicrobial compound. Both of these biopolymers have applications in food industry, biochemical fields, and have been extensively studied for pharmaceutical and biomedical purposes, namely for controlled release of drug, wound dressing and space filling implants [91–93]. Based on the knowledge that ILs have a high solvating ability for polymers derived from biomass, including agarose and chitosan [94, 95], powdered biopolymers were added to a preheated IL until their complete dissolution under continuous stirring and heating conditions. Afterwards, silver nitrate was added to the mixture, resulting in the formation of silver oxide nanoparticles [27]. The inclusion of silver oxide nanoparticles is useful for improving the mechanical strength, conductivity and antimicrobial properties of the composites, due to very strong optical/sensing, catalytic and antimicrobial properties [27]. Precipitation of the nanocomposite materials can be achieved by adding an antisolvent, resulting in the nanocomposite ionogels being produced after cooling.

Sol-gel ionogels have high potential to be used in a variety of fields. In addition to the targeted biomedical applications, sol-gel ionogels are promising materials for solid-state electrolytes, fuel cells, lithium batteries, quasi-solid dye sensitized solar cells, actuators, sensor or electronic devices [26, 27, 78, 83, 96]. Although ionogels obtained through polymerization have been the most studied, and therefore applied in more fields, sol-gel ionogels tend to be doped with other and new compounds targeting a specific application.

2.2. Ionogels in biomedical applications

The use of ionogels in the biomedical context is quite recent; nevertheless, this type of material seems to hold a great potential in this field [17, 26]. As aforementioned, one key property of these gels is their intrinsic task-specific nature associated to ILs, enabling to tailor their properties and, hence, the nature of their interactions and application performance [25]. Therefore, it can be assumed that the development of ionogels could have a significant impact on biomedicine by providing innovative solutions that might outperform current state-of-the-art technologies.

One of the shortcomings of synthetic polymers constituents of hydrogels, organogels or ionogels is their inherent nonbiodegradability, which in turn raises concerns when foreseeing biomedical applications. If on one hand this drawback is not a main obstacle if oral administration is envisaged, it is a critical issue for implantable biosensors or implantable drug delivery systems, further depending on the durability (temporary versus permanent) of the final application [97, 98]. Thus, current interest has been placed on developing materials with intrinsic biodegradability, namely based on polysaccharides, proteins, etc. [23]. Biopolymers such as cellulose, lignin, starch and keratin are examples of renewable polymers, which due

to their low price [27, 32, 96], are being increasingly applied to replace synthetic polymers [99, 100]. Nevertheless, even these biopolymers have drawbacks which limit their use in the development of new materials, e.g. the low solubility of lignin and cellulose. Remarkably, these limitations can be overcome with the use of ILs, in which lignin and cellulose dissolution is well-established [101, 102].

Ionogels for biomedical applications [26, 28] have focused on: (i) drug delivery and wound dressing; and (ii) bioelectronics and sensing. Impressive advances have been accomplished in this field, disclosing the versatility and utility of ionogels. A summary comprising the ionogel, preparation method, performance and target application is provided in Table 2. Their drug loading and drug delivery development is a well-researched area, where studies involving the loading and release of diclofenac, ibuprofen, insulin and doxorubicin by encapsulation or patches are included [20, 30, 103]. Since imidazolium- and pyrrolidinium-based ILs have been reported to have antibacterial properties, it has been investigated whether ionogels comprised of these ILs are of the same nature [25]. As verified with ILs, the corresponding ionogels also display antimicrobial activity, further supporting their use for antimicrobial purposes, including in wound dressing, scaffolding, and dressing materials [20, 27, 74]. Moreover, ionogels are used in real-time monitoring and detection of diseases [75]. These robust smart materials have multifunctional sensing properties, including pressure, bending, and twisting. These were demonstrated for designed sensors, which could be used to detect human breathing characteristics and in wearable equipment, as they can sense even slight changes in the surrounding environment [48].

Table 2. Summary of ionogel biomedical applications included in this chapter.

Ionogel	Preparation method	Performance (including main highlights e.g. drug loading, performance indicators of therapeutic efficiency)	Application	Ref
$[N_{VBn(C1)3}]$ Cl; N,N'-methylenebis(acrylamide); N,N,N',N'-tetramethylethylendiamine; ammoniumpersulfate $[N_{AOE(C1)3}]$Cl; N,N'-methylenebis(acrylamide); N,N,N',N'-tetramethylethylendiamine; ammoniumpersulfate $[N_{MAOE(C1)3}]$Cl; N,N'-methylenebis(acrylamide); N,N,N',N'-tetramethylethylendiamine; ammoniumpersulfate $[VC_2im]$Br; N,N'-methylenebis(acrylamide); N,N,N',N'-tetramethylethylendiamine; ammoniumpersulfate	polymerization	$[VC_2im]$Br achieved the best result in quantitative cell viability assay with a relative cell viability of 98.4%. The other gels are considered to have low toxicity, since they did not reduce the cell vitality by more than 20%.	Drug delivery, implant coating	[30]
$[VC_2im]$Br; tetramethylethylenediamine; $[VC_4im]$Br; tetramethylethylenediamine; $[VC_4im]$Cl; tetramethylethylenediamine; $[VC_2im][C_1COO]$; tetramethylethylenediamine;	polymerization	The gels were compressible more than 60%, pressing half of their initial length compared to Ca-alginate hydrogels.	Drug delivery, scaffolds	[18]

Table 2. continued

Ionogel	Preparation method	Performance (including main highlights e.g. drug loading, performance indicators of therapeutic efficiency)	Application	Ref
$[C_4C_1im][ibu]$; tetramethoxysilane	sol-gel	The loading of $[C_4C_1im][ibu]$ in the ionogels was about 0.80 g of ibuprofen/g of dried silica.	Drug delivery	[26]
$[C_2C_1im][C_2SO_4]$; Poly(N-isopropylacrylamide); N,N'-methylenebisacrylamide; 2,2-Dimethoxy-2-phenylacetophenone	polymerization	The ionogel is more flexible and transparent than the equivalent hydrogel. The rate of water uptake for the ionogel was found to be ≈≈30 times larger.	Drug delivery	[74]
$[C_{16}OCC_1im]$ Br	sol-gel	The opaque gel encapsulated ~40.4% of diclofenac, while 72.3% of imatinib mesylate was encapsulated. The transparent gel encapsulated 1.4% of diclofenac, whereas 53.59% of imatinib mesylate was encapsulated.	Drug delivery and adsorbent	[108]
$[C_4C_1im]Cl$; Chitosan; agarose	sol-gel	$T_{gelation}$ (°C): 38; $T_{melting}$ (°C): 80; Gel strength (g cm^{-2}) at 30 °C: 590; Conductivity κ ionogel (mS cm^{-1}) at 25 °C: 0.675	Drug delivery, antimicrobial agent	[27]
$[C_{16}EMorph]Br$; poly(vinyl alcohol); dextrose; $B(OH)^{4-}$	polymerization	A ≈≈82.3% cumulative release of doxorubicin at 37 °C, pH 5.0 after 50 h was noticed (~53 % release at 25 °C). Acidic pH accelerates the release of doxorubicin.	Drug delivery	[20]
$[N_{MAOE(C1)3}]Cl$; N,N0-methylenebis(acrylamide); ammoniumpersulfate $K[MAESO_3]$; N,N0-methylenebis(acrylamide); ammoniumpersulfate	polymerization	Release times could be increased by holding the drug back through developed electrostatic interactions.	Drug delivery	[9]

Table 2. continued

Ionogel	Preparation method	Performance (including main highlights e.g. drug loading, performance indicators of therapeutic efficiency)	Application	Ref
[Ch][Ge]; Poly(vinyl alcohol)	polymerization	*In vitro* transport experiments- show that patches enhance insulin transport by more than 30% in a coculture model when compared to equivalent concentrations of [Ch][Ge] solution. A reduction in the long-term effect on the epithelium, while also limiting the amount of drug lost by epithelial cell uptake in oral delivery, can be achieved by the localization of patches.	Insulin oral path delivery	[66]
[VC_2im]Br; N,N0-methylenebis(acrylamide); [VC_4im]Cl; N,N0-methylenebis(acrylamide); [VC_4im]Br; N,N0-methylenebis(acrylamide); [$N_{VBn(C1)3}$]Cl; N,N0-methylenebis(acrylamide); [$N_{AOE(C1)3}$]Cl; N,N0-methylenebis(acrylamide); [$N_{MAOE(C1\ )3}$]Cl; N,N0-methylenebis(acrylamide);	polymerization	Antibacterial effect. Outstanding results were achieved by using imidazolium-based hydrogels having a killing efficiency of at least 95% of *Staphylococcus aureus Xen 30* and *Pseudomonas aeruginosa Xen 5*.	Implants, drug delivery systems, stent coatings	[21]
[C_4C_1Pyrr]Br; poly(vinyl alcohol); $B(OH)^{4-}$ [C_6C_1Pyrr]Br; poly(vinyl alcohol); $B(OH)^{4-}$ [C_8C_1Pyrr]Br; poly(vinyl alcohol); $B(OH)^{4-}$ [$C_{12}C_1$Pyrr]Br; poly(vinyl alcohol); $B(OH)^{4-}$	polymerization	ILs with longer alkyl chain exhibited better antibacterial activities against *Escherichia coli* and *Staphylococcus aureus*.	Wound healing	[76]

Table 2. continued

Ionogel	Preparation method	Performance (including main highlights e.g. drug loading, performance indicators of therapeutic efficiency)	Application	Ref
$[C_4C_1im]Cl$; cellulose; chitin	sol-gel	Ionogel reinforced with chitosan DD 84% showed the greatest viscoelastic properties (G': 10.6 kPa, G": 20.6–1.7 kPa, and η*: 200–0.05 kPa s).	Scaffolds for wound management	[96]
$[N_{000Cy}][nap]$; methylsalicylate $[N_{000Bn}][nap]$; methylsalicylate $[N_{00(Bn)2}][pnap]$; methylsalicylate $[N_{000Bn}][dpnap]$; methylsalicylate $[N_{00(Bn)2}][dpnap]$; methylsalicylate	sol-gel	All the mice from two the groups were found to be healthy with fur grown on their back skin after two weeks of receiving the last dose of the topical gel.	Skin patch	[19]
[ChMet][Lac]; cellulose; 2-dimethylaminoethylmethacrylate; dimethoxy-2-phenylacetophenone	polymerization	These ionogels were comprised of 60 wt% free ionic liquid and 5% cellulose. The ionogels were transparent, indicating good cellulose processability.	Bioelectronics, sensor for health monitoring	[61]
$[C_4C_1im][dca]$; poly(vinyl alcohol); gallic acid	sol-gel	The supramolecular iongels are flexible and can withstand large elastic deformations with full recovery.	No application, yet useful as scaffold	[119]
$[C_2C_1im][C_1COO]$; glutaraldehyde; chitosan	sol-gel	High termal stability was shown by the ionogel. The confined $[C_2C_1im][C_1COO]$ and the chitosan matrix start to thermally decompose at 185 °C and 259 °C, respectively.	Sensor	[67]
$[VC_2im][dca]$; ammonium persulfate	polymerization	Electrical properties recovery after 4 s. The repaired ionogels bear stretching to about 150%.	Sensor for breathing monitoring	[75]

Table 2. continued

Ionogel	Preparation method	Performance (including main highlights e.g. drug loading, performance indicators of therapeutic efficiency)	Application	Ref
$[C_4C_1im][PF_6]$; graphite; ascorbic acid; nafion $[C_4C_1im][NTf_2]$; graphite; ascorbic acid; nafion $[C_4(C_1)_2im][NTf_2]$; graphite; ascorbic acid; nafion $[(C_2C_6)C_2im][PF_6]$; graphite; ascorbic acid; nafion $[P_{12,2,Ph,Ph}][NTf_2]$; graphite; ascorbic acid; nafion	sol-gel	Small quantities of catecholamines were detected, e.g., 5.03±0.03 μg mL^{-1} of adrenaline.	Sensing for biomolecules	[83]
$[P_{6,6,6,14}][dca]$; poly(N-isopropylacrylamide); N,N-methylenebis(acrylamide); dimethoxy-phenylacetophenone	polymerization	Ionogels were used for a visual monitoring the pH of sweat generated during exercise. Designed ionogel bars were comprised of the following pH indicators: bromocresol green (pH 3.8-5.6), bromocresol purple (pH 5.2-6.8) and bromothymol blue (pH 6.0-7.6).	Sensing for sweat pH	[47]
$[C_4C_1im][PF_6]$; cotton textile and CA film; silver nanowires	sol-gel	The sensitivities for the sensor are 4.46 kPa^{-1} below the pressure of 0.5 kPa, 0.312 kPa^{-1} in the pressure range 0.5-10 kPa, and 0.0143 kPa^{-1} in the pressure range 10-120 kPa.	Motion sensing	[48]
$[VC_2im][dca]$; N,N'-methylene bis(acrylamide), ammoniumpersulfate	sol-gel	The ionogel-based sensor showed high sensitivity of 15.4 kPa^{-1}, a small hysteresis of 5.36%, and a low detection limit of 5 Pa.	Motion sensing	[117]

2.2.1. Drug delivery and wound dressing

Throughout the past decades, drug delivery has been a target of research to improve therapeutic efficiency, aiming both a controlled and target-specific release. Developed materials for drug delivery include liposomes, microspheres, nanomaterials, gels, among others [3, 11, 104]. Drug carriers must have excellent biocompatibility and biodegradability. Recently, stimuli-responsive hydrogels have been developed since they can respond to external stimuli (e.g., heat and pH), enabling a controlled drug release [11, 104]. Meanwhile, major progress has been done for improving healthcare worldwide. In addition to drug delivery, there is a high interest in improving healing, with more than 3000 products designed to treat various forms of wounds [105]. Nonetheless, wound healing is a burdensome and sometimes painful process, which requires a suitable environment to promote healing process [106].

The ionogels, preparation methods, performance and target drug delivery of wound dressing application are summarized in Table 2. Kuddushi *et al.* (2020) studied the loading ability of polymeric ionogels comprising IL-based surfactants polymerized with poly(vinyl) alcohol for doxorubicin release. ILs based on morpholinium cation with distinct alkyl side chain lengths ([C_nEMorph]Br, with n = 12, 14 and 16) were used. The authors observed that [C_{16}EMorph]Br-based ionogels loaded with doxorubicin, an anthracycline chemotherapy drug, accelerated doxorubicin release at acidic pH, with cumulative release of ≈82.3% after 50h at 37 °C and pH 5.0. However, at 25 °C, doxorubicin release decreases to ≈53 % for the same remaining conditions. The same authors [103] further found that the critical concentration of gelation was 25.20, 22.60, and 8.80% (w/v) for [C_{12}EMorph]Br, [C_{14}EMorph]Br and [C_{16}EMorph]Br, respectively. The authors found that the inclusion of ester-functionalized groups in the cation side chain of IL-based surfactants exhibited better surface-active properties than the nonfunctionalized and vinyl-functionalized IL-based surfactants. Moreover, by substituting a methyl group in the IL by a methylcarboxylate (−CH_2COOH) group, it was found an increase in the surface activity [107] and biodegradability [108, 109]. As a result, ILs act as low molecular weight gelators (LMWGs), enabling the tailoring of ionogels properties. During the development of ionogels, the authors [103] observed a gel-to-gel transition (opaque to transparent) upon increasing the temperature above 48.5 °C, revealing that the solution undergoes a phase transition from isotropic to turbid due to the increased size of the aggregates. In this later work [103], the encapsulation efficiency of the opaque and transparent gels was investigated for two pharmaceuticals, sodium salt forms of diclofenac and imatinibmesylate. The opaque gel was able to encapsulate 40.4% of diclofenac and 72.3% of imatinibmesylate. On the other hand, the transparent gel encapsulates only 1.4% of diclofenac and 53.59% of imatinibmesylate.

Overall, by controlling ionogels preparation conditions and gel-to-gel transition, the encapsulation capacity can therefore be improved.

Owing to the large and adjustable pore size of the polymer matrix, drugs are often rapidly washed out from polymer-based ionogels. Claus, Eickner, *et al.* (2020) however, attempted to develop ionogels able to induce a decrease in the initial burst release and an eventual elongation of the total release. The authors decided to integrate an ionic drug into a counterionic gel matrix, in which sulfonic acid groups were selected to establish ion-ion interactions with the drug. Accordingly, the electrostatic nature of the interactions affected the release rate, demonstrating a strong decrease in the release rate. Polymerized IL gels comprised of poly[$N_{MAOE(C1)3}$]Cl and 3-sulfoprorylmethacrylate potassium (MAE-SO3) were loaded with ibuprofen and timolol maleate, respectively. The loaded drugs concentrations were almost 2000 µg/mL. The material showed promising applications for the subconjunctival space, middle or inner ear [30]. Other drugs have confined in ionogels, such as ibuprofen that was encapsulated by a one-step procedure in novel porous functionalized silica [26]. The authors synthesized [C_4C_1im][ibu] by ion-exchange reaction and further encapsulated the IL within functionalized silica, forming an ionogel. Loading of [C_4C_1im][ibu] in ionogels was evaluated by thermogravimetric analysis, and determined to be about 0.80 g of ibuprofen/g of dried silica. These novel ionogel materials had a release kinetics slower than with crystalline ibuprofen and pure ibuprofenate IL. At 10 min of drug release studies, around 35% ibuprofen was released from the ionogel, whereas 80% of ibuprofen was released from [C_4C_1im][ibu] in the same time period. These results demonstrate that ionogels act as drug depot for controlled delivery.

Due to the increasing number of patients with diabetes there is an urgent need for the development of a widely available, efficient and non-invasive, oral insulin drug delivery platform [110]. Peng *et al.* (2020) developed tunable ionogels and investigated their potential and applicability in insulin drug delivery. The authors described a method of encapsulating [Ch][Ge] within a poly(vinyl) alcohol solid network. The authors described two preparation methods of the patches – by drying and free thawing. The ionogels demonstrated the potential to improve intestinal absorption of insulin. Due to the ability of [Ch][Ge] to disrupt epithelial tight junctions, enabling drugs to pass through the paracellular route, they designed the application of the materials for oral delivery. It has also been shown that [Ch][Ge] has the potential to extend the storage of insulin and reduce the activity of enzymes such as trypsin, which usually pose an additional threat to biologics administered orally. These mucoadhesive ionogel patches are designed to adhere to the intestine. Insulin was released rapidly in the dried patch mentioned, completing 100% release within 2 h. In comparison, the freeze thawed type, with 40% release after 5 h, released insulin in a more regulated fashion. The tested cells showed a significantly lower uptake of drug, 2-fold lower when using the ionogel in comparison with the saline control system. Localizing the developed patches allows a

reduction in the long-term effects on the epithelium, and quite beneficially limits the amount of drug lost by epithelial cell uptake.

Among other applications, ionogels presenting antibacterial activity can be used as scaffolds and as wound dressing materials. Villar-Chavero *et al.* (2019) developed new ionogels using $[C_4C_1im]Cl$ reinforced with chitosan (deacetylation degree: 54, 62, 69, 77 and 84%) as scaffolds for wound management. The authors provided rheological and thermal properties of the materials, with the rheological properties revealing a strong dependence on the deacetylation degree (DD) of chitosan. Elasticity, as well as the gel strength and the complex viscosity, generally increased as the DD increased because of the physical interactions between chitosan and cellulose in the ionogel. The thermal properties of these thermoreversible materials were shown to be independent of the chitosan DD. Lastly, authors highlighted the ionogel reinforced with chitosan DD 84% for having the greatest viscoelastic properties (G': ≈10.6 kPa, G": 20.6–1.7 kPa, and η*: 200–0.05 kPa s), although no application of the developed ionogels was performed. Moreover, Arvind Kumar and K. Srinivasa Rao (2014) designed a similar ionogel also based on $[C_4C_1im]Cl$ and chitosan and agarose. These ionogels were coated with silver oxide nanoparticles, which along with chitosan also display antimicrobial activity.

Given the potential applications of ionogels in antibacterial dressings and topical administration, Yu *et al.* (2020) designed multifunctional gels that are expected to overcome multiple limitations of currently available antibiotics. Authors subjected tetrahydroxyborate anions to interact with two distinct cis-diol groups on PVA to yield the formation of a gel in the presence of 1-alkyl-1-methylpyrrolidinium-based ILs ($[C_nC_1Pyrr]Br$, with n = 4, 6, 8, 12). Considering that $[C_nC_1Pyrr]Br$ displays antibacterial activity, the corresponding ionogels were evaluated and proven to have a bactericidal effect on *Escherichia coli* and *Staphylococcus aureus*, which intensifies with the length of the alkyl chain of the IL cation. Also, the injectable gel has high plasticity and good adhesive properties, which can be adapted to the shape of various wounds, such as on human knuckle skin. A synergistic effect of multihydroxyl structures and dynamic covalent bonds results in a self-healing process occurring in approximately 2 min. These materials are also susceptible to the presence of saccharide molecules, such as glucose, meaning that they can be further employed for glucose sensing or self-regulated insulin release.

In summary, polymeric ionogels are predominantly used in drug delivery and wound dressing application. If properly designed, they can display better performance (e.g., drug loading capacity, mechanical characteristics, and thermal stability) than conventional materials. Contrarily to drug delivery and wound dressing, mainly obtained by polymerization, sol-gel produced ionogels are mainly used in bioelectronics and sensing. Recently, raw material-based ionogels are being used since the use of potentially toxic cross-

linkers is avoided and ionogels properties can be further improved by incorporating additional compounds.

2.2.2. Bioelectronics and sensing

The integration of ILs into gels is beneficial since it can lead to materials with the inherent advantages of ILs, ready for bioelectronics and sensing applications within a solid or semi-solid gel-type structure [28]. Especially interesting is the potential of wearable devices [111]. This field is growing quickly, as the healthcare economy gradually leads to the need for online control of patient progress rather than the existing hospital-focused model [28, 48, 75]. The ionogels, preparation methods, performance and target bioelectronics and sensing applications are summarized in Table 2.

An example of ionogels applied in bioelectronics was reported by Guyomard-Lack *et al.* (2015) They have produced thermally stable ionogels based on chitosan chemically crosslinked with glutaraldehyde in $[C_2C_1im][Ac]$. This IL was already reported for biopolymer dissolution due to its desirable properties, such as low toxicity (LD_{50} > 2000 mg kg^{-1}), low corrosiveness, low melting point, low viscosity, and favorable biodegradability [109, 112]. This is due to its short alkyl side chain and benign acetate anion. In comparison with most used imidazolium-based ILs, $[C_2C_1im][Ac]$ is predicted to be less toxic and already reached the REACH licensing [40]. Despite their relevance, the authors have not tested these biopolymer-based ionogels for any application. Isik *et al.* (2014) produced a biocompatible cellulose/cholinium-based ionogel comprising [ChMet][Lac], which was afterwards photopolymerized in the presence of crosslinkers (2-dimethylaminoethylmethacrylate, dimethoxy-2-phenylacetophenone). Up to 5 wt% of cellulose, the obtained ionogel was a soft, jelly-like transparent material, but above this value the ionogel decreased in transparency. Compared with ionogels without the crosslinker, ionogels with 4 wt% crosslinker displayed an enhanced integrity. These materials are important for emerging technologies comprising low toxicity cholinium-based ILs, widening their application in fields such as bioelectronics discussed below.

Adrenalin plays an important role in the central nervous and cardiovascular systems, and it is also active in a broad variety of metabolic processes, as well as other catecholamine neurotransmitters such as dopamine and dobutamine (the latter a cardiovascular pharmaceutical). Awareness of the effect of these biomolecules on the human body and their monitoring is highly important in clinical medicine [113]. Chernyshov *et al.* (2008) designed printable sensors based on carbon paste electrodes modified with ILs ($[P_{12,2,Ph,Ph}][NTf_2]$, $[(C_2C_6)C_2im][PF_6]$, $[C_4(C_1)_2im][NTf_2]$, $[C_4C_1im][NTf_2]$, $[C_4C_1im][PF_6]$) for the detection of these biomolecules. They reported that catecholamine selectivity is improved in the presence of ascorbic acid (Nafion additive), and that analyte pre-concentration was achieved with

different ILs. These ionogels were used as sensors for the electrochemical determination of aqueous solutions of adrenaline, dobutamine and dopamine with detection limits of (5.3 ± 0.1) × 10^{-8} M, (1.3 ± 0.1) × 10^{-7} M, and (1.2 ± 0.1) × 10^{-6} M, respectively, as determined by cyclic voltammetry. Moreover, the authors reported that the detection limit can be lowered with the introduction of additional components (Co(III)tetrakis-(tert-butyl)-phthalocyanine additive) into the paste [83]. This type of sensor can be useful within biomedical applications for the monitoring of catecholamines, as they can be clinically relevant biomarkers and are associated with several diseases, such as Alzheimer's and Parkinson [114].

Monitoring human body signs comes along with illness treatment and recovery. Therefore, wearable sensors are relevant for personalized health monitoring and assessment, as well as disease diagnosis. They must be convenient, portable and available at any location to all, including the elderly people with serious diseases [115, 116]. Wang *et al.* (2019) developed temperature-sensitive polymeric ionogels comprising [VC_2im][dca] that could detect characteristic signs in human breathing and could be used for disease detection. The designed ionogels exhibited high transparency, high conductivity, exceptional stretchability and self-healing characteristics. Surprisingly, just 4s after cutting the ionogel into two pieces, it recovers its electrical properties and the ionogels could endure stretching to about 150%. This temperature-sensitive sensor could detect various states of human respiration under different conditions, suggesting a potential opportunity for the use in health monitoring and illness recovery. These materials can be used as wearable devices; however, current wearable electronic devices often serve as an external part of clothing and demonstrate minimal flexibility with different textile materials. Remarkably, Yang *et al.* (2019) overcame this limitation and reported a straightforward, low-cost, and user-friendly approach to the manufacturing of wearable sensors based on commercial textiles, represented in Figure 7. Accordingly, the ionogel is an active sensing material and this is achieved by loading the IL onto the textile fabric. The authors selected [C_4C_1im][PF_6] and loaded it onto the fabric skeleton, and then coated the material with silver nanowires as electrodes. The textile can detect different human movements from athletic or natural movements, and it can also track biomechanical signals such as breathing, heartbeat, and pulse waveform.

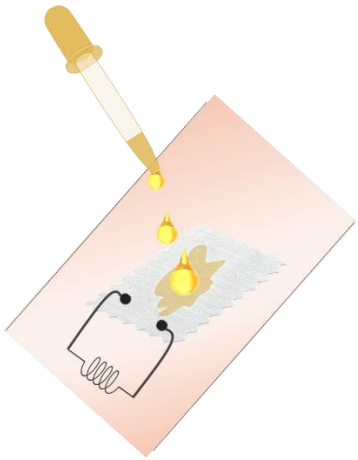

Figure 7. Illustration of an IL-loaded textile material, acting as a wearable ionogel-based sensor for human health monitoring.

On the other hand, Zhang *et al.* (2018) have fabricated ionogels by *in situ* polymerization of [VC_2im][dca]. These highly sensitive ionogels were able to detect slight ambient changes, including a gentle touch, a small leaf or flower petal and even weak gas flow. Other than exhibiting force-sensing characteristics and high conductivity, the developed ionogels showed high sensitivity of 15.4 kPa^{-1}, a hysteresis of 5.36%, and a low detection limit of 5 Pa. Having such features allow these materials to be used for the detection of human or robot interactions with the environment – e.g. as artificial skin scaffolds [118]. Benito-Lopez *et al.* (2010) reported the design of an outstanding ionogel-based wearable, robust, flexible and disposable barcode system that can be used for the real-time monitoring of sweat pH. It is an entirely non-invasive method of assessing the bodily status of the wearer, guaranteeing well-being. Moreover, the authors could accurately obtain pH values by simply observing the [$P_{6,6,6,14}$][dca] comprised barcode color and comparing them with a standard color chart. In addition, by using built-in Light Emitting Diodes (LEDs), the response can be tracked online, providing continuous feedback of the sweat chemistry with a minimal power demand.

Luque *et al.* (2020) prepared ionogels by supramolecular crosslinking between polyphenol molecules such as gallic acid, pyrogallol, and tannic acid with a biocompatible polymer - poly(vinyl alcohol), in the presence of [C_2C_1im]Br and [C_2C_1im][DCA]. The supramolecular interactions, which take place between poly(vinyl alcohol) and polyphenol molecules via hydrogen bonding while crosslinking the IL, affords the gel-like nature of these materials. The authors have also noted that these ionogels show a thermoreversible behavior with transition temperatures between 87 and 110 °C. Moreover, the formed gels are flexible and can withstand large elastic deformations (40% under compression) with full recovery. Authors have not reported any specific application. However, these polyphenol-based thermoreversible ionogels demonstrate ample justification for their future use as printable

electrolytes for bioelectronics and as dressing materials due to their flexibility and ability to withstand large elastic deformations with full recovery.

In conclusion, sol-gel derived ionogels have been the main type investigated in the field of sensing and bioelectronics. Overall, ionogels have shown great potential for application in wearable electronics due to their excellent conductivity, stability, and biocompatibility.

3. Critical assessment of ionogels application in the biomedical field

Ionogels, either polymer-based or prepared by sol-gel procedures, have been extensively investigated as advanced materials for wound dressing and drug delivery, as well as in bioelectronics and biosensing, as overviewed above. Based on the current state-of-the-art technologies, a SWOT analysis on the ionogels application in the biomedical field was carried out, being shown in Figure 8.

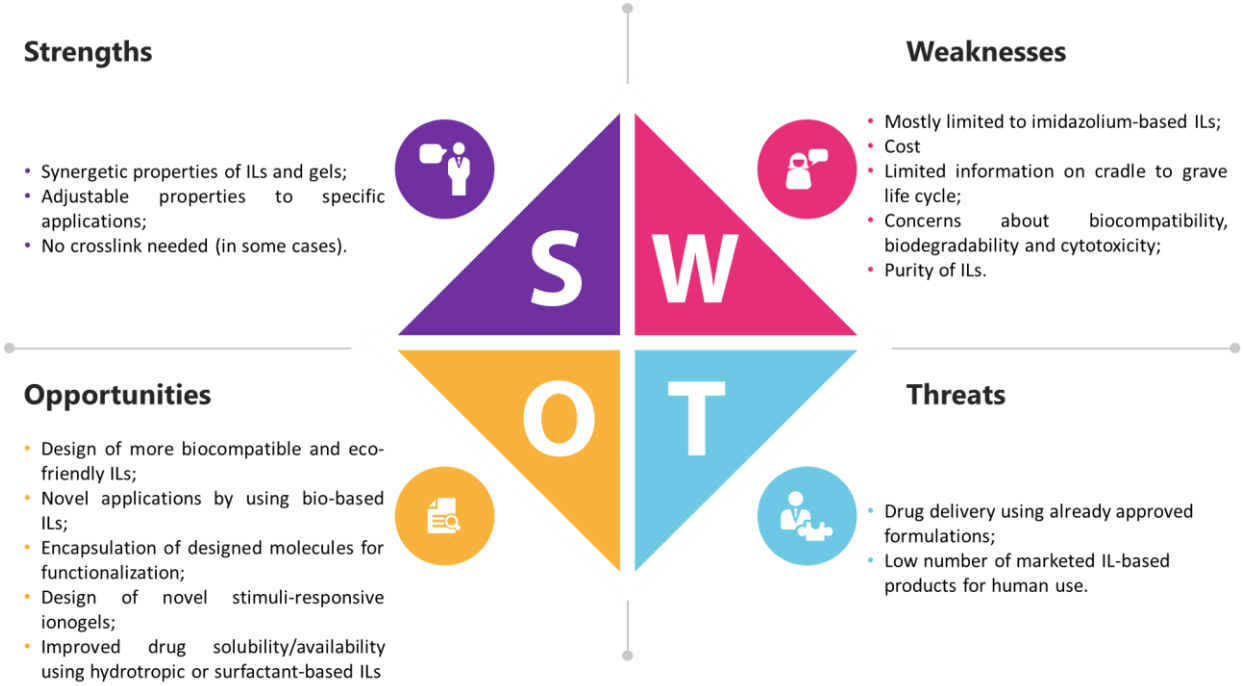

Figure 8. SWOT analysis of the application of ionogels in biomedicine.

Strengths. Unlike other products, ionogels represent a promising class of advanced materials in which the properties of ILs are integrated into polymers or organic/inorganic materials, being responsible for their enhanced performance in a wide range of applications. In general, as ILs exhibit a negligible vapor pressure at ambient temperature, solvent losses are minimized throughout time, which ultimately prevent brittleness while extending shelf-lives of ionogels. Furthermore, the tunable character displayed by ILs, achieved by the manipulation of the cation-

anion design, allows to tailor the ionogels properties to meet the requirements of specific applications, namely: (i) ionic conductivity is used in biosensing; [43, 83, 117] (ii) the high ability displayed by ILs to bind biomolecules [66] has been investigated in drug delivery for the controlled release of bioactive compounds; and (iii) ILs can act themselves as active pharmaceutical ingredients with potential application in wound dressing and drug delivery [76]. Also, the ability to prepare ionogels without a crosslinker can be advantageous since a potentially harmful chemical is avoided. Ionogels often display improved rheological properties, namely elasticity [96], integrity [24], stretchability [75], which account for their improved performance in most applications. Moreover, ionogels show high transparency, which varies in color from white to yellowish, allowing the examination of the skin for potential infection and track healing progress. Ionogels that demonstrated good stretchability and exceptionally fast self-healing properties are pre-ordained as a wound dressing material, demonstrating up to 5-fold faster self-healing than other products, such as hydrogels [75, 120].

Weaknesses. Ionogels fate inevitably follows that of ILs, which are sometimes costly and with limited information on cradle to grave life cycle. Limited data are available on ionogels comprising ILs other than imidazolium-based ILs. Concerns raised from the possible lack of biodegradability and biocompatibility as well as possible cytotoxic, occupational safety and health issues of some imidazolium-based ILs and, consequently, ionogels, limits their application for human use. Indeed, information on the risk of ionogels to health are still scarce [17, 80]. Up to date, the diversity of ILs chemical structures investigated is almost limited to imidazolium, and relatively few works dealing with ionogels for biomedical applications (if compared to electronics) are available, justifying the need for deeper and more extensive investigations on this field [28, 81, 114]. Moreover, ILs are viscous solvents with a high affinity towards moisture, resulting in additional laborious steps such as drying, which in turn dictate the cost of the final product. Also, related to their synthetic procedure, is the presence of impurities in the IL that, depending on their nature, may significantly change the properties/effectiveness of the IL itself and the prepared ionogel. If the development of (bio)sensing platforms is envisaged, impurities may lead to non-reliable and non-reproductible results. On the other hand, if human use is envisaged (e.g., drug delivery, wound dressing), the safety and efficiency of the ionogel-based biomedical approaches may also be compromised. Due to these reasons, not only the starting materials/solvents quality and synthetic procedure of the IL, but also the ionogel preparation route should be properly programmed to minimize impurities to levels acceptable/safe for the final application.

Opportunities. Given the wide range of advantages that ILs bring forth, the possibilities for ionogels application seem to be expanding steadily. By taking full advantage of their tunable nature, ILs may be engineered to present enhanced bio- and eco-friendliness, as well as potential recyclability. Another key opportunity is the design and use of bio-based ILs in ionogels [23, 61,

121–123]. It will unlock doors of opportunity for ionogels to be applied in relevant areas of the biomedical field. Moreover, the possibility of encapsulating designed molecules in the immobilized IL-phase opens infinite possibilities of functionalization with potential application, for instance in biosensing [80]. The hydrotropic or surfactant character of some ILs can be explored to improve solubility and bioavailability of active pharmaceutical ingredients insoluble or sparingly soluble in water [124]. Additionally, the application of magnetic ILs can open new perspectives in drug delivery owing to their responsiveness to magnetic fields. On the other hand, the designer solvent ability of ILs, not yet fully explored, will enable tailored and improved performances of ionogels for distinct biomedical applications.

Threats. As an alternative to ionogels, drug delivery systems using formulations already approved by regulatory agencies will continue to be predominant due to the time and cost involved to reach a new approval. Even though the path for commercialization of ILs is being paved [33] and the suitability of ILs for biomedical uses has been shown in literature, commercial applications of ionogels and/or related to biomedicine still faltered. To be highlighted is the case of the pharmaceutical company MEDRX, which uses ILs to develop innovative transdermal medicines. Beyond other medicines undergoing preclinical or clinical studies, MEDRX has reached a NDA acceptance from FDA in 2020 with their IL-based technology for the transdermal delivery of lidocaine [125]. Considering the types of application overviewed in the present chapter, there is the need to assure the quality and safety of the proposed applications for human use. For instance, in bioelectronic and sensing applications, the developed ionogel-based devices should be validated using human samples. In turn, wound dressing and drug delivery related products may need to undergo clinical trials. These tasks involve multiple resources (e.g., time, money, volunteers, etc.), so that many proposed applications will not move towards validation/approval or take a long time to reach the final consumer. It is thus important to underline that to foster commercial implementation of ionogel-based biomedical products, a multi-stakeholder perspective should be adopted. Collaborations involving academia, industry, governments, healthcare professionals and patients are essential to boost competition with currently available and/or approved options.

4. Concluding remarks and future perspectives

Ionogels represent an innovative class of materials joining the chemical versatility of ILs with favorable mechanical properties (elasticity, stretchability, integrity, self-healing, among others) of (bio)polymers. If properly designed, ionogels may exhibit high ionic conductivity, high thermal and electrochemical stability, enhanced biocompatibility and low (cyto)toxicity, and be stimuli-responsive, and thus represent smart materials for advanced applications in biomedical applications, ranging from drug delivery and wound dressing to bioelectronics and sensing.

Depending on the solid-like network, synthetic pathways of ionogels fall within three groups, namely organic (using low molecular weight gelators or polymers), inorganic (*e.g.*, oxide nanoparticles or carbon nanomaterials), or hybrid organic-inorganic (polymers reinforced with inorganic fillers). Polymer-based ionogels can either be obtained from polymerizable ILs or rely on the application of ILs as solvents that fill the cross-linked network of a polymer, being the last one the most common method for preparing ionogels for drug delivery. Furthermore, an underdeveloped aspect that holds high promise is the development of better IL gelators once their diversity is comparatively lower than organogelators. Distinctly, ionogels preparation by sol-gel processing in ILs can be obtained by the confinement of ILs within a matrix, or by ionogel formation through the conditioning of raw materials, which have found wide application in sensing. Based on the high solvating ability of ILs for polymers derived from biomass, ionogels comprising *e.g.*, chitosan, chitin and cellulose have been a hot topic of research. In addition to the sustainable character of this approach for ionogels formation, biopolymers bring additional advantages to these ionogels such as biodegradability and biocompatibility.

The versatility and utility of ionogels has been demonstrated in drug delivery and wound dressing, as well as in bioelectronics and sensing. Ionogels allow improvements on the solubility and availability of pharmaceuticals (*e.g.,* doxorubicin), and maintain the stability of biomolecules (*e.g.,* insulin). By tailoring their composition, controlled release of therapeutic products can be achieved, with potential application in cancer therapies, diabetes mellitus, among others. On the other hand, ionogels have shown to present antimicrobial activity, derived either from pharmaceutically active ILs or from the polymeric material (*e.g.*, chitosan), which coupled to the improved rheological properties of these ionogels make them promising materials for wound dressing applications. The high ionic conductivity displayed by ionogels make them good candidates for bioelectronics and sensing applications. Thermally stable and high integrity ionogels have shown an improved performance for electrochemical detection of catecholamines. Moreover, wearable, flexible and stimuli-responsive ionogels have been applied in health monitoring and illness recovery, with enhanced ability to sense movements, vital signs, and biological characteristics of fluids, in a faster way and requiring minimal energy inputs.

Up to date, most studies on ionogels for biomedical applications resorts to imidazolium-based ILs, which however are often challenged by their poor biocompatibility and high toxicity. Moreover, some ionogels make use of crosslinkers which raise additional concerns with respect to the safety of these biodevices. Although the use of crosslinkers can be avoided, the transition towards bio-based ILs (*e.g.*, based on cholinium cation and glycine-betaine analogs) of a more biocompatible character remains an urgent need in the biomedical field. The development of tailored ionogels to fulfil unmet needs in drug delivery, while demonstrating an improved performance over the current state of art technologies based on compounds already approved for drug delivery is critical to meet the requirements of regulatory agencies when considering their application in humans.

Further investigation of ionogels is still required, namely: (i) to tailor ILs properties to specific applications by manipulation of the cation-anion design; (ii) to develop novel functionalized ionogels targeting unmet needs in biomedical research; and (iii) to further explore the hydrotropic or surfactant character of ILs in ionogels to improve solubilization of hydrophobic active pharmaceutical ingredients. It is also important to pinpoint that efficient recycling procedures should be designed to decrease the ILs carbon footprint. Research intensification on the field will be crucial to upgrade the performance of ionogels over cost-effective alternatives and devices already approved for human use.

An additional potential field in which ionogels could evolve substantially is in artificial muscle mimicking. Their properties, namely outstanding conductivity, rigidness and self-healing makes them promising candidates in this field. Moreover, magnetic ILs can provide an additional and promising route towards the development of magnetic-responsive ionogels. On the other hand, the apparent disadvantage related to the low miscibility of polymers in ILs can in some cases be explored towards the development of novel and improved stimuli-responsive ionogels with potential application in drug delivery.

Overall, it was already demonstrated that ionogels exhibit an improved performance for distinct biomedical applications, spanning from wound dressing and drug delivery to bioelectronics and sensing. However, given the plethora of ILs chemical structures, types of inorganic and organic matrices that can be modified, and novel envisaged applications, this topic is still in its infancy. Accordingly, more related investigations are expected in coming years, ultimately resulting in materials with commercial potential in biomedical applications.

Acknowledgements

This work was developed within the scope of the project CICECO Aveiro Institute of Materials, UIDB/50011/2020 & UIDP/50011/2020, financed by national funds through the Portuguese Foundation for Science and Technology/MCTES, and the project POCI-01-0145-FEDER-031106 (IonCytDevice) funded by FEDER, through COMPETE2020—Programa Operacional Competitividade e Internacionalização (POCI), and by national funds (OE), through FCT/MCTES. Francisca A. e Silva acknowledges FCT – Fundação para a Ciência e a Tecnologia, I.P. for the researcher contract CEECIND/03076/2018 under the Scientific Employment Stimulus - Individual Call 2018. Augusto Q. Pedro acknowledges the research contract under the project PTDC/BII-BBF/30840/2017. Bojan Kopilovic acknowledges the University of Aveiro for the PhD grant Contrato de Bolsa (RH) 85281.

References

[1] A. Sinclair, P. Saeedi, A. Kaundal, S. Karuranga, B. Malanda, and R. Williams, "Diabetes and global ageing among 65–99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9th edition," *Diabetes Res. Clin. Pract.*, vol. 162, p. 108078, Apr. 2020, doi: 10.1016/j.diabres.2020.108078.

[2] S. Pilleron *et al.*, "Global cancer incidence in older adults, 2012 and 2035: A population-based study: Global cancer incidence in older adults," *Int. J. Cancer*, vol. 144, no. 1, pp. 49–58, Jan. 2019, doi: 10.1002/ijc.31664.

[3] C. de las H. Alarcón, S. Pennadam, and C. Alexander, "Stimuli responsive polymers for biomedical applications," *Chem Soc Rev*, vol. 34, no. 3, pp. 276–285, 2005, doi: 10.1039/B406727D.

[4] E. M. Ahmed, "Hydrogel: Preparation, characterization, and applications: A review," *J. Adv. Res.*, vol. 6, no. 2, pp. 105–121, Mar. 2015, doi: 10.1016/j.jare.2013.07.006.

[5] 5. Sun Z et al (2020) Hydrogel-based controlled drug delivery for cancer treatment: A review. Mol Pharmaceutics 17(2):373-391. https://doi.org/10.1021/acs.molpharmaceut.9b01020

[6] W. T. Truong, Y. Su, J. T. Meijer, P. Thordarson, and F. Braet, "Self-Assembled Gels for Biomedical Applications," *Chem. - Asian J.*, vol. 6, no. 1, pp. 30–42, Jan. 2011, doi: 10.1002/asia.201000592.

[7] M. Talelli, M. Barz, C. J. F. Rijcken, F. Kiessling, W. E. Hennink, and T. Lammers, "Core-crosslinked polymeric micelles: Principles, preparation, biomedical applications and clinical translation," *Nano Today*, vol. 10, no. 1, pp. 93–117, Feb. 2015, doi: 10.1016/j.nantod.2015.01.005.

[8] J. Delaey, P. Dubruel, and S. Van Vlierberghe, "Shape-Memory Polymers for Biomedical Applications," *Adv. Funct. Mater.*, vol. 30, no. 44, p. 1909047, Oct. 2020, doi: 10.1002/adfm.201909047.

[9] J. Claus, A. Brietzke, C. Lehnert, S. Oschatz, N. Grabow, and U. Kragl, "Swelling characteristics and biocompatibility of ionic liquid based hydrogels for biomedical applications," *PLOS ONE*, vol. 15, no. 4, p. e0231421, Apr. 2020, doi: 10.1371/journal.pone.0231421.

[10] J. Claus, F. O. Sommer, and U. Kragl, "Ionic liquids in biotechnology and beyond," *Solid State Ion.*, vol. 314, pp. 119–128, Jan. 2018, doi: 10.1016/j.ssi.2017.11.012.

[11] N. Sood, A. Bhardwaj, S. Mehta, and A. Mehta, "Stimuli-responsive hydrogels in drug delivery and tissue engineering," *Drug Deliv.*, vol. 23, no. 3, pp. 748–770, Mar. 2016, doi: 10.3109/10717544.2014.940091.

[12] A. K. Nayak and B. Das, "Introduction to polymeric gels," in *Polymeric Gels*, Elsevier, 2018, pp. 3–27.

[13] T. Sakai, "Definition of Polymer Gels and Rubber Elasticity," in *Physics of Polymer Gels*, 1st ed., T. Sakai, Ed. Wiley, 2020, pp. 45–75.

[14] J. Douglas, "Weak and Strong Gels and the Emergence of the Amorphous Solid State," *Gels*, vol. 4, no. 1, p. 19, Feb. 2018, doi: 10.3390/gels4010019.

[15] X. Chen and H. Fuchs, Eds., *Soft Matter Nanotechnology*. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA, 2015.

[16] J. F. Miravet and B. Escuder, "CHAPTER 11. Supramolecular Gels for Pharmaceutical and Biomedical Applications," in *Monographs in Supramolecular Chemistry*, H.-J. Schneider, Ed. Cambridge: Royal Society of Chemistry, 2013, pp. 331–354.

[17] J. Le Bideau, L. Viau, and A. Vioux, "Ionogels, ionic liquid based hybrid materials," *Chem Soc Rev*, vol. 40, no. 2, pp. 907–925, 2011, doi: 10.1039/C0CS00059K.

[18] J. Bandomir *et al.*, "Synthesis and Characterization of Polymerized Ionic Liquids: Mechanical and Thermal Properties of a Novel Type of Hydrogels," *Macromol. Chem. Phys.*, vol. 215, no. 8, pp. 716–724, Apr. 2014, doi: 10.1002/macp.201400009.

[19] J. Majumder, J. Deb, M. R. Das, S. S. Jana, and P. Dastidar, "Designing a simple organic salt-based supramolecular topical gel capable of displaying in vivo self-delivery application," *Chem. Commun.*, vol. 50, no. 14, p. 1671, 2014, doi: 10.1039/c3cc48513g.

[20] M. Kuddushi, D. Ray, V. Aswal, C. Hoskins, and N. Malek, "Poly(vinyl alcohol) and Functionalized Ionic Liquid-Based Smart Hydrogels for Doxorubicin Release," *ACS Appl. Bio Mater.*, vol. 3, no. 8, pp. 4883–4894, Aug. 2020, doi: 10.1021/acsabm.0c00393.

[21] 21. Claus J, Jastram A, et al (2020) Polymerized ionic liquids-based hydrogels with intrinsic antibacterial activity: modern weapons against antibiotic-resistant infections. J Appl Polym Sci 138(16): 50222. https://doi.org/10.1002/app.50222"

[22] S. Banerjee, R. K. Das, and U. Maitra, “Supramolecular gels ‘in action,’” *J. Mater. Chem.*, vol. 19, no. 37, p. 6649, 2009, doi: 10.1039/b819218a.
[23] E. Secchi, T. Roversi, S. Buzzaccaro, L. Piazza, and R. Piazza, “Biopolymer gels with ‘physical’ cross-links: gelation kinetics, aging, heterogeneous dynamics, and macroscopic mechanical properties,” *Soft Matter*, vol. 9, no. 15, p. 3931, 2013, doi: 10.1039/c3sm27153f.
[24] M. Isik, R. Gracia, L. C. Kollnus, L. C. Tome, I. M. Marrucho, and D. Mecerreyes, “Cholinium Lactate Methacrylate: Ionic Liquid Monomer for Cellulose Composites and Biocompatible Ion Gels,” *Macromol. Symp.*, vol. 342, no. 1, pp. 21–24, Aug. 2014, doi: 10.1002/masy.201300176.
[25] W. P. Singh, U. Koch, and R. S. Singh, “Gelation of ionic liquids by small-molecule gelators and their applications,” *Soft Mater.*, vol. 18, no. 4, pp. 386–410, Oct. 2020, doi: 10.1080/1539445X.2019.1697706.
[26] L. Viau, C. Tourné-Péteilh, J.-M. Devoisselle, and A. Vioux, “Ionogels as drug delivery system: one-step sol–gel synthesis using imidazolium ibuprofenate ionic liquid,” *Chem Commun*, vol. 46, no. 2, pp. 228–230, 2010, doi: 10.1039/B913879J.
[27] Trivedi TJ, Srinivasa Rao K, Kumar A (2014) Facile preparation of agarose-chitosan hybrid materials and nanocomposite ionogels using an ionic liquid via dissolution, regeneration and sol-gel transition. Green Chem 16:320-330. https://doi.org/10.1039/C3GC41317A.
[28] A. Kavanagh, R. Byrne, D. Diamond, and K. J. Fraser, “Stimuli Responsive Ionogels for Sensing Applications—An Overview,” *Membranes*, vol. 2, no. 1, pp. 16–39, Feb. 2012, doi: 10.3390/membranes2010016.
[29] V. Di Noto, E. Negro, J.-Y. Sanchez, and C. Iojoiu, “Structure-Relaxation Interplay of a New Nanostructured Membrane Based on Tetraethylammonium Trifluoromethanesulfonate Ionic Liquid and Neutralized Nafion 117 for High-Temperature Fuel Cells,” *J. Am. Chem. Soc.*, vol. 132, no. 7, pp. 2183–2195, Feb. 2010, doi: 10.1021/ja906975z.
[30] J. Claus, T. Eickner, N. Grabow, U. Kragl, and S. Oschatz, “Ion Exchange Controlled Drug Release from Polymerized Ionic Liquids,” *Macromol. Biosci.*, vol. 20, no. 9, p. 2000152, Sep. 2020, doi: 10.1002/mabi.202000152.
[31] L. Tan, X. Dong, H. Wang, and Y. Yang, “Gels of ionic liquid [C4mim]PF6 formed by self-assembly of gelators and their electrochemical properties,” *Electrochem. Commun.*, vol. 11, no. 5, pp. 933–936, May 2009, doi: 10.1016/j.elecom.2009.02.025.
[32] Liu X et al (2020) Silicone-ionic liquid elastomer composite with keratin as reinforcing agent
780 utilized as pressure sensor. Macromol Rapid Commun 42(5):e2000602.
https://doi.org/10.1002/marc.202000602.
[33] M. B. Shiflett, Ed., *Commercial Applications of Ionic Liquids*. Cham: Springer International Publishing, 2020.
[34] A. J. Greer, J. Jacquemin, and C. Hardacre, “Industrial Applications of Ionic Liquids,” *Molecules*, vol. 25, no. 21, p. 5207, Nov. 2020, doi: 10.3390/molecules25215207.
[35] T. Itoh and Y.-M. Koo, Eds., *Application of Ionic Liquids in Biotechnology*, vol. 168. Cham: Springer International Publishing, 2019.
[36] X. Chen *et al.*, “Bis-imidazolium based poly(ionic liquid) electrolytes for quasi-solid-state dye-sensitized solar cells,” *J. Mater. Chem.*, vol. 22, no. 34, p. 18018, 2012, doi: 10.1039/c2jm33273f.
[37] Z. Lv *et al.*, “Electrochemical and Physical Properties of Imidazolium Chloride Ionic Liquids with Pyrrolidinium or Piperidinium Cation Addition and Their Application in Dual-Ion Batteries,” *Energy Technol.*, vol. 8, no. 9, p. 2000432, Sep. 2020, doi: 10.1002/ente.202000432.
[38] S. V. Muginova, D. A. Myasnikova, S. G. Kazarian, and T. N. Shekhovtsova, “Applications of Ionic Liquids for the Development of Optical Chemical Sensors and Biosensors,” *Anal. Sci.*, vol. 33, no. 3, pp. 261–274, 2017, doi: 10.2116/analsci.33.261.
[39] Jastorff B et al (2003) How hazardous are ionic liquids? Structure–activity relationships and biological testing as important elements for sustainability evaluation. Green Chem 5:136-142.
https://doi.org/10.1039/B211971D.
[40] Magina S et al (2021) Evaluating the hazardous impact of ionic liquids—challenges and
opportunities. J Hazard Mater 412:125215. https://doi.org/10.1016/j.jhazmat.2021.125215
[41] F. A. e Silva, J. A. P. Coutinho, and S. P. M. Ventura, “Aquatic Toxicology of Ionic Liquids (ILs),” in *Encyclopedia of Ionic Liquids*, S. Zhang, Ed. Singapore: Springer Singapore, 2019, pp. 1–18.

[42] R. Md Moshikur, Md. R. Chowdhury, M. Moniruzzaman, and M. Goto, “Biocompatible ionic liquids and their applications in pharmaceutics,” *Green Chem.*, vol. 22, no. 23, pp. 8116–8139, 2020, doi: 10.1039/D0GC02387F.

[43] Li Z et al (2012) Design of environmentally friendly ionic liquid aqueous two-phase systems for the efficient and high activity extraction of proteins. Green Chem 14(10):2941-2950. https://doi.org/10.1039/c2gc35890e

[44] S. Shahriari *et al.*, “Aqueous biphasic systems: a benign route using cholinium-based ionic liquids,” *RSC Adv*, vol. 3, no. 6, pp. 1835–1843, 2013, doi: 10.1039/C2RA22972B.

[45] M. G. Freire, Ed., *Ionic-Liquid-Based Aqueous Biphasic Systems: Fundamentals and Applications*. Berlin, Heidelberg: Springer Berlin Heidelberg, 2016.

[46] M. Domínguez-Pérez, L. I. N. Tomé, M. G. Freire, I. M. Marrucho, O. Cabeza, and J. A. P. Coutinho, “(Extraction of biomolecules using) aqueous biphasic systems formed by ionic liquids and aminoacids,” *Sep. Purif. Technol.*, vol. 72, no. 1, pp. 85–91, Mar. 2010, doi: 10.1016/j.seppur.2010.01.008.

[47] F. Benito-Lopez, S. Coyle, R. Byrne, C. O’Toole, C. Barry, and D. Diamond, “Simple Barcode System Based on Inonogels for Real Time pH-Sweat Monitoring,” in *2010 International Conference on Body Sensor Networks*, Singapore, Singapore, Jun. 2010, pp. 291–296, doi: 10.1109/BSN.2010.9.

[48] J. Yang *et al.*, “Ionic liquid–activated wearable electronics,” *Mater. Today Phys.*, vol. 8, pp. 78–85, Mar. 2019, doi: 10.1016/j.mtphys.2019.02.002.

[49] R. R. Naik and S. Singamaneni, “Introduction: Bioinspired and Biomimetic Materials,” *Chem. Rev.*, vol. 117, no. 20, pp. 12581–12583, Oct. 2017, doi: 10.1021/acs.chemrev.7b00552.

[50] A. Q. Pedro, J. A. P. Coutinho, and M. G. Freire, “Immobilization of Ionic Liquids, Types of Materials, and Applications,” in *Encyclopedia of Ionic Liquids*, S. Zhang, Ed. Singapore: Springer Singapore, 2019, pp. 1–12.

[51] Z. Ma, J. Yu, and S. Dai, “Preparation of Inorganic Materials Using Ionic Liquids,” *Adv. Mater.*, vol. 22, no. 2, pp. 261–285, Jan. 2010, doi: 10.1002/adma.200900603.

[52] R. Sahrash, A. Siddiqa, H. Razzaq, T. Iqbal, and S. Qaisar, “PVDF based ionogels: applications towards electrochemical devices and membrane separation processes,” *Heliyon*, vol. 4, no. 11, p. e00847, Nov. 2018, doi: 10.1016/j.heliyon.2018.e00847.

[53] W. T. Truong, L. Lewis, and P. Thordarson, “CHAPTER 6. Biomedical Applications of Molecular Gels,” in *Soft Matter Series*, B. Escuder and J. F. Miravet, Eds. Cambridge: Royal Society of Chemistry, 2013, pp. 157–194.

[54] M. McLaughlin, M. A. Gilea, M. J. Earle, K. R. Seddon, B. F. Gilmore, and S. A. Kelly, “Characterization of ionic liquid cytotoxicity mechanisms in human keratinocytes compared with conventional biocides,” *Chemosphere*, vol. 270, p. 129432, May 2021, doi: 10.1016/j.chemosphere.2020.129432.

[55] N. S. M. Vieira, J. C. Bastos, L. P. N. Rebelo, A. Matias, J. M. M. Araújo, and A. B. Pereiro, “Human cytotoxicity and octanol/water partition coefficients of fluorinated ionic liquids,” *Chemosphere*, vol. 216, pp. 576–586, Feb. 2019, doi: 10.1016/j.chemosphere.2018.10.159.

[56] P. Stepnowski, A. C. Skladanowski, A. Ludwiczak, and E. Laczyńska, “Evaluating the cytotoxicity of ionic liquids using human cell line HeLa,” *Hum. Exp. Toxicol.*, vol. 23, no. 11, pp. 513–517, Nov. 2004, doi: 10.1191/0960327104ht480oa.

[57] X. Xia, R. Wan, P. Wang, W. Huo, H. Dong, and Q. Du, “Toxicity of imidazoles ionic liquid [C16mim]Cl to Hela cells,” *Ecotoxicol. Environ. Saf.*, vol. 162, pp. 408–414, Oct. 2018, doi: 10.1016/j.ecoenv.2018.07.022.

[58] M. Cvjetko, K. Radošević, A. Tomica, I. Slivac, J. Vorkapić-Furač, and V. Srček, “Cytotoxic Effects of Imidazolium Ionic Liquids on Fish and Human Cell Lines,” *Arch. Ind. Hyg. Toxicol.*, vol. 63, no. 1, pp. 15–20, Mar. 2012, doi: 10.2478/10004-1254-63-2012-2132.

[59] X. Li, J. Ma, and J. Wang, “Cytotoxicity, oxidative stress, and apoptosis in HepG2 cells induced by ionic liquid 1-methyl-3-octylimidazolium bromide,” *Ecotoxicol. Environ. Saf.*, vol. 120, pp. 342–348, Oct. 2015, doi: 10.1016/j.ecoenv.2015.06.018.

[60] S. Stolte *et al.*, “Effects of different head groups and functionalised side chains on the cytotoxicity of ionic liquids,” *Green Chem*, vol. 9, no. 7, pp. 760–767, 2007, doi: 10.1039/B615326G.

[61] M. Isik, R. Gracia, L. C. Kollnus, L. C. Tomé, I. M. Marrucho, and D. Mecerreyes, “Cholinium-Based Poly(ionic liquid)s: Synthesis, Characterization, and Application as Biocompatible Ion Gels and Cellulose Coatings,” *ACS Macro Lett.*, vol. 2, no. 11, pp. 975–979, Nov. 2013, doi: 10.1021/mz400451g.

[62] J. Raeburn and D. J. Adams, “Multicomponent low molecular weight gelators,” *Chem. Commun.*, vol. 51, no. 25, pp. 5170–5180, 2015, doi: 10.1039/C4CC08626K.

[63] A. Ikeda *et al.*, "Gelation of Ionic Liquids with a Low Molecular-Weight Gelator Showing T_{gel} above 100 °C," *Chem. Lett.*, vol. 30, no. 11, pp. 1154–1155, Nov. 2001, doi: 10.1246/cl.2001.1154.

[64] A. Kavanagh, R. Byrne, D. Diamond, and A. Radu, "A two-component polymeric optode membrane based on a multifunctional ionic liquid," *The Analyst*, vol. 136, no. 2, pp. 348–353, 2011, doi: 10.1039/C0AN00770F.

[65] F. O. Sommer, J.-S. Appelt, I. Barke, S. Speller, and U. Kragl, "UV-Polymerized Vinylimidazolium Ionic Liquids for Permselective Membranes," *Membranes*, vol. 10, no. 11, p. 308, Oct. 2020, doi: 10.3390/membranes10110308.

[66] Peng K et al (2020) Mucoadhesive ionic liquid gel patches for oral delivery. ACS Biomater Sci Eng. In Press. https://doi.org/10.1021/acsbiomaterials.0c01024.

[67] A. Guyomard-Lack, N. Buchtová, B. Humbert, and J. Le Bideau, "Ion segregation in an ionic liquid confined within chitosan based chemical ionogels," *Phys. Chem. Chem. Phys.*, vol. 17, no. 37, pp. 23947–23951, 2015, doi: 10.1039/C5CP04198H.

[68] N. Kimizuka and T. Nakashima, "Spontaneous Self-Assembly of Glycolipid Bilayer Membranes in Sugar-philic Ionic Liquids and Formation of Ionogels," *Langmuir*, vol. 17, no. 22, pp. 6759–6761, Oct. 2001, doi: 10.1021/la015523e.

[69] L. A. Estroff and A. D. Hamilton, "Water Gelation by Small Organic Molecules," *Chem. Rev.*, vol. 104, no. 3, pp. 1201–1218, Mar. 2004, doi: 10.1021/cr0302049.

[70] P. Terech and R. G. Weiss, "Low Molecular Mass Gelators of Organic Liquids and the Properties of Their Gels," *Chem. Rev.*, vol. 97, no. 8, pp. 3133–3160, Dec. 1997, doi: 10.1021/cr9700282.

[71] J. J. van Gorp, J. A. J. M. Vekemans, and E. W. Meijer, "C_3-Symmetrical Supramolecular Architectures: Fibers and Organic Gels from Discotic Trisamides and Trisureas," *J. Am. Chem. Soc.*, vol. 124, no. 49, pp. 14759–14769, Dec. 2002, doi: 10.1021/ja020984n.

[72] W. P. Singh and R. S. Singh, "A new class of organogelators based on triphenylmethyl derivatives of primary alcohols: hydrophobic interactions alone can mediate gelation," *Beilstein J. Org. Chem.*, vol. 13, pp. 138–149, Jan. 2017, doi: 10.3762/bjoc.13.17.

[73] S. Ghosh, V. K. Praveen, and A. Ajayaghosh, "The Chemistry and Applications of π-Gels," *Annu. Rev. Mater. Res.*, vol. 46, no. 1, pp. 235–262, Jul. 2016, doi: 10.1146/annurev-matsci-070115-031557.

[74] S. Gallagher, A. Kavanagh, L. Florea, D. R. MacFarlane, K. J. Fraser, and D. Diamond, "Temperature and pH triggered release characteristics of water/fluorescein from 1-ethyl-3-methylimidazolium ethylsulfate based ionogels," *Chem. Commun.*, vol. 49, no. 41, p. 4613, 2013, doi: 10.1039/c3cc41272e.

[75] F. Wang *et al.*, "Facile Fabrication of a Self-Healing Temperature-Sensitive Sensor Based on Ionogels and Its Application in Detection Human Breath," *Nanomaterials*, vol. 9, no. 3, p. 343, Mar. 2019, doi: 10.3390/nano9030343.

[76] Y. Yu, Z. Yang, S. Ren, Y. Gao, and L. Zheng, "Multifunctional hydrogel based on ionic liquid with antibacterial performance," *J. Mol. Liq.*, vol. 299, p. 112185, Feb. 2020, doi: 10.1016/j.molliq.2019.112185.

[77] M.-A. Néouze, J. L. Bideau, F. Leroux, and A. Vioux, "A route to heat resistant solid membranes with performances of liquid electrolytes," *Chem Commun*, no. 8, pp. 1082–1084, 2005, doi: 10.1039/B416267F.

[78] M.-A. Néouze, J. Le Bideau, P. Gaveau, S. Bellayer, and A. Vioux, "Ionogels, New Materials Arising from the Confinement of Ionic Liquids within Silica-Derived Networks," *Chem. Mater.*, vol. 18, no. 17, pp. 3931–3936, Aug. 2006, doi: 10.1021/cm060656c.

[79] S. Dai, Y. H. Ju, H. J. Gao, J. S. Lin, S. J. Pennycook, and C. E. Barnes, "Preparation of silica aerogel using ionic liquids as solvents," *Chem. Commun.*, no. 3, pp. 243–244, 2000, doi: 10.1039/a907147d.

[80] A. Vioux, L. Viau, S. Volland, and J. Le Bideau, "Use of ionic liquids in sol-gel; ionogels and applications," *Comptes Rendus Chim.*, vol. 13, no. 1–2, pp. 242–255, Jan. 2010, doi: 10.1016/j.crci.2009.07.002.

[81] L. Zhang *et al.*, "Overview of Ionogels in Flexible Electronics," *Chem. Rec.*, vol. 20, no. 9, pp. 948–967, Sep. 2020, doi: 10.1002/tcr.202000041.

[82] J. Zhang, Y. Ma, F. Shi, L. Liu, and Y. Deng, "Room temperature ionic liquids as templates in the synthesis of mesoporous silica via a sol–gel method," *Microporous Mesoporous Mater.*, vol. 119, no. 1–3, pp. 97–103, Mar. 2009, doi: 10.1016/j.micromeso.2008.10.003.

[83] D. V. Chernyshov, N. V. Shvedene, E. R. Antipova, and I. V. Pletnev, "Ionic liquid-based miniature electrochemical sensors for the voltammetric determination of catecholamines," *Anal. Chim. Acta*, vol. 621, no. 2, pp. 178–184, Jul. 2008, doi: 10.1016/j.aca.2008.05.042.

[84] Z. Li, Y. Zhang, and N. Feng, “Mesoporous silica nanoparticles: synthesis, classification, drug loading, pharmacokinetics, biocompatibility, and application in drug delivery,” *Expert Opin. Drug Deliv.*, vol. 16, no. 3, pp. 219–237, Mar. 2019, doi: 10.1080/17425247.2019.1575806.
[85] Y. Zhou, “Recent Advances in Ionic Liquids for Synthesis of Inorganic Nanomaterials,” *Curr. Nanosci.*, vol. 1, no. 1, pp. 35–42, Jan. 2005, doi: 10.2174/1573413052953174.
[86] J. Le Bideau, P. Gaveau, S. Bellayer, M.-A. Néouze, and A. Vioux, “Effect of confinement on ionic liquids dynamics in monolithic silica ionogels: 1H NMR study,” *Phys. Chem. Chem. Phys.*, vol. 9, no. 40, p. 5419, 2007, doi: 10.1039/b711539c.
[87] F. Borghi and A. Podestà, “Ionic liquids under nanoscale confinement,” *Adv. Phys. X*, vol. 5, no. 1, p. 1736949, Jan. 2020, doi: 10.1080/23746149.2020.1736949.
[88] T. Fukushima, “Molecular Ordering of Organic Molten Salts Triggered by Single-Walled Carbon Nanotubes,” *Science*, vol. 300, no. 5628, pp. 2072–2074, Jun. 2003, doi: 10.1126/science.1082289.
[89] X. Mei and J. Ouyang, “Gels of carbon nanotubes and a nonionic surfactant prepared by mechanical grinding,” *Carbon*, vol. 48, no. 1, pp. 293–299, Jan. 2010, doi: 10.1016/j.carbon.2009.09.032.
[90] E. Fernández, D. López, C. Mijangos, M. Duskova-Smrckova, M. Ilavsky, and K. Dusek, “Rheological and thermal properties of agarose aqueous solutions and hydrogels,” *J. Polym. Sci. Part B Polym. Phys.*, vol. 46, no. 3, pp. 322–328, Feb. 2008, doi: 10.1002/polb.21370.
[91] R. Muzzarelli *et al.*, “Reconstruction of parodontal tissue with chitosan,” *Biomaterials*, vol. 10, no. 9, pp. 598–603, Nov. 1989, doi: 10.1016/0142-9612(89)90113-0.
[92] J. A. Hubbell, “Biomaterials in Tissue Engineering,” *Nat. Biotechnol.*, vol. 13, no. 6, pp. 565–576, Jun. 1995, doi: 10.1038/nbt0695-565.
[93] R. Muzzarelli *et al.*, “Biological activity of chitosan: ultrastructural study,” *Biomaterials*, vol. 9, no. 3, pp. 247–252, May 1988, doi: 10.1016/0142-9612(88)90092-0.
[94] M. E. Zakrzewska, E. Bogel-Łukasik, and R. Bogel-Łukasik, “Solubility of Carbohydrates in Ionic Liquids,” *Energy Fuels*, vol. 24, no. 2, pp. 737–745, Feb. 2010, doi: 10.1021/ef901215m.
[95] S. S. Y. Tan and D. R. MacFarlane, “Ionic Liquids in Biomass Processing,” in *Ionic Liquids*, vol. 290, B. Kirchner, Ed. Berlin, Heidelberg: Springer Berlin Heidelberg, 2009, pp. 311–339.
[96] M. M. Villar-Chavero, J. C. Domínguez, M. V. Alonso, M. Oliet, and F. Rodriguez, “Tuning the rheological properties of cellulosic ionogels reinforced with chitosan: The role of the deacetylation degree,” *Carbohydr. Polym.*, vol. 207, pp. 775–781, Mar. 2019, doi: 10.1016/j.carbpol.2018.12.041.
[97] D. Kumarasamy, M. K. Ghosh, and T. K. Giri, “Polymer-Based Responsive Hydrogel for Drug Delivery,” in *Polymer Gels*, V. K. Thakur, M. K. Thakur, and S. I. Voicu, Eds. Singapore: Springer Singapore, 2018, pp. 1–25.
[98] Huang J et al (2018) Novel in situ forming hydrogel based on xanthan and chitosan re-gelifying in liquids for local drug delivery. Carbohydr Polym 186:54–63. https://doi.org/10.1016/j.carbpol.2018.01.025"
[99] V. K. Thakur and M. K. Thakur, “Recent advances in green hydrogels from lignin: a review,” *Int. J. Biol. Macromol.*, vol. 72, pp. 834–847, Jan. 2015, doi: 10.1016/j.ijbiomac.2014.09.044.
[100] R.-L. Wu, X.-L. Wang, F. Li, H.-Z. Li, and Y.-Z. Wang, “Green composite films prepared from cellulose, starch and lignin in room-temperature ionic liquid,” *Bioresour. Technol.*, vol. 100, no. 9, pp. 2569–2574, May 2009, doi: 10.1016/j.biortech.2008.11.044.
[101] R. M. Dias, L. C. G. Petrin, F. H. B. Sosa, A. M. da Costa Lopes, J. A. P. Coutinho, and M. C. da Costa, “Investigation of Kraft Lignin Solubility in Protic Ionic Liquids and Their Aqueous Solutions,” *Ind. Eng. Chem. Res.*, vol. 59, no. 40, pp. 18193–18202, Oct. 2020, doi: 10.1021/acs.iecr.0c02605.
[102] M. G. Freire, A. R. R. Teles, R. A. S. Ferreira, L. D. Carlos, J. A. Lopes-da-Silva, and J. A. P. Coutinho, “Electrospun nanosized cellulose fibers using ionic liquids at room temperature,” *Green Chem.*, vol. 13, no. 11, p. 3173, 2011, doi: 10.1039/c1gc15930e.
[103] M. Kuddushi, N. K. Patel, S. Rajput, A. Shah, O. A. El Seoud, and N. I. Malek, “Thermo-Switchable de Novo Ionic Liquid-Based Gelators with Dye-Absorbing and Drug-Encapsulating Characteristics,” *ACS Omega*, vol. 3, no. 9, pp. 12068–12078, Sep. 2018, doi: 10.1021/acsomega.8b01984.
[104] P. Bawa, V. Pillay, Y. E. Choonara, and L. C. du Toit, “Stimuli-responsive polymers and their applications in drug delivery,” *Biomed. Mater.*, vol. 4, no. 2, p. 022001, Apr. 2009, doi: 10.1088/1748-6041/4/2/022001.
[105] S. Dhivya, V. V. Padma, and E. Santhini, “Wound dressings – a review,” *BioMedicine*, vol. 5, no. 4, p. 22, Dec. 2015, doi: 10.7603/s40681-015-0022-9.

[106] Moeini A et al (2020) Wound healing and antimicrobial effect of active secondary metabolites in chitosan-based wound dressings: a review. Carbohydr Polym 233:115839. https://doi.org/10.1016/j.carbpol.2020.115839.
[107] X. Wang, L. Yu, J. Jiao, H. Zhang, R. Wang, and H. Chen, "Aggregation behavior of COOH-functionalized imidazolium-based surface active ionic liquids in aqueous solution," *J. Mol. Liq.*, vol. 173, pp. 103–107, Sep. 2012, doi: 10.1016/j.molliq.2012.06.023.
[108] M. Petkovic *et al.*, "Novel biocompatible cholinium-based ionic liquids—toxicity and biodegradability," *Green Chem.*, vol. 12, no. 4, p. 643, 2010, doi: 10.1039/b922247b.
[109] A. Jordan and N. Gathergood, "Biodegradation of ionic liquids – a critical review," *Chem. Soc. Rev.*, vol. 44, no. 22, pp. 8200–8237, 2015, doi: 10.1039/C5CS00444F.
[110] A. Banerjee, K. Ibsen, T. Brown, R. Chen, C. Agatemor, and S. Mitragotri, "Ionic liquids for oral insulin delivery," *Proc. Natl. Acad. Sci.*, vol. 115, no. 28, pp. 7296–7301, Jul. 2018, doi: 10.1073/pnas.1722338115.
[111] M. S. Mahmud, H. Fang, and H. Wang, "An Integrated Wearable Sensor for Unobtrusive Continuous Measurement of Autonomic Nervous System," *IEEE Internet Things J.*, vol. 6, no. 1, pp. 1104–1113, Feb. 2019, doi: 10.1109/JIOT.2018.2868235.
[112] Sun N et al (2009) Complete dissolution and partial delignification of wood in the ionic liquid 1-ethyl-3-methylimidazolium acetate. Green Chem 11(5):646-655. https://doi.org/10.1039/b822702k
[113] S. Baluta, A. Lesiak, and J. Cabaj, "Graphene Quantum Dots-based Electrochemical Biosensor for Catecholamine Neurotransmitters Detection," *Electroanalysis*, vol. 30, no. 8, pp. 1781–1790, Aug. 2018, doi: 10.1002/elan.201700825.
[114] J. A. Ribeiro, P. M. V. Fernandes, C. M. Pereira, and F. Silva, "Electrochemical sensors and biosensors for determination of catecholamine neurotransmitters: A review," *Talanta*, vol. 160, pp. 653–679, Nov. 2016, doi: 10.1016/j.talanta.2016.06.066.
[115] H. Xue *et al.*, "A wearable pyroelectric nanogenerator and self-powered breathing sensor," *Nano Energy*, vol. 38, pp. 147–154, Aug. 2017, doi: 10.1016/j.nanoen.2017.05.056.
[116] Z. Lin *et al.*, "Triboelectric Nanogenerator Enabled Body Sensor Network for Self-Powered Human Heart-Rate Monitoring," *ACS Nano*, vol. 11, no. 9, pp. 8830–8837, Sep. 2017, doi: 10.1021/acsnano.7b02975.
[117] S. Zhang, F. Wang, H. Peng, J. Yan, and G. Pan, "Flexible Highly Sensitive Pressure Sensor Based on Ionic Liquid Gel Film," *ACS Omega*, vol. 3, no. 3, pp. 3014–3021, Mar. 2018, doi: 10.1021/acsomega.7b01575.
[118] H. Debels, M. Hamdi, K. Abberton, and W. Morrison, "Dermal Matrices and Bioengineered Skin Substitutes: A Critical Review of Current Options," *Plast. Reconstr. Surg. Glob. Open*, vol. 3, no. 1, p. e284, Jan. 2015, doi: 10.1097/GOX.0000000000000219.
[119] G. C. Luque *et al.*, "Elastic and Thermoreversible Iongels by Supramolecular PVA/Phenol Interactions," *Macromol. Biosci.*, vol. 20, no. 11, p. 2000119, Nov. 2020, doi: 10.1002/mabi.202000119.
[120] R. Peng, Y. Yu, S. Chen, Y. Yang, and Y. Tang, "Conductive nanocomposite hydrogels with self-healing property," *RSC Adv*, vol. 4, no. 66, pp. 35149–35155, 2014, doi: 10.1039/C4RA05381H.
[121] Hou X-D et al (2013) Evaluation of toxicity and biodegradability of cholinium amino acids ionic liquids. PLoS ONE 8(3):e59145. https://doi.org/10.1371/journal.pone.0059145.
[122] A. Q. Pedro *et al.*, "Cholinium-Based Good's Buffers Ionic Liquids as Remarkable Stabilizers and Recyclable Preservation Media for Recombinant Small RNAs," *ACS Sustain. Chem. Eng.*, vol. 6, no. 12, pp. 16645–16656, Dec. 2018, doi: 10.1021/acssuschemeng.8b03900.
[123] K. Fukumoto, M. Yoshizawa, and H. Ohno, "Room Temperature Ionic Liquids from 20 Natural Amino Acids," *J. Am. Chem. Soc.*, vol. 127, no. 8, pp. 2398–2399, Mar. 2005, doi: 10.1021/ja043451i.
[124] S. N. Pedro, C. S. R. Freire, A. J. D. Silvestre, and M. G. Freire, "The Role of Ionic Liquids in the Pharmaceutical Field: An Overview of Relevant Applications," *Int. J. Mol. Sci.*, vol. 21, no. 21, p. 8298, Nov. 2020, doi: 10.3390/ijms21218298.
[125] MEDRX (2021, accessed 12 March 2021) http://www.medrx.co.jp/english/business_5.html.