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Ionogels as advanced materials for overcoming challenges in wound healing and drug delivery

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ABSTRACT

Despite relevant advances, the pharmaceutical industry continues to strive with the limited adaptability, moisture management, and discomfort caused by existing wound dressings. Adding to these challenges are the bioavailability and pharmacokinetics of common (bio)therapeutics, overall leading to unmet clinical demands, safety concerns, and poor patient compliance. Ionogels, a versatile class of materials comprising ionic liquids (ILs) confined in an organic or inorganic solid network, have been proposed to overcome these drawbacks. They have demonstrated the ability to enhance the antimicrobial and mechanical properties of the resulting materials while allowing remarkable improvements in drug solubility and their delivery to targeted sites. Nowadays, safety investigations and clinical trials are still required to fully leverage the potential of ionogels for human applications. However, the recent FDA approval of the New Drug Application MRX-5LBT®, a transdermal drug delivery system, opens promising perspectives toward the clinical translation of ionogels. This review focuses on recent advances achieved in the design of ionogels for pharmaceutical applications, viz. in topical formulations to promote wound healing with antimicrobial activity, and as platforms to improve drug pharmacokinetics (solubility and bioavailability), and their delivery at targeted specific sites with controlled release behaviour.

1. Current challenges in wound healing management and drug delivery

Nowadays, the incidence and burden caused by acute and chronic wounds account for significant healthcare concerns in which inadequate treatment can lead to ulceration, local physiological disfunction, or even death [1–3]. In chronic wounds, the presence of persistent inflammatory stimuli causes the continuous attraction of macrophages and neutrophils to the wound bed with the secretion of inflammatory cytokines, ultimately interrupting physiological healing mechanisms. Moreover, wounds can become contaminated by complex populations of many different bacteria arising from distinct sources, including the external environment, the surrounding skin, or endogenous sources [4]. To counteract these actions, current wound management approaches encompass debridement, mitigation of conditions resulting in wounds (*e.g.*, employment of off-loading devices, or use of negative pressure wound therapy), and the application of dressings [1]. A broad variety of dressings tailored to the requirements of the wound (dry or exuding, clean or infected, superficial or deep) as well as more advanced devices able to reduce the bacterial load in the wound bed by releasing antimicrobial agents (*e.g.*, iodine or silver) have been developed [4]. Although these dressings have significantly improved wound management, a device capable of effectively healing chronic wounds while tackling infection does not exist [4]. In fact, issues related to inadequate mechanical properties and weakness in terms of adhesion, extensibility, and elasticity, and the limited efficiency of the topical delivery of therapeutics such as growth factors and antibiotics remain to be solved [1]. Adding to these challenges is the low bioavailability, non-controlled pharmacokinetics, and tolerance acquired by the host organism to existing pharmaceutical drugs, resulting in unmet clinical demands and drug safety concerns [5,6]. In recent years, novel drug delivery systems (DDS) have proven their importance at delivering therapeutic molecules with site-specific and localized effects. Additionally, these systems have facilitated drug release at desired rates and simultaneously reduced undesired side effects [7].

Another important aspect in the pharmaceutical field is the administration route that can limit the therapeutic effect of a given drug, being generally divided between enteral (oral and rectal), parenteral (intravenous, intramuscular, intranasal, intradermal, among others), and transdermal modes of administration [8,9]. Overcoming biological

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barriers, including skin, mucosal membranes, blood-brain barrier, as well as cell and nuclear membrane, is a key obstacle, limiting the efficient delivery of drugs into the body [10]. Since each route poses its own obstacles to drug delivery, the designed DDS must consider a series of factors such as the amount of drug, the distribution and location of particulates, the molecular weight, the physicochemical characteristics, the presence of enzymes and electric fields, the physiological environment, the type and concentration of polymers and excipients, and the surface morphology (shape, charge, size, and density) of the carrier system [8,9]. Overall, fundamental issues associated with drug administration remain to be surpassed, particularly those related to the solubility of a particular therapeutic in aqueous solutions, drug permeability, low absorption in the gastrointestinal tract, and high degradation rates of the target drugs [11,12].

1.1. Opportunities brought by ionogels as dressings and drug delivery systems

The use of gels, whereby polymers (*e.g.*, cellulose, chitosan, polyethylene glycol) or inorganic matrices (*e.g.*, silica, metal oxides or metal organic frameworks – MOFs) are swollen with solvents, have been proposed to overcome some of these issues regarding wound dressings and pharmacological delivery [13–15]. Unlike liquid substances or ointments, gels have the advantage of remaining stable in the area to be treated with the primary goal of maximizing efficacy while improving patient compliance. Despite the progress achieved up to date, some limitations prevail in gel-related applications for wound healing and drug delivery, such as inadequate circulation, unresolved inflammation and infections, and lack of angiogenesis [16], as well as poor aqueous solubility, low drug selectivity, non-controlled drug release, and low bioavailability [17]. Over the years, due to the intense research on gel-type materials, it became essential to organize and classify gel types according to widely accepted and adopted terminologies [18]. In this review article, depending on the solvents applied, gels are classified into hydrogels and ionogels, respectively, if water or ionic liquids (ILs) are applied as solvents [13]. Among ionogels, these are further classified according to the nature of the solid network and the type of molecular interactions established between the solid matrix and the IL, as addressed in more detail in the next section.

ILs are a class of organic salts, usually composed of a large unsymmetrical organic cation and a small inorganic or organic anion. As a result, they end up having many advantages over traditional organic solvents, including negligible vapor pressure at room temperature, as well as high thermal and chemical stability [19]. In aqueous solutions, ILs also afford an improved and unique solvation performance for a wide range of compounds, achieved by their hydrotropic nature or as surface-active ingredients. Due to the large number of ion combinations, ILs are generally recognized as tunable designer solvents and task-specific fluids [20]. If ILs are confined in a solid polymeric or inorganic network, designable structures termed as ionogels can be obtained [21]. Ionogels combine the properties of the IL and of the solid confining network, having high ionic conductivity, high permeation and adsorption capabilities, anti-freezing performance, a wide range of biological activities (including antimicrobial, antioxidant, and anti-inflammatory properties), and may be stimuli-responsive and self-healable. These properties allow them to stand out as promising candidates for different applications in the pharmaceutical field, as sketched in Fig. 1.

Over the years, ILs have been investigated for application in pharmaceutical sciences due to their flexible properties, *e.g.*, as solvents and catalysts for active pharmaceutical ingredient synthesis [22], as solubilization agents for hydrophilic and hydrophobic drug molecules [23], and being themselves drugs comprising active pharmaceutical ingredients (API-ILs) [24]. Due to their remarkable structural diversity, ILs have been engineered to promote the dissolution, stability, and bioavailability of pharmaceuticals [25]. Furthermore, biologically active ILs were synthesized, displaying antimicrobial, antimalarial, anti-inflammatory, and antitumour therapeutic activities [26], among which some of these features have already been reported to be transferred to the corresponding ionogels [27–30]. They can also have a positive impact on the formulation and delivery of products since ILs can disrupt the physiological skin barriers to deliver drugs to targeted sites [31]. However, some ILs may display some cytotoxicity, and therefore, a judicious choice of their cationic and anionic constituents is important to obtain biocompatible compounds [24,32].

This review focuses on recent advances achieved on the design of ionogels for pharmaceutical applications, especially those aimed to obtain high-performance antimicrobial materials as improved dressings for wound healing, and to design formulations with the ability to enhance drug solubility and bioavailability. The aptitude of ionogels to allow targeted delivery in specific sites in the human body, with

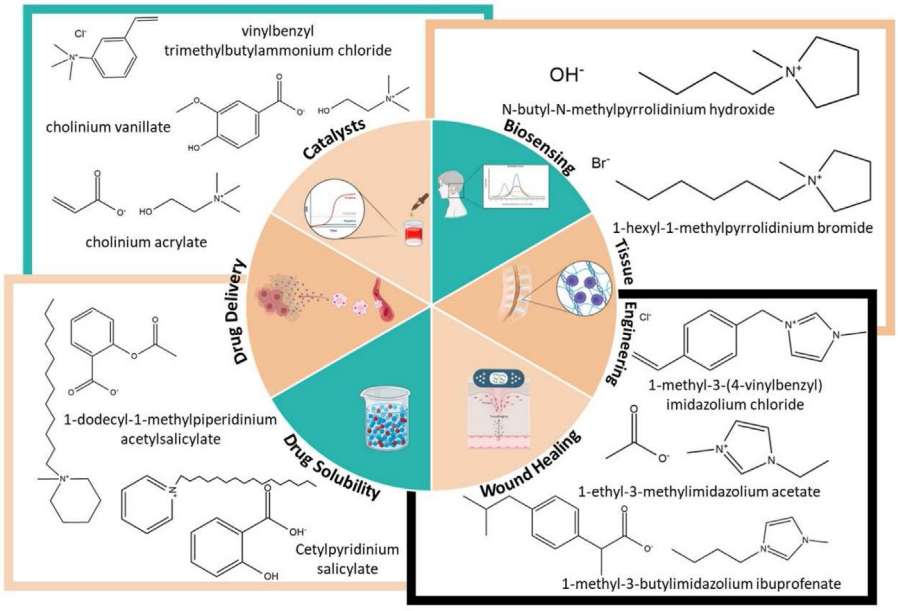

Fig. 1. Examples of applications of ionogels in the pharmaceutical field and representative chemical structures of ILs frequently used in their preparation.

controlled release behaviour, is also discussed. Throughout the reviewed and discussed works, issues related to the biocompatibility of the prepared ionogels are also addressed. Resorting to a SWOT analysis, future perspectives on the application of ionogels in the field are finally discussed.

2. Ionogels: preparation and main properties

2.1. Synthetic routes

The main event in the preparation of ionogels is the formation of crosslinked networks that will disperse the IL inside the ionogel and determine the topological configuration of the polymer network while having an effect on the properties of the resulting materials [33]. Depending on the nature of interactions between the solid network and the dispersed IL, ionogels can be divided into physically and chemically cross-linked networks. Physically cross-linked networks usually include hydrogen bonding, van der Waals, and π-π interactions established between the IL and the solid support. On the other hand, chemically cross-linked networks resort to the establishment of covalent bonds and therefore present good mechanical strength [34]. ILs assist ionogel formation in a variety of ways and regulate their structure and properties by providing hydrogen bonds, electrostatic, host-guest interactions, and IL-philic and IL-phobic interactions [35]. As proposed by Bideau et al. (2011) [14], and according to the nature of the solid network (elucidated in Fig. 2), ionogels can be classified into inorganic, organic, and hybrid (inorganic-organic).

In general, synthetic routes (Fig. 2) commonly used for ionogels preparation include direct mixing, *in situ* polymerization/gelation, and solvent exchange [33], as represented in Fig. 3. These methods can generally be applied to ionogels composed of solid networks of an inorganic or organic nature. Furthermore, inorganic networks typically employ oxide nanoparticles, carbon nanotubes, or oxide networks arising from sol-gel processing while organic networks make use of low molecular weight gelators (LMWG) or resort to polymers/poly ionic liquids (PILs) obtained from monomer polymerization. Finally, hybrid organic-inorganic networks are generally composed of polymers reinforced with inorganic fillers [14,36,37].

According to the works reviewed in the next sub-sections, a summary of the main advantages and limitations of the methods commonly used for ionogels preparation is presented in Table 1.

2.1.1. Direct mixing

The direct mixing of ILs and the solid network constitutes the simplest approach to prepare inorganic or organic ionogels, being however this last option restricted to the cases in which the IL and polymer are compatible [33]. Herein, the morphology of the ionogel is determined by the polymer [37]. Moreover, this method is limited by the choice of the polymer and the IL used, being the composition of the ionogel determined by the maximum swelling capacity of the polymer [47]. In the cases where the reactants are not compatible, a secondary solvent will help in mixing the polymer networks and ILs [48]. As an example, Yu et al. [48] prepared multifunctional ionogels as candidates for joint skin wound healing by directly mixing polyvinyl alcohol (5 wt% in water) with bromide-based ILs (0.5 M) at a volume ratio of 2:1 under stirring, from which water was remover by freeze-drying.

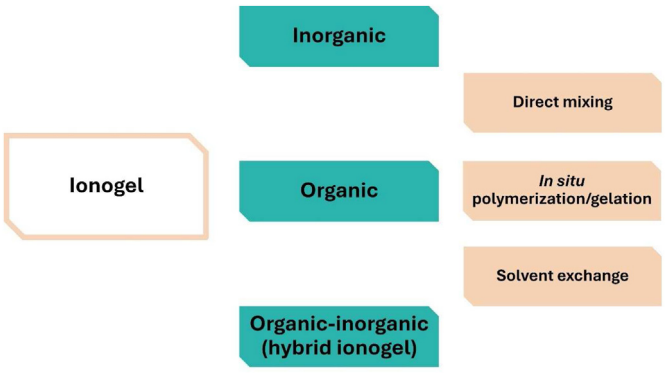

Fig. 2. Classification of ionogels based on the nature of the solid network and the most common methods used for their preparation.

Inorganic ionogels are usually prepared by dispersion of inorganic nanoparticles or silica in ILs, or using the sol-gel technique to confine ILs in conducting or oxide matrices [41]. By taking advantage of the stability of nanoparticles in IL media, Shimano et al. [49] prepared hybrid materials by a simple mechanical milling process involving silica particles in the IL 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide.

The sol-gel strategy usually uses alkoxide precursors, such as tetramethoxysilane (TMOS), that can undergo hydrolysis and condensation in the presence of the IL, thus forming a porous gel matrix with the IL filling the porous phase [50]. Vioux and co-workers [38] used the API-IL 1-butyl-3-methylimidazolium ibuprofenate in sol-gel synthesis (sketched in Fig. 3A) using pure tetramethoxysilane (TMOS) or TMOS/methyltrimethoxysilane (MTMOS) at different molar ratios and diluted hydrochloric acid. Gelation took place for 1h and after an ageing period of 14 days, transparent monolithic ionogels were obtained as efficient drug releasing systems with kinetics controlled by the silica wall [38]. Wu et al. [51] synthesized an ionogel by modifying its silica-supported ionogel organically, leading to the fabrication of a mechanically and ionic conductive compliant ionogel. Silica-aerogel-based ionogels were prepared using tetraethylorthosilicate (TEOS) and phosphoric acid, after which different concentrations of cholinium dihydrogen phosphate IL were added and left for gelation during one week [52]. The authors found that the addition of IL to the sol-gel system favored the formation of a more interconnected silica network structure, and highlight the potential application of these materials for encapsulating biological molecules so that they can retain their conformation for a longer duration [52].

In addition to silica, distinct inorganic matrices can also be used for ionogels preparation. The preparation of "bucky" gels is accomplished by mechanically mixing ILs and carbon nanotubes, namely single-walled carbon nanotubes or multiple-walled carbon nanotubes [53]. Carbon nanotubes are dispersed in ILs due to intermolecular ionic interactions, with physical cross-links being established between the ILs and CNTs, thus leading to the formation of physical gels [36].

2.1.2. In situ polymerization/gelation

Organic ionogels result from gelation using LMWG or the *in situ* polymerization of monomers in ILs [14,36]. The addition of LMWG to ILs at high temperatures induces physical gelation upon cooling [37]. This self-assembly process in solution occurs through supramolecular bonding, including hydrogen bonding, π-π interactions or electrostatic interactions [14]. Gelation of ILs by LMWGs has been achieved using derivatives of acids [54], benzenetricarboxamides [55], amino acids [56], and carbohydrates and polysaccharides [57,58]. Kimizuka and Nakashima [59] investigated the gelation of ether-containing ILs using L-glutamic acids or carbohydrates and observed the formation of fibrous nanostructures due to the establishment of strong interactions between carbohydrates and ether groups. Overall, and for ionogels prepared with LMWG, the high IL content and low cross-linking density of ionogels allow them to exhibit excellent ionic conductivity, but poor mechanical strength. Due to these properties, ionogels are often applicable for flexible electronics and as stimuli-responsive materials [60]. Moreover, the natural origin of LMWG make them environmentally-friendly and biodegradable [45].

Polymer-based ionogels rely on the use of polymeric materials, being prepared by different routes: i) doping of polymers (either by solvent blending – solution casting methods –, or impregnation – soaking method); ii) *in situ* polymerization induced by temperature or light of

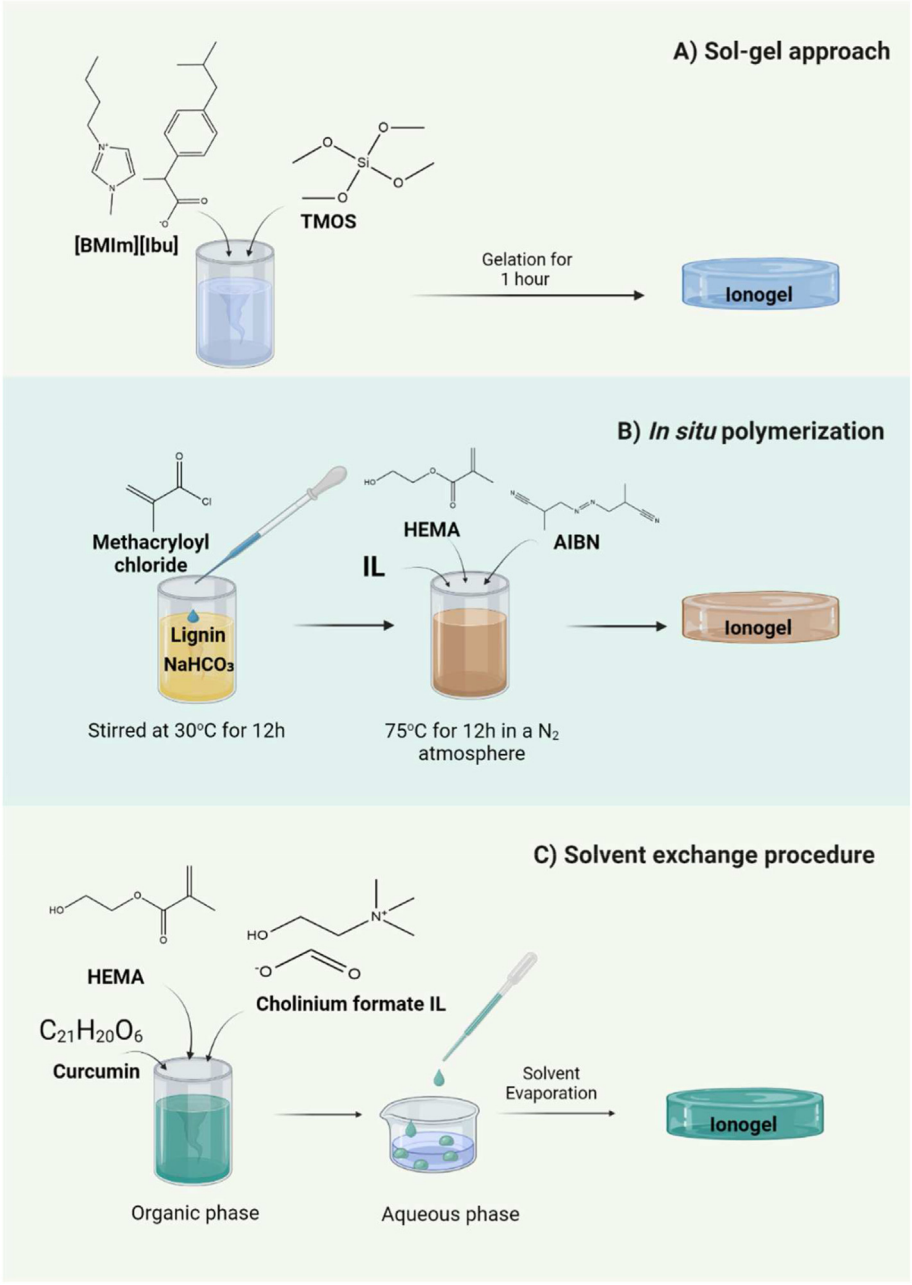

Fig. 3. Schematic representation of different synthetic routes of ionogels with application in the pharmaceutical field: A) Direct mixing (Sol-Gel approach); B) *In situ* polymerization; C) Solvent exchange procedure. Adapted, respectively, from Vioux and co-workers [38], Zhou and co-workers [39], and Macfarlane and co-workers [40]. Created with BioRender.com. Abbreviations and ILs nomenclature: AIBN – Azobisisobutyronitrile; [BMIm][Ibu] – 1-methyl-3-butylimidazolium ibuprofenate; HEMA - Hydroxyethyl methacrylate; IL – Ionic liquid; TMOS - Tetramethoxysilane.

monomers in ILs; and iii) polymeric ionic liquids, also referred as poly(ionic liquids) (PILs) [37]. Polymers are extensively used in the formation of ionogels due to their versatile skeleton design and high IL encapsulation ability, further allowing them to combine the mechanical flexibility of a polymer and the high conductivity of ILs [14]. In the approach involving the doping of a polymer, the ionogel is obtained by swelling a polymer in an IL or blending the polymer and the IL to form a homogeneous solution. Afterward, drying is required to remove the solvent, leaving the IL-polymer mixture. The IL content and type of polymer material in composite membranes can be controlled using this method, further allowing to tailor the ionic conductivity of the ionogel [37].

Zhou and co-workers [39] prepared lignin/PILs ionogel dressings by a process (Fig. 3B) involving initially the modification of lignin with methacryloyl chloride, followed by the addition of hydroxyethyl methacrylate (HEMA), the IL 3-butyl-1-isopropyl-1H-imidazole-3-ium bromide and the polymerization initiator azobisisobutyronitrile (AIBN). This mixture was incubated at 75 °C for 12h until the resulting gelatinous solid was placed in water to remove the organic solvent, allowing to obtain the ionogel dressing [39]. The prepared ionogel displayed improved mechanical properties due to the presence of lignin, as well as antibacterial properties, and effectively promoted wound healing [39].

Physically crosslinked polyacrylamide ionogels were obtained *via* the photopolymerization of the acrylamide monomer in several imidazolium-based ILs combined with the bromide anion [42]. In addition to improved mechanical properties (tensile strength of 31.1 MPa, tensile modulus of 319.8 MPa, compressive yield strength of 112.2 MPa), the authors highlighted the simplicity of this process (two steps), the rapid preparation times (<30 min), low cost (bromide-based ILs), high transparency (90–96 %), easy shaping (3D printing), and good stability (vacuum and heat) of the resulting materials [42].

Another approach for ionogel formation encompasses mixing ILs and all reactants before the crosslinking or the polymerization reaction. This process allows high amounts of monomers to be confined in the IL [37].

Table 1
Advantages and limitations of common preparation methods of ionogels.

Ionogel preparation method	Advantages	Limitations
Direct mixing	- Simplicity [33].	- In the case of polymeric ionogels, is restricted to ILs and polymers that are compatible. Secondary solvents may be used to increase miscibility between polymers and ILs [33].
In situ polymerization/ gelation	- Light-induced polymerization is rapid (seconds to minutes), carried out at room temperature, and fully controlled by switching on/off the light [41–43]. Can additionally allow the preparation of materials with high transparency and good stability (vacuum and heat) [42]. - Solution casting allows film formation at low temperatures, easy incorporation of additives, and single-step manufacturing of multi-layer films [44]. - Direct polymerization of monomers dissolved in ILs avoids the use of additional solvents, and the use of monomers with different structures for the precise design of the properties of the gel [43]. - Low molecular weight gelators of natural origin makes them neutral to the environment and biodegradable [45].	- Thermal-induced polymerization need relatively high temperatures (70–80 °C) and long reaction times (2–24h) [41]. - Solution casting leaves residual compounds on the cast [44].
Solvent exchange	- Can be used for complex gelation reactions that cannot occur in ionic liquids and in the cases where monomers and not adequately dissolved in ILs and hence no control over phase behaviour is achieved [33,46].	More laborious process [46].

By studying the polymerization of methyl methacrylate in the IL 1-butyl-3-methylimidazolium hexafluorophosphate, Jiang et al. [61] found a compatible binary system with decreased IL loading and increased transition temperature. Marcinkowska et al. [62] polymerized trimethylolpropane tris(3-mercaptopropoinate) in ILs using photo-induced polymerization. The resulting ionogel exhibited a "colloidal gel" structure with interconnected microspheres, high ionic conductivity, and anti-plasticization effect due to phase separation and ILs' anti-plasticization effect [62]. Usually, these chemically cross-linked ionogels exhibit high mechanical strength and high thermal stability. As for polymeric ILs such as those derived from 1-vinyl-3--butylimidazolium bromide, they can generally be obtained by free-radical polymerization [63]. In this approach, the IL forms the continuous phase of the gel, and initiators like ammonium persulfate or benzoyl peroxide are required to promote the formation of free radicals while allowing the polymerizable functional groups of monomers to participate in the polymerization reaction to form gels [63]. Walsh and co-workers [64] described a class of gel–polymer electrolytes (GPEs) formed by polymerizing 1-butyl-3-(4-vinylbenzyl)imidazolium bis(trifluromethanesulfonyl)imide. GPEs are formed by polymerizing the ionic monomers in the presence of the ILs diethylmethylammonium trifluoromethanesulfonate, diethylmethylammonium trifluoroacetate, and diethylmethylammonium bis[trifluoromethanesulfonyl]imide. In comparison with materials based on the neutral host, GPEs are more electrochemically and thermally stable, and up to six times more conductive [64].

Hybrid (organic-inorganic) ionogels result from ILs, nanofillers, and polymer matrices, which are prepared by mixing the polymer solution in ILs in an inorganic oxide nanofiller. This can be attained through *in situ* formation of the inorganic filler in IL/polymer solutions in the non-aqueous sol-gel route [37]. In contrast, the incorporation of inorganic nanoparticles is widely used because of their ability to improve mechanical properties. This method also allows for reducing the plasticizing effect of high IL loadings while maintaining the ionogels' flexibility and tractability [37]. Based on multifunctional cross-linkable and ionic-group functionalized ladder-like polysisesquioxane, hybrid ionogels were created [65]. The use of a ladder-like crosslinker endowed the ionogel with increased thermal stability and lithium mobility for lithium-ion batteries [65]. Yang et al. [66] created a functional ionogel with a hybrid host composed of silicon dioxide (SiO_2) and methyl methacrylate. The resulting composite is a uniform and homogenous monolith that blends the rigidity of the silica network with the softness of polymethyl methacrylate, making it appropriate for use in optical data storage technologies [66].

The combination of an IL and a solid matrix, and their physicochemical and electronic/ionic interactions with the material, results in unique and controlled properties of the resulting material. Ionogels have various qualities that set them apart from regular gels. They have better viscoelastic and mechanical characteristics, superior electrochemical characteristics, high thermal and chemical stability, and high wear and corrosion resistance [63]. The chemical structure and viscosity of ILs have a high impact on the conductivity of the prepared ionogels. Longer alkyl side chains in the IL cation increase the viscosity and reduce the cation mobility, thus lowering the conductivity of ionogels. Liu et al. [67] reported ionogels prepared with imidazolium-based ILs and exhibiting differences in conductivity, which depend on the viscosity and ion size of the IL. Ionogels prepared with 1-ethyl-3-methylimidazolium tetrafluoroborate present higher ionic conductivity in comparison with those resorting to 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl) imide [67]. Considering that ILs are also known for having high thermal stabilities, poly(2-hydroxyethyl acrylate) ionogels synthesized *via* polymerizing 2-hydroxyethyl acrylate monomers in the IL 1-ethyl-3-methylimidazolium ethylsulfate possesses excellent thermal stability as it started to decompose only at 250 °C [68].

An inorganic-organic double network consisting of a silica particle network and a poly-2-hydroxyethyl methacrylate network in which the IL 1-butyl-3-methylimidazolium tetrafluoroborate was confined, was prepared to be applied a gel electrolyte [69]. These materials exhibited high ion conductivity of 3.8–12.8 mS cm^{-1} over a wide temperature range of 30–150 °C and mechanical integrity with a maximum toughness of 1.8 MJ m at 30 °C [69]. Another report by Matsuura and co-workers [70] disclosed the utilization of a one-pot synthesis sol-gel method to prepare novel organic/inorganic hybrid ionogels fabricated from [3-(2, 3-Epoxypropoxy)propyl]-trimethoxysilane, 1-butyl-3-methylimidazolium tetrafluoroborate IL, $AgBF_4$, and catalysts. According to the envisaged application, the results indicate that the presence of epoxy and silanol groups on the solid framework could enhance the ionic dissociation of silver salt and IL, providing more free silver ions to form a complex via propylene molecules and hence confirming the promising potential for propylene/propane separation [70].

2.1.3. Solvent exchange procedure

The solvent exchange procedure is useful for preparing ionogels in which monomer molecules cannot be dissolved in ILs and hence no control over phase behaviour is achieved, as well to carry out complex gelation reactions that cannot occur in ILs [33]. For instance, poly(2-acrylamido-2-methyl-1-propanesulfonic acid) double-networks

hydrogels were prepared using a three-step method, in which after the formation of the hydrogel, it was soaked into the IL to exchange from water [46,71]. Macfarlane and co-workers [40] prepared poly(2-hydroxyethyl methacrylate) (PHEMA) nanoparticles for curcumin encapsulation and delivery. The preparation process (Fig. 3C) involved an initial step of curcumin dissolution in the cholinium formate IL, mixture with 2-hydroxyethyl methacrylate, followed by washing with methanol and drying the polymer. Thereafter, it was dissolved in an organic phase (acetone and ethanol 4:1) and added dropwise to an aqueous phase for nanoparticle formation. In addition to avoid radical initiators to initiate HEMA polymerization, the authors highlight the biocompatibility and anti-therapeutic potential of encapsulated curcumin [40].

2.2. *Properties: ILs as customizing agents of ionogels*

The increasing attention drawn to ionogels in the pharmaceutical field over the last decade follows the well-described aptitude of ILs and their aqueous solutions to dissolve and stabilize a wide range of relevant (bio)molecules and macromolecules (synthetic drugs, therapeutic proteins, nucleic acids, among others), combined with the evolving concept of biologically active ILs [20,26,72]. Ionogels emerged then as a versatile class of materials with promising potential in the pharmaceutical field, retaining the favourable properties of ILs (Fig. 4).

Generally, the confined ILs retain or display enhanced functional properties, with ILs being able to play both a structural and functional role [73]. If properly designed, ionogels can display good compatibility profiles [74,75] and relevant biological activities, acting for instance as antibacterial [76] or anti-inflammatory agents [27]. Smart ionogels hold promising potential for drug delivery, which can be achieved by including solid networks, ILs that exhibit stimuli-responsiveness (*e.g.*, to temperature, pH, magnetic fields), and thus be applied for the controlled and targeted release of (bio)pharmaceuticals [77,78]. Ionogels can also promote an increase in the solubility of therapeutic drugs [79] and enhance the stability of biopharmaceuticals (Fig. 4) [80]. These properties are crucial in pharmaceutical applications, and are further discussed in the next sub-sections while delving into the role of ILs as customizing agents of ionogels characteristics. A summary of different ionogels properties according to the nature of the solid network is presented in Table 2.

2.2.1. *Conventional features*

Ionogels and hydrogels share similar structures, but the presence of ILs instead of water as the dispersed phase ascribes interesting properties to ionogels (Fig. 5): i) more stable over time due to the non-volatility of ILs preventing mass changes; ii) ionogels can operate over a much broader range of temperatures (-70 to 350 °C) than hydrogels; iii) water in hydrogels can undergo hydrolysis for voltages above 1.3 V, contrasting with ionogels that are electrochemically stable over a much wider potential range, up to 4 V; iv) water is a poor conductor relative to many ILs; and v) the remarkable structural diversity exhibited of ILs [82].

Table 2
Ionogel properties according to the nature of the solid network.

Property	Nature of the solid network		
	Inorganic	Organic	Hybrid (Organic-inorganic)
Mechanical	Carbon nanotubes are recognized by excellent mechanical properties [44].	PILs can improve the mechanical properties [81].	Double networks improve mechanical properties [46, 82].
Temperature-resistance (Low and High)	The addition of inorganic nanoparticles can increase the thermal stability of ionogels [33].	–	–
Conductivity	Mostly determined by ILs but the migration of ILs inside ionogels is influenced by the cross-coupled polymer networks [33].		
Stimuli-responsiveness	–	Along with ILs, the use of responsive polymers (*e.g.*, to temperature) is responsible for providing stimuli-responsiveness [78].	
Self-healing	–	Mostly arise from hydrogen bonding and coulombic interactions between gelators and ILs [60].	
Biological activity	Mostly determined by the type of IL. The solid network can influence the biological activity, as in the case of the antioxidant activity of lignin [39].		

As a result of the negligible volatility at ambient conditions displayed by most aprotic ILs [20], ionogels are inherently nonvolatile, *i. e.*, they do not "dry out" over time [82]. Moreover, ionogels exhibit superior thermal stability over hydrogels so that they can be used in open environments without encapsulation [83]. Yiming et al. [83] prepared ionogels containing the IL 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl) imide and a polymeric network formed by ethylene glycol methyl ether acrylate and isobornyl acrylate with a wide working temperature range of – 60 to 250 °C. By combining the monomers hexafluorobutyl methacrylate and butyl acrylate (or ethyl acrylate, pentyl acrylate) and the IL 1-butyl-3-methylimidazolium bis(trifuoromethylsulfonyl) imide, effective ionogels able to be used within a temperature range from – 60 to 350 °C were obtained [84]. A physically cross-linked ionogel based on the IL 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide and a copolymer resulting from the polymerization of methyl methacrylate and acrylic acid monomers with the ability to maintain the gel state at high temperatures (up to 200 °C) was reported by Lyu et al. [85] Resorting to a PIL based on poly(1-butyl-3-vinyl imidazolium tetrafluoroborate) and polyethylene glycol diacrylate and several cross-linkers and catalysts, IL-based click-ionogels using thiol-ene click chemistry with stable mechanical properties from - 70 °C to 200 °C have been reported [86]. Anti-freezing and non-drying ionogels with application as wound dressings based on polyvinylpyrrolidone and a PIL resulting from the monomer 1-vinyl-3-butylimidazolium were prepared by Wang et al. [15] and were shown to keep their properties after freezing at – 20 °C or heating at

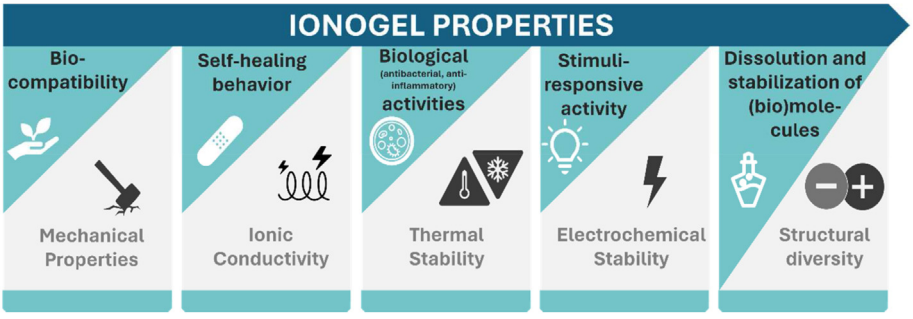

Fig. 4. Properties and features displayed by ionogels. Emerging properties favouring the application of ionogels in the pharmaceutical field are shown in light blue.

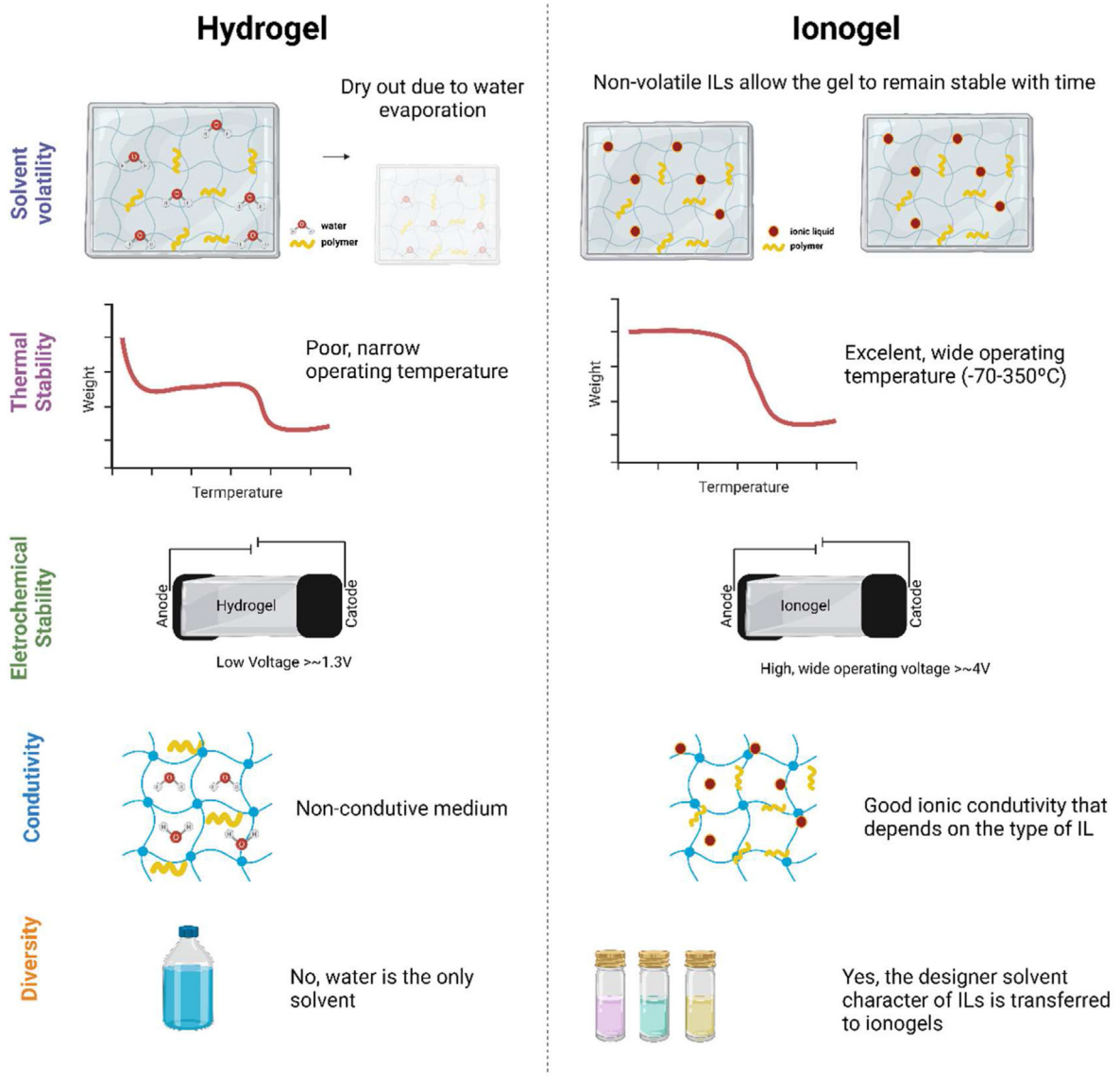

Fig. 5. Comparison of ionogels and hydrogels in terms of volatility, thermal and electrochemical stability, conductivity, and structural diversity of the solvent (IL – ionic liquid). Information retrieved from Wang et al. [82]. Created with Biorender.com.

70 °C. This ensures that they can be reused (sterilized at high temperatures) and adapted to cold weather conditions [15]. The nonvolatility and high-temperature resistance of ionogels enable their application on harsh environments, including high vacuum and low/high temperature, also allowing their sterilization. Moreover, ionogels often display good water and swelling properties, which are important parameters in the context of wound repair since the wound exudate is likely to cause to secondary infections [87].

Over hydrogels, ionogels are generally much more electrochemically stable with higher ionic conductivity. The conductivity of ionogels is mostly determined by the chemical structure of ILs and increases with a higher content of ILs, being however necessary to find an ideal balance as too much IL leads to IL exudation and low mechanical strength [33]. A way to improve the ion migration capacity and electrolyte stability is by the use of covalent organic frameworks (COF) which confine IL anions through strong interactions [88]. Cationic ethidium bromide-COF and neutral diaminoanthraquinone-COF were, respectively, physically mixed with diethylmethyl(2-methoxyethyl)ammonium bis(trifluoromethyl sulfonyl)imide IL and lithium bis(trifluoromethylsulfonyl)imide (the anion as Li^+ carrier) to increase their conductivity, being observed that the hydrogen bonding between the COFs and ILs facilitate the release of Li^+ promoting their transfer [88]. Ionogel's conductivity and electrochemical stability are generally critical for electronics and sensing technologies, including health monitoring and human motion detection [60,89,90]. Nevertheless, semi-interpenetrating copolymer networks formed by chitosan and electro-responsive imidazolium-based PILs have proven to be useful for iontophoretic applications, in which under an external electrical stimulus, faster permeation and release rates of lidocaine hydrochloride were observed [76].

Mechanical and rheological properties of ionogels are crucial parameters depending on the application. Among them, the fracture strain and strength are the strain and stress at break, representing, respectively, the deformability and strength of the material. On the other hand, the Young's modulus describes the material stiffness [33]. Since the poor mechanical properties (*e.g.*, fracture strength <1 MPa, modulus <0.1 MPa, and thoughness <1000 J m^{-2}) hinder the application of ionogels in several domains, efforts have been made to overcome these issues. Ionogels' thoughening can be achieved by the introduction of energy dissipation mechanisms within the network during deformation, namely by the introduction of double polymer networks, phase-separated domains, sacrificial bonds (*e.g.*, hydrogen and ionic bonds) between polymer chains, entanglements, and fillers [46,82]. Soft tissues such as skin, blood

vessels, and nerves possess high mechanical toughness and extensibility, exhibiting as well strain-induced viscoelastic behaviour. In this regard, wound dressings must be able to change shape as the soft tissue expands and contracts [39]. Stereocomplex nanocrystallites polyurethane scaffolds (scPLA-PEG) prepared from poly/L-lactide), poly (D-lactide), and polyethylene glycol and the IL 1-butyl-3-methylimidazolium tetrafluoroborate exhibited great stretchability (elongation at break near 1500 %). Moreover, the authors showed that the Young's modulus, elongation and stress at break of the ionogels gradually decreases with the increase in the IL content from 0 % to 40 % [91]. Zhang et al. [39] found that the tensile strength and elastic modulus of lignin-PIL ionogel composites increases up to 7 times (60 wt% lignin) as the content of lignin increases and that the prepared materials are not break during loading-unloading cyclic extension. These improved mechanical properties are attributed to two factors: i) three-dimensional network structure of lignin which can absorb the most of the external force through its own deformation, resulting in improved tensile strength, beaking elongation, and elastic modulus; ii) the negative ions of lignin reflect the positive ions of PILs to form the dynamic bonds, effectively improving the fatigue resistance and self-healing properties of the designed dressings [39]. Photoelectric-driven composite ionogel patches obtained using 1-ethyl-3-methylimidazole and $Ti_3C_2T_x$ (MXene) with break strength and strain, respectively, of 6.1 MPa and 686 % were prepared by Jin and co-workers [92]. Herein, the doping with MXene allows the formation of hydrogen bonds in ionogels by functional groups of MXene, which can promote energy conduction, dissipation and effective recombination of polymer chains under external stimulation, allowing the patches to exhibit alterable mechanical properties in the context of wound healing applications [92]. Multifunctional gels comprising MXene, the IL 1-Hydroxyethyl-2-methylimidazolium chloride, acrylamide, anthocyanidin, and different pectin contents presented high stretchability and low stress, in comparison with hydrogels (without IL) [87]. The behaviour shown by ionogels could be ascribed to hydrogen bonding and electrostatic interaction between ILs and polymer backbone, which could damage the crystallization of the polymer and induce the plasticizing process [87]. PILs comprised by hydrophilic vinyl ILs based on the cholinium cation and amino acids (proline, isoleucine, serine and glycine), acrylamide and the hydrophobic monomer stearyl methacrylate were used to form ionogels with bacterial cellulose. These materials exhibit excellent mechanical strength (5.8 MPa) and extensive elongation at break (4250 %), being additionally shown that the molecular structure and content of cholinium-based vinyl ILs played an important role in modulating the mechanical properties of the resulting ionogels [81]. The presence of ILs influence ionogels' mechanical properties, either by the existence of hydrogen bonds or electrostatic interactions [35]. In particular, PILs can form hydrogen bonds with other scaffold molecules, helping in stabilizing the shape while strengthening the mechanical properties of ionogels [35].

Overall, the presence of ILs and the type of solid network ascribe different properties to ionogels. Due to the remarkable structural diversity exhibited of ILs and by combining different cations and anions, their properties can be tuned for specific applications, allowing therefore the design of task-specific fluids [20]. As ionogels retain most of the properties of ILs, they can also be customized for specific applications by adequately selecting the optimal chemical structure, including for wound healing and drug delivery approaches.

2.2.2. *Emerging properties*

Adding to the conventional properties previously analysed, a number of emerging properties such as stimuli-responsiveness, self-healing ability, biocompatibility, ability to stabilize and dissolve (bio)pharmaceuticals and anti-inflammatory/antimicrobial activities can be attributed to ionogels, enabling their use in pharmaceutical applications.

Stimuli-responsive ionogels to internal (to the human body) and external stimuli can be achieved by carefully engineering their composition. Up to date, ionogels responsive to pH [48], temperature [78], magnetic [93] and electric fields [76], as well as microwave radiation [94] have been designed as advanced materials in the field of drug delivery. If the use of thermo-responsive polymers such as N-isopropylacrylamide (NIPAM) [78] endows ionogels of temperature-responsive behaviour, the stimuli-responsive behaviour of ionogels can also be provided by ILs, *e.g.* by using ILs responsive to magnetic [93] or electric fields [76].

Current strategies to obtain gels with self-healing properties encompass the application of dynamic physical [95] and chemical interactions [96]. Gels with physical interactions acquire self-healing properties through hydrophobic interactions, hydrogen bonding, or crystallization while chemically cross-linked gels come from dynamic chemical bonds such as phenylboronic acid complexes, disulfide bonds, imide bonds, among others [97]. Among ionogels, self-healing behaviour arise from hydrogen bonding and coulombic interactions between gelators and ILs [60]. Ionogels prepared based on N- isopropylacrylamide (NIPAM), N, N-dimethylacrylamide (DMA), and the 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([EMI][TFSI]) showed fast-healing ability at ambient conditions for which synergistic hydrogen-bonding between PNIPAM chains, PDMA chains and the IL largely contributed [91]. On the other hand, self-healing (self-healed in 30 min at room temperature) polyurethane ionogels were fabricated by introducing reversible boronic ester bonds into the polymer as a cross-linking agent through the click reaction of the double bonds on the dihydroxy ILs monomers and the sulfhydryl group on the boronic ester [98]. Self-healing and mechanical properties are closely related, being crucial to ensure that the ionogels retain their original state after an external perturbation, which in the case of dressings ensures they would perfectly fit the wound and withstand mechanical forces.

Over the years, ILs have been proposed to overcome the shortcomings faced in the formulation development stage of (bio)pharmaceuticals [32,99], namely to improve dissolution and preserve the stability of proteins [100], antibodies [101], nucleic acids [102], or viruses [103], as well as synthetic pharmaceuticals [104,105] (including as API-ILs [27,106]) and natural products [79,107]. Up to date, this feature has been explored to design ionogels for the targeted delivery of drugs with improved solubility, as analysed in detail in section 3.2.

Generally resulting from ILs with biological activity [26], ionogels endowed with antimicrobial or anti-inflammatory properties have drawn attention from the scientific community. ILs' antimicrobial effect and toxicity to humans are closely related features in which understanding the mechanisms of bacterial and mammalian cellular damage is the key to affording effective and biocompatible antimicrobial ILs [108]. In general, the antibacterial activity of ILs is attributed to the insertion of alkyl chains into the bacterial membrane, as well as the electrostatic interactions between the cationic groups of ILs and bacterial cell walls, increasing the permeability of cell membrane and even destroying cell membranes [60,109]. As discussed in more detail in the next section, the increase of alkyl chains will enhance the surface activity of IL, ultimately providing a stronger ability to disrupt cell wall and cell membrane to a certain extent [109]. The mechanism of Gram-positive and Gram-negative cell wall destruction by ionic liquids include four different stages, sketched in Fig. 6: i) Adsorption – ILs approach bacterial cell wall/membrane; ii) Electrostatic interaction – deactivation of membrane proteins and interaction of the IL with phospholipids; iii) Penetration – disorganization of cell membrane and release of cytoplasm content; iv) cell wall destruction and, consequently, cell lysis [110]. ILs endowed of antimicrobial activity comprise cationic ILs, PILs, and anionic ILs, the latter composed of anionic antibiotics as API-ILs with potential to increase the solubility and bioavailability of antibiotics, reverse bacterial drug resistance, and improve antimicrobial activity *via* synergistic effects [109].

Similarly to antimicrobial anionic ILs, anti-inflammatory ILs are usually obtained as API-ILs [24] in which non-steroidal anti-inflammatory drugs (NSAIDs) [27,106,111–113], or phenolic acids [114–117] are introduced as ionic constituents of ILs. NSAID-based

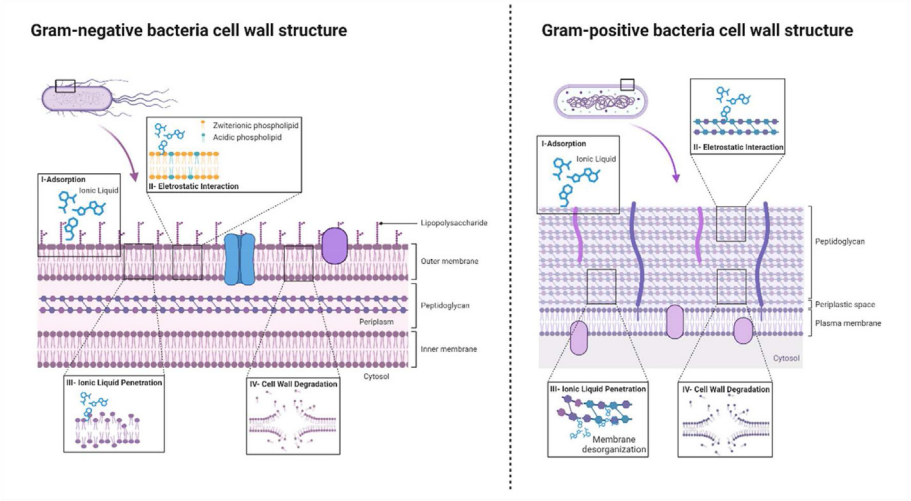

Fig. 6. Mechanism of action of ILs in cell wall destruction of Gram-negative and Gram-positive bacteria. Information retrieved from Nikfarjam et al. [110] Created with Biorender.com.

API-ILs can be obtained from the combination of the cholinium cation with ketoprofen, naproxen, ibuprofen, etodolac or lidocaine as anions [106,111–113], or designed to incorporate simultaneously pharmacologically active compounds in the cations and the anions, *e.g.* lidocainium ibuprofenate, lidocainium naproxenum or lidocainium diclofenac [27]. From a different point of view, the combination of the cholinium cation with anions derived from caffeic, ellagic, and gallic acids [115], caffeic acid [116], caffeic, vanillic, gallic and salicylic gallic acids [117] allowed to obtain biocompatible biomaterials with relevant anti-inflammatory and antioxidant properties. Although the mechanism of action of these anti-inflammatory API-ILs is not clearly understood, they are able to significantly decrease the lipopolysaccharide-induced oxide nitric production and block the secretion of pro-inflammatory cytokines [115, 116]. Finally, if the ionization of drugs is a promising approach with benefits in terms of solubility and availability, the potential for adverse reactions is still unknown, deserving further investigations [118].

2.2.3. *Biosafety and biodegradability*

The ever-growing interest of ionogels in pharmaceutical applications justifies the need to accurately evaluate their toxicity and biodegradability profiles. As the debate whether ILs (and inherently IL-derived materials) are safe or not for humans continues, it remains clear that a judicious choice of the IL chemical structure is critical to obtain IL-based materials with improved safety and biodegradable character, irrespective of the intended purpose [119].

The toxicity of ILs has been evaluated through inhibition assays using different microorganisms, enzymes, mammalian cell lines, and mammals. Besides the assessment of their safety to humans, their high solubility in water and persistence in soils highlight the importance of ecotoxicity evaluations to prevent potential environmental problems [120]. Under the framework of this review, we will focus our attention on mammalian *in vitro* and *in vivo* testing. Overall, the effect of the alkyl chain length exerts a profound influence on the toxicity of ILs. An increase in the alkyl chain length of cations will generally increase the toxicity of ILs, due to an increase in the lipophilic character ultimately causing the disintegration of the lipid bilayer [60]. This is also evidenced for mammals where the oral administration of 3000 mg kg^{-1} day^{-1} of 1-ethyl-3-methylimidazolium chloride - [C_2mim]Cl –in mice did not promote morphological defects in the fetus. However, fetal weight and apparent teratogenic effects were associated with ILs comprising longer alkyl chain lengths, namely, 1-butyl-3-methylimidazolium chloride - [C_4mim]Cl – and 1-decyl-3-methylimidazolium chloride - [C_{10}mim]Cl [121]. Landry et al. [122] also investigated the acute oral toxicity of [C_4mim]Cl in female Fischer 344 rats and found that the oral LD_{50} (amount of compound that kills 50 percent of the test sample) was 550 mg/kg of body weight. The effect of different head groups of the cationic counterparts of ILs is less pronounced [60], being however shown that piperidinium-based ILs are more toxic than those based on the pyrrolidinium moiety [123], while dicationic pyridinium-based ILs exhibit less cytotoxicity than their monocationic counterparts [124].

Adding to oral administration, toxicity assessment of ILs in the skin is equally important, especially considering the application of ionogels as wound healing dressings. Hwang et al. [125] evaluated the toxicity of a series of ILs, namely 1-ethyl-3-methylimidazolium bis (trifluoromethanesulfonyl)imide ([EMIM][TFSI]), 1-ethyl-3-methylimidazolium hexafluorophosphate ([EMIM][PF_6]), 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIM][BF_4]), 1-ethyl-3-methylimidazolium dicyanamide ([EMIM][DCA]), 1-butyl-1-methylpyrrolidinium bis (trifulormethanesulfonyl)imide ([BMPY][TFSI]), tributylmethylammonium bis(trifuloromethanesulfonyl) imide ([TBA][TFSI]) using human keratinocyte and fibroblast cell lines. In general, [TFSI]-containing ILs exhibited significant cytotoxicity, leading to necrotic cell death and an increase in the levels of reactive oxygen species (ROS) [125]. Even though favourable toxicity and biodegradability profiles are not always guaranteed, ILs constituents derived from biological sources have been investigated due to their reported biocompatibility. In addition to amino acids, artificial sweeteners, sugars, and organic acids [126], cholinium-based ILs derived from choline, a precursor of the phospholipids that comprise biological cell membranes, are the most studied [127]. Due to the potential use of ILs as preservation media for biopharmaceuticals, Freire and co-workers investigated the cytotoxicity of cholinium-based ILs (combined with Good's buffers [102] or amino acids [128] as anions) onto human fibroblasts cell lines, prototypical cells of the human epithelium. With exception of cholinium lysinate, all the ILs in study were found to be harmless at a concentration of 2 % (w/w) [102,128]. Mixtures of cholinium bicarbonate and geranic acid (CAGE) exhibit remarkable abilities to enhance the permeation of drugs across the skin. In this regard, Jorge et al. [129] found that the half maximal inhibitory concentration (IC_{50}, a measure of the effectiveness of a substance in inhibiting a specific biological or biochemical function, which determines the concentration of product needed to kill 50 % of the cells) of a mixture of cholinium bicarbonate and geranic acid (CAGE) 1:1 and 1:2 were, respectively, 2.45 and 2.01 mM toward HaCaT (immortalized human keratinocytes) cells. Upon oral or transdermal administration, most ILs are absorbed into the bloodstream and excreted relatively quickly from the body as feces and urine in processes believed to be related to organic cation transporters [130].

Regarding ionogels themselves, their biocompatibility has been evaluated as well using cell lines or *in vivo* experiments. Using human

dermal fibroblasts and blood red cells, polymeric ionic liquids-based ionogels resulting from imidazolium- and ammonium-based monomers (vinylbenzyl dimethylbutylammonium chloride, 1-methyl-3-(4-vinylbenzyl) imidazolium chloride, and 1-butyl-3-(4-vinylbenzyl) imidazolium chloride) were shown to fulfill the general acceptance criteria for biocompatibility of medical materials, respectively, a relative growth rate >75 % and low hemolysis rate [131]. Additional works using human and mouse fibroblasts further reinforced the low cytotoxic character of ionogels with different compositions, including PILs comprised by imidazolium-based monomers and polyvinyl alcohol [48], vinyl-modified lignin/HEMA [39], or polyethylene glycol [29], as well as imidazolium-based PILs with ionically- and chemically-bonded amino acid groups [30]. *In vivo* studies using mice models generally show that ionogels composed *e.g.* by catechol-containing PILs [112], or a mixture of cholinium bicarbonate and geranic acid and polyvinyl alcohol/chitosan [132] do not induce obvious lesions at the oral cavity, the application site.

Being able to be recycled or not, ionogels will at the end of their life cycle inevitably enter the environment. If considering human applications, particularly for drug delivery using enteral and parenteral administration routes, it is also of utmost importance to decrease the levels of residues in the human body while avoiding persistent inflammatory responses due to their extended half-lives [33,127]. These requirements can be met if fully biodegradable ionogels are designed, which generally depends both on the IL and the solid network applied.

Biodegradation, the 10th Principle of Green Chemistry, is one method of analysis to determine and predict how a molecule interacts with the environment and is crucial to avoid the introduction of persistent molecules [133]. As a result of the quest for ILs of a more biocompatible nature, the biodegradability of ILs (including comprehensive data on biodegradation data of hundreds of ILs) [133] and respective standardized tests for their evaluation has been thoroughly reviewed [120, 133–137] Biodegradation tests of ILs must consider the anion and cation as a pair, and caution should be taken regarding the anionic component as inorganic anions do not contribute directly as a carbon source for biodegradation determination [133]. Unlike fluorinated anions, alkylsulfates as well as carboxylate anions like lactate, acetate, propionate, succinate present good biodegradation rates [135]. Regarding IL cations, the results from biodegradation studies are mixed and largely depend on the side chain functional groups, being generally shown that longer alkyl side chains turn ILs more biodegradable [138]. This raises a challenge for chemists in the design of biodegradable ILs with low toxicity as an increase in the IL alkyl side chain will, simultaneously, increase its toxicity [138]. In addition to avoiding the use of imidazolium-based cations, current trends to obtain ILs with low toxicity and good biodegradability profiles seek to use side chains comprising ester and anion chains, preferably alkyl sulphates, alkyl sulphonates, and salts of organic acids and avoiding the use of fluorine [120].

Up to date, many ionogels employ nondegradable materials as network scaffolds, including silicone or acrylic elastomers, which may cause secondary environmental pollution at the end of their functional life [91]. Ionogels formed by a mixture of cholinium bicarbonate and geranic acid and PVA aimed at the oral delivery of insulin were found to be completely disintegrated and dissolved in the release medium (phosphate buffered saline) [132]. Noshadi et al. [127] studied the *in vivo* biodegradation of gelatin methacryloyl (GelMA) and cholinium acrylate-based ionogels. The gels were subcutaneously implanted *in vivo* in rats, and explanted samples revealed that the ionogels exhibited sustained biodegradation throughout the 28-day experiment, suggesting that the gels were efficiently degraded *in vivo* through enzymatic hydrolysis of the matrix [127]. Additional reports demonstrate that polycarbonate/1-butyl-3-methylimidazolium lactate-based gels are completely degraded in water at room temperature after 5h [139], and that the hydrolysis rate of thioimidazolium-based PILs in the presence of different anions can be described by the Hofmeister series. While hydrolysis is inhibited in solutions containing phosphate anions, the presence of chloride anions increases the degradation rate [140]. Liu and co-workers [91] prepared biodegradable ionogels using the IL 1-butyl-3--methylimidazolium tetrafluoroborate and stereocomplex nanocrystallites polyurethane scaffolds (scPLA-PEG), prepared from poly/L-lactide), poly (D-lactide), and polyethylene glycol. According to the authors, the reversible and biodegradable properties of the "sc" cross-linking accounts for the recyclability and biodegradable properties of these ionogels [91].

Overall, further studies to determine the safety and biodegradability levels of ionogels are still required. These should be based on standardized tests (choice of animal models and exposure conditions) and broadened to allow an understanding of the environmental fate of ionogels and evaluation of spread, uptake, bioaccumulation, and biotransformation. The tests suggested by the European Union REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) and global OECD (Organization for Economic Co-operation and Development) for a comprehensive and systematic approach should be followed to assess the toxicity and biodegradability profiles [134,141]. The use of artificial intelligence and machine learning techniques may play a role in mining and modeling toxicity data to make meaningful predictions while aiding in the identification of the most promising chemical structures to obtain ILs of an enhanced biocompatible nature [142].

3. Ionogels in pharmaceutical applications

In the early days, ionogels were subject of high interest by the scientific community for electronic applications, a result from their high ionic conductivity and improved mechanical properties. As neat ILs and their aqueous solutions evolved in the pharmaceutical field, either as biologically active agents with antimicrobial and anti-inflammatory properties or as solvents able to improve the pharmacokinetic properties of several (bio)pharmaceuticals, ionogels started to be investigated in this field as well. This review considers the application of ionogels in the pharmaceutical field and is divided into two main sub-sections: the first addresses the use of ionogels as dressings for wound healing with emphasis on their antimicrobial character, while the second is focused on the performance of ionogels as drug delivery systems with controlled-release behaviour and high drug solubility.

3.1. Dressings for wound healing with antimicrobial properties

Over the years, gels have been studied as biomaterials for wound dressing applications to improve the healing of wounds while preventing bacterial infections. Since traditional wound dressings, such as bandages and gauzes, require regular application and may have poor adhesion properties and wound drainage [143], ionogels have been approached to overcome these limitations. In general, the traditional dressings can be loaded with antibiotics or silver ions to help reducing the possibility of infections, but their overuse can trigger the tolerance of bacteria and other side effects [74,143]. However, If properly designed, ILs can cross bacterial membranes, alter cell wall characteristics, lead to membrane dysfunction, and cause irreversible damage by the creation of pores in bacterial membranes, thus presenting antimicrobial properties [110]. As schematized in Fig. 7, the scientific publications herein reviewed focus on the creation of ionogel dressings for wound healing applications with relevance to their antimicrobial character, divided across two sub-sections: the first comprising the works where the influence of ionogels composition on their antimicrobial activity was investigated, while the second compiles reports where attention was drawn to multifunctional gels with other biological activities than the antimicrobial character. Topical formulations mainly focused on the transdermal delivery of bioactive drugs, including for wound dressing applications, are considered in the next section.

3.1.1. Effect of ionogels composition on their antimicrobial character

Having in mind the current rise in antimicrobial resistance, the

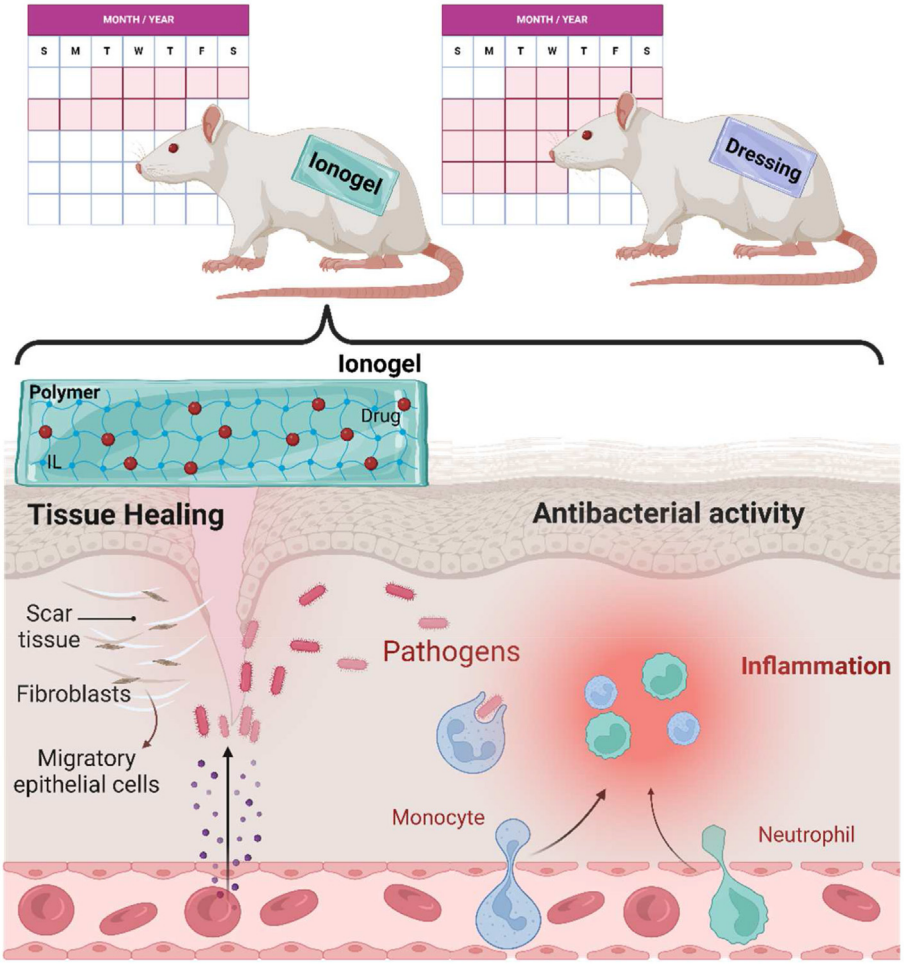

Fig. 7. Schematic representation on the use of ionogels as wound dressings and the benefits brought by their multiple biological activities (*e.g.*, antibacterial and anti-inflammatory properties), ultimately accelerating the wound healing process. Created with BioRender.com.

application of ionogels with antimicrobial activity, a property that may be conferred either by the IL or the solid network applied (building blocks of ionogels), is a hot topic of research and several manuscripts have addressed this issue. Table 3 summarizes the analysed works, listing the IL and solid network used for material preparation, the ionogel's preparation method, whether they present antimicrobial activity and for which microorganisms, and if *in vivo* studies were performed, a crucial aspect if envisaging their translation onto the clinical setting.

An antibacterial gel using PVA (Poly(vinyl alcohol)-tetrahydroxyborate anion hydrogel as a vector and pyrrolidinium ILs as antibacterial drugs was reported by Zheng and co-authors [48]. The prepared gel exhibited effective antimicrobial activity against *E. coli* and *S. aureus*, which was more pronounced for materials containing ILs with longer alkyl chains, causing irreversible physical damage to weaken bacterial resistance. Due to the moisture retention, self-healing, syringeability, and multi-responsive behaviour to pH and concentration of glucose, the authors highlight these antibacterial gels as ideal candidates to be applied as dressing materials for joint skin wound healing [48]. Non-releasing PIL/PVA hydrogel dressings with high-strength and excellent activity against bacteria (*B. subtilis*, *E. coli,* and *S. aureus*), fungus (*C. albicans*) and mold (*Asp. niger, Asp. oryzae* and *Rhizopus* spp.) were designed to overcome issues associated with uncontrolled release of antibiotics or silver ions potentially causing drug resistance, argyrism and other side effects [144]. The authors concluded that the antibacterial mechanism of cationic compounds is mainly related with two aspects: electrostatic interaction between phosphate groups in bacteria's cell membrane and PIL functional groups, and the hydrophobic segment insertion into the bacteria's lipid membrane, leading to cell death. Furthermore, the authors confirmed the good biocompatibility of the prepared materials using mouse osteoblasts (MC3T3-E1) cells. The wound healing capability was ascertained using *in vivo* mice models with wound contraction being significantly enhanced when treated with the materials at the 10th day [144].

Having in mind the importance of developing antibacterial materials to treat skin wounds infected by methicillin-resistant *S. aureus* (MRSA), Yan and co-workers [30] investigated different synthetic routes for the preparation of PIL-membranes based on amino acids (proline - Pro and tryptophan - Trp). To study the effects of chirality (*D*- or *L*-enantiomers) and chemical bonding (ionic or covalent) of the amino acid groups attached to the PIL on the antibacterial properties of the resulting membranes, the authors prepared: i) ionically-bonded membranes (denoted as I-*D*-Trp, I-*D*-Pro, I-*L*Trp and I-*L*-Pro), synthesized by photopolymerization of 3-Hexyl-1-vinylimidazolium bromide ([HVIm]Br), styrene, acrylonitrile, divinylbenzene and 1-hydroxycyclohexyl phenyl ketone, after which these PIL membranes were immersed in a solution of amino acid to convert the anion bromide into the target amino acid; ii) covalent-bonded monomers (abbreviated as C-*D*-Trp, C-*D*-Pro, C-*L*-Trp, and C-*L*-Pro), synthesized by photopolymerization as previously described and using the IL monomers described in Table 3. The antibacterial effectiveness of PIL bromide-based membranes was lower compared to covalently and ionically-bonded PIL membranes. This highlights the role of amino acids in enhancing the antibacterial properties of the resulting membranes. Furthermore, D-enantiomeric amino acid groups exhibited superior antimicrobial activity in comparison with

Table 3
Summary of the works reported on the use of ionogels as dressings for wound healing applications with relevance to the effect of their composition on the resulting antimicrobial character.

Goal	Preparation method	Ionic Liquid	Solid support	Antimicrobial activity	*In vivo* assays
Preparation of gels with PVA-tetrahydroxyborate as a vector and antibacterial pyrrolidinium-based ILs and properties' evaluation: syringeability, self-healing ability, pH-/glucose-responsiveness and antibacterial activity [48].	Direct mixing.	1-butyl-1-methylpyrrolidinium bromide - [C_4MP]Br; 1-hexyl-1-methylpyrrolidinium bromide - [C_6MP]Br; 1-octyl-1-methylpyrrolidinium bromide - [C_8MP]Br; 1-dodecyl-1-methylpyrrolidinium bromide - [C_{12}MP]Br.	PVA-tetrahydroxyborate anion.	Yes (*E. coli*; *S. aureus*).	No.
Synthesis of non-releasing antimicrobial PIL/PVA gel dressings for wound healing [144].	*In situ* polymerization.	PIL based on 1-vinyl-3-butylimidazolium bromide - [VBIM]Br.	PVA.	Yes (*A. Niger*; *A. Oryza*; *B. subtilis*; *C. albicans*; *E. coli*; *Rhizopus* spp.; *S. aureus*).	Yes (*In vivo* wound healing study using Kunming female mice).
Synthesis of amino-acid-based ILs and PIL membranes as antibacterial materials to treat skin wounds infected by MRSA. Additional assessment of the effect of chirality (*D*- or *L*-enantiomers) and chemical bonding (ionic or covalent) on antibacterial properties [30].	*In situ* polymerization.	PILs prepared from: i) 1-vinyl-3-hydroxyl-heptylimidazolium bromide - [HVIm]Br - ionically-bonded membranes; ii) *L-/D*-3-heptyl-1-vinylimidazolium proline bromohexyl ester bromide (IL-*L-/D*-Pro); *L-/D*-3-heptyl-1-vinyl-imidazolium tryptophan bromohexyl ester bromide (IL-*L-/D*-Trp) - covalent-bonded membranes.	Co-monomers: acrylonitrile and styrene.	Yes (*E. coli*; *S. aureus*).	Yes (Wound healing assay using mouse previous spread with a suspension of MRSA in dorsal skin wounds).
Synthesis of antibacterial and antifungal gels with anti-freezing, non-drying and self-healing properties, able to be used as a wound healing dressing, even under extreme conditions [15].	*In situ* polymerization.	1-vinyl-3-butylimidazolium bromide - [VBIM]Br.	PVP, acrylamide, PEGDA.	Yes (*E. coli*, *S. aureus* and *C. albicans*).	Yes (*In vivo* wound healing study using Kun Ming female mice).
Development of a simple and fast-one pot method for the preparation of cellulose gels and characterization of the swelling behaviour, mechanical properties and antibacterial activity [145].	*In situ* polymerization.	N-butyl-N-methylpyrrolidinium hydroxide.	Cellulose.	Yes (*B. subtilis*; *E. coli*).	No.
Preparation of a series of quaternary ammonium (Qa) or imidazolium (Im) cation-based PIL membranes and their corresponding zinc ion coordinated PIL membranes with antimicrobial efficacy for wound healing applications [131].	*In situ* polymerization.	PILs resulted from the following IL monomers: vinylbenzyl trimethylammonium chloride (IL-Qa-C1); vinylbenzyl dimethylbutylammonium chloride (IL-Qa-C4); 1-methyl-3-(4-vinyl-benzyl) imidazolium chloride (IL-Im-C1); 1-butyl-3-(4-vinylbenzyl) imidazolium chloride (IL-Im-C4).	Co-monomers: acrylonitrile and styrene.	Yes (*C. albicans; E. coli;* MRSA*; S. aureus*).	Yes (Wound healing test using methicillin-resistant *S. aureus* infected mouse as the model).
Synthesis by electrospinning of PIL-based fibrous membranes complexed with cerium (IV) ions and evaluation of their antimicrobial properties [146].	*In situ* polymerization.	PILs resulted from 3-Hexyl-1-vinylimidazolium bromide - [HVIm]Br.	Co-monomers: AANTA and polyacrylonitrile.	Yes (*E. coli*; *S. aureus*).	Yes (Using mice with an open excision wound inoculated with drug-resistant bacterial suspensions).

Abbreviations – AANTA - 2,2-(5-acrylamido-1-carboxypentylazanediyl) diacetic acid; *A. niger – Aspergillus niger*; *A. oryza – Aspergillus oryza*; *E. coli – Escherichia coli*; *B. subtilis. – Bacillus subtilis*; *C. albicans – Candida albicans*; HEMA - Hydroxyethyl methacrylate; IL – Ionic liquid; MRSA – Methicillin-resistant *Staphylococcus aureus*; PEG – Polyethylene glycol; PEGDA - polyethyleneglycol dimethacrylate; PIL – Poly(ionic liquid); PVA – Poly(vinyl alcohol); PVP – polyvinylpyrrolidone; *S. aureus – Staphylococcus aureus*.

PIL membranes based on L-enantiomers. On the other hand, ionically-bonded PIL membranes demonstrated higher antibacterial activities compared with the corresponding covalently-bonded PIL membranes, and the authors hypothesized that the free amino acid anions of the ionically-bonded PIL membranes would be easier to connect to the bacteria surface, making the naked cations more accessible to the bacteria. Using MRSA-infected mouse models, the I-D-Pro membrane was successfully used for skin wound healing, demonstrating that it could significantly promote wound healing, decrease local tissue inflammation, and decrease the influence of bacteria on vital organs (liver and spleen). In general, these results indicate that the amino acid-based PIL membranes display good biocompatibility and excellent antibacterial activity [30].

To overcome issues associated with traditional gel dressings due to water loss at high temperature or water freezing at low temperature while investigating the effect of the concentration of PIL in their antimicrobial character, wound dressings gels prepared *via* a one-pot method based on polyvinylpyrrolidone (PVP), acrylamide, 1-vinyl-3-butylimidazolium bromide ([VBIM]Br) and polyethylene glycol dimethacrylate were reported by Li and co-workers [15]. Unlike the gel without IL, ionogel dressings exhibited antimicrobial activities either to bacteria (*E. coli* and *S. aureus*) and fungus (*C. albicans*), more evident as the proportion of [VBIM]Br increases. The prepared gels additionally possess high water content, swelling ratio, and self-healing, anti-freezing, and non-drying properties. Based upon the results of wound closure and histopathological examinations, it was demonstrated that the fabricated gel wound dressing effectively promotes the wound healing process in a full-thickness skin defect model and could be both reused (sterilized at high temperatures) and adapted to cold weather conditions [15]. A distinct work reported the application of N-butyl-N-methylpyrrolidinium hydroxide in aqueous solution to dissolve 20 wt% cellulose, after which the gelation behaviour of cellulose was investigated after crosslinker

(epichlorohydrin) addition [145]. By tuning the concentration of cellulose, very soft gels or soft to slightly brittle gels more resistant to mechanical stress were prepared, respectively, if cellulose concentrations within the ranges of 5/7.5 wt% or 10/15 wt% are applied. The authors additionally demonstrated that the antimicrobial activity of the materials was higher by decreasing the amount of crosslinker and increasing the cellulose concentration. Overall, the prepared ionogels showed antimicrobial activity against two bacterial strains that are commonly found in wound infections, namely *E. coli* B/r and *B. subtilis* [145].

Previous reviewed research has shown that the synthetic route [30], PIL content [15], and solid network composition [145] impact the antimicrobial activity of ionogels. Adding to these, coordination of membranes with cations is a crucial factor influencing the antimicrobial effectiveness of ionogels designed for wound dressing applications. In this regard, Yan and co-authors [131] reported a variety of PIL membranes based on quaternary ammonium (Qa) or imidazolium (Im) cations, as well as the corresponding zinc ion coordinated PIL membranes. PIL membranes were obtained *via in situ* photo-crosslinking of a mixture containing the target IL monomer (see Table 3), acrylonitrile, and styrene, using divinylbenzene as cross-linking agent and benzoin ethyl ether as the photoinitiator. The corresponding zinc ion coordinated membranes were prepared by immersing PIL membranes in a zinc chloride-saturated ethanol solution. The effects of the PIL chemical structure, namely organic cations, alkyl side chain, and zinc atoms on their antimicrobial properties against *E. coli, S. aureus,* and *C. albicans* were then investigated. Among PIL membranes uncoordinated with zinc chloride, the Qa-type PIL membranes show antimicrobial efficiencies higher than those of Im-based membranes, and the longer alkyl side chains, the lower the antimicrobial activities. In addition, the antibacterial activity was further enhanced through coordination with zinc, resulting from synergistic attributes of organic cations and zinc atoms. After 4 h of contact with zinc-containing PIL membranes, the viable colonies of *S. aureus, E. coli,* and *C. albicans* almost completely disappeared. Additional biocompatibility tests showed that with exception of PIL-Qa-C1-Zn, all the remaining membranes fulfill the general acceptance criteria for biocompatibility of medical materials. Based on the *in vitro* antimicrobial activity and cytotoxicity evaluations, PIL-Qa-C1 and PIL-Im-C4-Zn were selected for additional wound healing tests using a mouse model, being concluded that zinc-containing PIL membranes are biologically safe and have potential applications as antimicrobial wound dressings in a clinical setting [131]. In addition to zinc, doping membranes with cerium cations may also affect the antimicrobial properties of ionogels with effects at the genetic level. This hypothesis was confirmed by Mao and co-authors [146] who fabricated nanofibrous membranes by electrospinning a mixture containing P(IL-co-AANTA-co-AN) and polyacrylonitrile (PAN) in N, N-dimethylformamide solution, and then immersed in a ceric ammonium nitrate solution to form Ce^{4+} ion complexed PIL membranes. P(IL-co-AANTA-co-AN) resulted from the free-radical copolymerization of the metal-ligand monomer 2,2′-(5-acrylamido-1-carboxypentylazanediyl) diacetic acid (AANTA) and the IL monomer 3-hexyl-1--vinylimidazolium bromide ([HVIm][Br]). The effect of the PIL and cerium moieties allowed the membranes to exhibit similar antimicrobial efficiencies against *E. coli* and MRSA. However, it is worth noting that unlike PIL membranes, cerium-treated membranes were found to be able to break down drug-resistant genes placed either on a plasmid or on a chromosome. Finally, the membranes were tested in mice infected with MRSA with the *in vivo* results confirming that Ce-containing PIL nanofibrous membranes combine both antibacterial and deoxyribonuclease-mimic properties, having thus potential applications as a new antimicrobial wound dressings to block the drug resistance spread in a clinical setting [146].

Since ionogels were introduced, several reports on the preparation of these materials acting as antimicrobial gels for wound healing applications have emerged, and often proven efficient in reducing the activity of Gram-negative (*E. coli*) and Gram-positive bacteria (*S. aureus*, including MRSA) and also of some fungus like *C. albicans*. However, one should note that even though these bacterial species are amongst the most prevalent in wound infections [147], other commonly reported species such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* should be studied as well and increasing attention should be paid for multi-drug resistant strains. This will enlighten on the real applicability of ionogels to help control infections in wound management without antibiotic supplementation. Contrarily to bacteria and fungus, the ability of ionogels to kill or inhibit the growth of viruses has been seldom studied, being a topic of interest to be considered in the future. Moreover, it is worth noting that the antimicrobial effect of ionogels largely depends on the type of IL and solid network, as well as the synthetic route applied.

3.1.2. Multifunctional ionogels

In addition to bacterial colonization, prolonged inflammatory phase, angiogenesis difficulties, and other serious complications can impede the infected wound repair process [148]. In this sense, ionogels with multiple biological activities have been approached to tackle these challenges. Table 4 summarizes the works focusing on the application of multifunctional ionogels for wound healing, listing the IL and solid network used for material preparation, the ionogel's preparation method, whether they present antimicrobial activity and for which microorganisms, and if *in vivo* studies were performed.

A novel composite gel dressing for wound healing was obtained from copolymerization of vinyl-modified lignin, hydroxyethyl methacrylate (HEMA) and the IL 3-butyl-1-isopropyl-1H-imidazole-3-ium bromide. Herein, lignin was shown to improve the mechanical properties of the gel dressing, while the PIL was responsible for the observed antibacterial activity and self-healing properties [39]. Also, the authors observed that the antioxidant activity of the dressings significantly increased with the increase of the lignin content. The antibacterial activity of the dressings was evaluated with *E. coli* and *S. aureus* by the colony forming units counting method, being observed a decrease in the number of viable colonies after contact for 24 h with the prepared dressings. Continuous antibacterial experiments proved that the composite hydrogel dressing has long-term and stable antibacterial properties, and thus can be used repeatedly. Furthermore, no significant decrease in mouse fibroblasts activity was detected after incubation with the prepared dressings, confirming that they are non-toxic and do not hinder cell proliferation. Finally, the authors used *in vivo* rat models to study wound healing and histomorphology, proving that the composite gel dressing effectively accelerates wound healing [39].

In a distinct strategy, two antibacterial imidazolium PILs, poly(N-butylimidazolium) propiolic acid and poly(N-(3,6-dioxaoctane) imidazolium propiolic acid) were synthesized by a polycondensation reaction, and later crosslinked with 4 arm thiol PEG (4 arm PEG-SH) to fabricate fast gelation and injectable antibacterial hydrogels by thiol-yne click reaction [29]. In comparison with the control, *i.e.,* gels without PILs, the fabricated ionogels had higher mechanical strength and shorter gelation time. The antibacterial activity of the gels was evaluated using *E. coli* and *S. aureus* colonies, and both gels could reduce the bacterial activity over 95 %. Since those gels were to be injectable, the authors also evaluated their cytotoxicity using two cell lines, human skin fibroblasts cells and human umbilical vein endothelial cells. The prepared gels demonstrated lower cytotoxicity than the control and showed anti-inflammatory activity by suppressing nitric oxide production activated by lipopolysaccharides, deemed advantageous to accelerate wound healing [29].

Zhang and co-authors [113] created an injectable wound dressing gel with self-healing and biocompatible properties, able to integrate antioxidant, anti-inflammatory and wound healing properties. It is important to highlight that despite the authors did not address the antimicrobial activity of the designed ionogels, previous reports indicate that the solid network applied, *i. e.,* silk sericin, presents antibacterial properties [150] and that PVA-silk sericin hydrogels had excellent antibacterial effects [149]. The authors used, for the first time, an etodolac-based IL as a drug template to enhance the bioavailability of the drug etodolac and

Table 4
Summary of the works reported on the use of multifunctional ionogels as dressings for wound healing applications.

Goal	Preparation method	Ionic Liquid	Solid support	Antimicrobial activity	*In vivo* assays
Preparation of lignin/PILs composite gel dressing with excellent mechanical strength, self-healing properties, bactericidal and antioxidant activities for wound healing [39].	*In situ* polymerization.	PILs resulted from 3-butyl-1-iso-propyl-1H-imidazole-3-ium bromide – [VMIM]Br.	Co-monomers: vinyl-modified lignin and HEMA.	Yes (*E. coli*; *S. aureus*).	Yes (Effect on wound healing using rats).
Fabrication of fast gelation and injectable gels by crosslinking of imidazolium-based PILs with PEG and characterization of their antibacterial and anti-inflammatory properties [29].	Direct mixing.	Poly(N-butylimidazolium) propiolic acid; Poly(N-(3,6-dioxaoctane) imidazolium propiolic acid).	PEG (4 arm thiol PEG).	Yes (*E. coli*; *S. aureus*).	No.
Preparation of silk sericin/PVA dressing gels loaded with etodolac-based ILs with antioxidant and anti-inflammatory properties to treat chronic wound healing [113].	Direct mixing.	Etodolac-based IL.	PVA and silk sericin.	Yes (Addressed in a previous work [149]).	Yes (Wound healing ability test using BALB/C (Bagg's albino) male mice).
Development of a transparent, pH-sensitive, highly stretchable, and biocompatible anthocyanidin ionogel dressing [87].	*In situ* polymerization.	1-Hydroxyethyl-3-methylimidazolium chloride.	Titanium carbide ($Ti_3C_2T_x$, MXene) and pectin.	Yes (Antibacterial)	Yes (Wound healing tests in Kun Ming mice)
Preparation of ionogel patches comprising ILs with phenolic acids as anions with antimicrobial, anti-inflammatory and antioxidant properties for wound healing [117].	Direct mixing.	Cholinium salicylate, cholinium gallate, cholinium vanillate, and cholinium caffeate.	PVA.	Yes (*E. coli*).	No.
Construction of a conductive antibacterial multifunctional gel and combination with exogenous electrical stimulation for *S. aureus*-infected wound healing [148].	*In situ* polymerization.	1-Vinyl-3-butylimidazolium bromide - [VBIM]Br.	PVA and PEGDA.	Yes (*C. albicans*, *E. coli*, *S. aureus*).	Yes (Using a *S. aureus*-infected diabetic total skin defect model).

Abbreviations –*E. coli* – *Escherichia coli*; IL – Ionic liquid; PEG – Polyethylene glycol; PEGDA - polyethyleneglycol dimethacrylate; PIL – Poly(ionic liquid); PVA – Poly(vinyl alcohol); *S. aureus* – *Staphylococcus aureus*.

hypothesized to be responsible for the observed anti-inflammatory properties of the constructed ionogels. The migration tendency of the cells (L929) was detected by a scratch test, which confirmed the wound healing activity *in vitro*. The gel's remarkable ability to speed up wound healing was further demonstrated by its strong reactive oxygen species scavenging capacity and comparable levels of control over inflammatory cytokines (TNF- and PGE-2) in an experiment using a mouse wound model [113]. Feng and co-workers [87] took advantage of the antioxidant and free radical scavenger ability of anthocyanidin to design improved ionogel dressings, prepared using pectin, $Ti_3C_2T_x$ MXene, acrylamide and the IL 1-hydroxyethyl-3-methylimidazolium chloride. In this case, the IL acted both as a solvent and as a backbone for hydrogen bond donors and acceptors to bind with anthocyanidin. The prepared ionogels display the ability to bind metabolites, evaluated using bovine serum albumin, and good water retention and swelling properties that are of paramount importance in the context of wound repair. In comparison with hydrogels (formulated without IL), ionogels showed high stretchability and low stress. According to the authors, the presence of anthocyanidin, the IL 1-hydroxyethyl-3-methylimidazolium chloride, and pectin ascribed interesting properties to the fabricated ionogels, namely a sensitive pH monitoring, antibacterial activity, and biocompatible behaviour. Collectively, these multifunctional properties provided the ionogel with excellent re-epithelialization in a 14-day wound healing process [87]. With a similar goal, soft and bioactive ionogels were prepared based on PVA and ILs composed of the cholinium cation paired with different anions derived from phenolic acids, namely the anions salicylate ([Ch][Sal]), gallate ([Ch][Ga]), vanillate ([Ch][Val]), and caffeate ([Ch][Caff]) [117]. Herein, the phenolic motif of ILs plays a dual role, acting as a PVA crosslinker and a bioactive compound endowing the materials with antioxidant and anti-inflammatory activities. The viability of these patches for wound healing applications was ascertained using different biological assays. The cytotoxicity upon peritoneal macrophages from *Mus musculus* CD 1 revealed that [Ch][Caff]-based gels decrease cell viability and induce changes in cell morphology. All the materials in study demonstrated no hemolytic effect and agglutination after 24 h of exposure to mice blood. The anti-inflammatory activity of the prepared ionogels was assessed based on their ability to decrease lipopolyssacharide-induced nitric oxide production, which was found to be more evident for PVA-[Ch][Caff] with a reduction of nitric oxide production of more than 63 %, in comparison with the positive control parthenolide. The antioxidant activity of the synthesized materials was determined based on their ability to react with a stable radical and reducing it to 2,2-diphenyl-1-hydrazine. The antioxidant activity values obtained were 57 %, 51 %, 32 %, 31 %, and 3 %, respectively, for PVA-[Ch]Caff], ascorbic acid (positive control), PVA-[Ch][Ga], PVA-[Ch][Van], and PVA-[Ch][Sal]. Finally, the antibacterial activity against *E. coli* was more pronounced for ionogels comprising PVA-[Ch][Sal] [117].

Aiming to take advantage of electrical stimulation as an emerging therapy to promote skin regeneration, conductive antibacterial multifunctional gels were prepared and combined with exogenous electrical stimulation for improving the *S. aureus*-infected wound healing process [148]. The multifunctional gels were composed of an IL [VBIM]Br polymer network crosslinked with polyethyleneglycol dimethacrylate (PEGDA), and a PVA-borax dynamic borate network, in which electrostatic interactions between the imidazole cation of the IL polymer network and the boron anion in the PVA-borax network takes place. The dynamic cross-linking between PVA and borax confers the gel with enhanced physical properties, fitting the wound perfectly and preventing local stress damage during application. On the other hand, the presence of the IL [VBIM]Br provides the gel with antimicrobial activity to *E. coli*, *C. albicans* and *S. aureus*, while improving light transmission facilitating the observation of the wound site. It also endows the fabricated gels with excellent electroconductivity, which could further promote cell proliferation and migration, heighten angiogenesis and collagen deposition with exogenous electrical stimulation. Built upon the favourable properties displayed by these multifunctional gels, the wound healing process was significantly accelerated, shortening the closure period of infected diabetic chronic wounds [148].

Up to date, few reports on the design of multifunctional ionogels with antimicrobial, anti-inflammatory, and antioxidant properties were disclosed as a comprehensive solution to accelerate the wound healing process. Yet, the number of studies with ILs that have shown biological activity (other than antimicrobial properties) is low. For instance, the antioxidant properties of phenolic acids can be enhanced by their conversion into cholinium-based ILs [114,115]. Thus, efforts should be addressed to the preparation of ionogels containing ILs with these improved properties since they can have additional advantages and the

gels could act not only as antibacterial and regenerative means, but a synergistic effect could be achieved. Apart from antimicrobial activity, mammalian cell cytotoxicity and *in vivo* studies are essential criteria to assess the biocompatibility nature of ionogels intended for human uses. Most of the works reviewed in this and the former sub-sections either demonstrated *in vitro* the low cytotoxicity profile of ionogels or their therapeutic efficiency, and to some extent their safety using *in vivo* mouse models.

3.2. Systems for targeted and controlled drug delivery with improved solubility

As a result of the increasing demand for efficient medical therapies without unwanted side effects, effective DDS for the targeted administration of toxic, sensitive, and poorly soluble medicines have been developed, ensuring suitable protection and distribution in different organs of the human body [17,151]. Being synthetic materials whose interaction with the human body is entirely different from biological ones, the biocompatibility of DDS is a crucial factor for their acceptability [10]. From a different point of view and aiming an improvement of API solubility, organic solvents may be required, raising however health and environmental concerns. The use of ILs in the preparation of gels can help in addressing some of those drawbacks, also bringing novel biological functionalities in comparison with conventional gels. The next sub-sections address the preparation of ionogels envisaging their application as DDS for enteral (3.2.1), parenteral (restricted to those involving injection) (3.2.2), and transdermal administration (3.2.2).

3.2.1. Ionogels for enteral administration

Enteral administration involves absorption of the drug *via* the gastrointestinal tract, including oral, gastric, duodenal, or rectal administration [152]. Oral delivery is among the most popular routes of drug administration, mainly due to self-administration easiness, safety, and patient compliance. However, it has some limitations since the drugs are prone to first-pass metabolism and generally have poor stability in the gastrointestinal system [153], which are challenges to overcome by DDS designed for this mode of administration. This sub-section addresses scientific publications focusing on the preparation of ionogels as DDS for oral administration, as depicted in Fig. 8.

Table 5 presents a summary of the works addressed and respective goals, the proposed route of administration, the IL and solid support used, the ionogel's preparation method, whether biocompatibility studies were performed, and the drug in study. Works where the authors do not directly envisaged ionogels for any route of administration nor assess their syringeability and injectability, are herein considered as well.

Aiming at the delivery of stomach-specific therapeutic agents, polymerized bio-IL-based nanogel matrices were fabricated and tested for the delivery of an anticancer drug [154]. Nanogel systems with an average hydrodynamic size of 41 ± 15 nm were developed by the simultaneous polymerization and cross-linking of the polymerizable bio-based-IL cholinium acrylate [154]. The nanogel thus obtained showed prolonged drug delivery (10 days) for an anticancer drug (5-fluorouracil) at pH 1.2 (stomach pH) and at the physiological human body temperature (37 °C). Remarkably, no substantial drug delivery was observed at pH values of 5 and 7.4, further confirming the effectiveness of these systems for the *in vivo* delivery of stomach-specific therapeutic agents [154]. Upon oral administration, gastroretentive DDS have been designed to prolong the release and enhance the absorption of drugs in the stomach or the upper gastrointestinal tract, from which gastric-floating DDS stand out due to the low risk of gastric injuries and minimal side-effects. Having this in mind, Xie and co-workers [155] prepared a low density hybrid gel based on starch and cellulose to be applied as gastric-floating sustained-release tablets. The gel was prepared using 1-ethyl-3-methylimidazolium acetate for polymer dissolution and loaded afterward with ranitidine hydrochloride as a model drug. With an increasing proportion of cellulose, the ranitidine hydrochloride loading content was lower but with a high starch content, the structure became less stable, which was consistent with the results of equilibrium swelling ability. Using *in vitro* assays that simulated gastric fluid, the authors demonstrated that the ionogel releases 45.87 % of the drug during the first 1 h and then a sustained release for up to 10 h. This represents a better-sustained release behaviour than that from ranitidine hydrochloride capsules where the accumulated release percentages at 0.5 h, 1.5 h and 2 h were, respectively, 62.16 %, 97.27 %, and 99.55 %. Finally, the authors also demonstrated that the hybrid materials could immediately float on the surface of water at 37 °C [155].

A PIL buccal tissue adhesive patch for treating oral aphthous was prepared *via* polymerization of a catechol-containing IL, acrylic acid, and butyl acrylate, followed by anion exchange to diclofenac anions [112]. The patch can adhere to wet tissues in the wound site and exhibits antimicrobial properties against bacteria and fungi, as well as anti-inflammatory activity due to the efficient delivery of diclofenac. The high stretchability (extending to 1100 %) and self-healing properties allow the developed patch to adapt to the complex oral environment, and *in vivo* studies using mouse models demonstrate their ability to accelerate oral aphthous ulcer healing, overall confirming their suitability as an oral mucosa patch [112]. In this context, ionogels can be used not only for targeted and controlled release of pharmacological substances but also have the potential to be used in biopharmaceutical applications [132]. In this regard, a biodegradable polymeric patch for buccal delivery of insulin was designed to readily dissolve at slightly acidic pH and effectively release the IL/insulin gel in the buccal pouch. By taking advantage of the

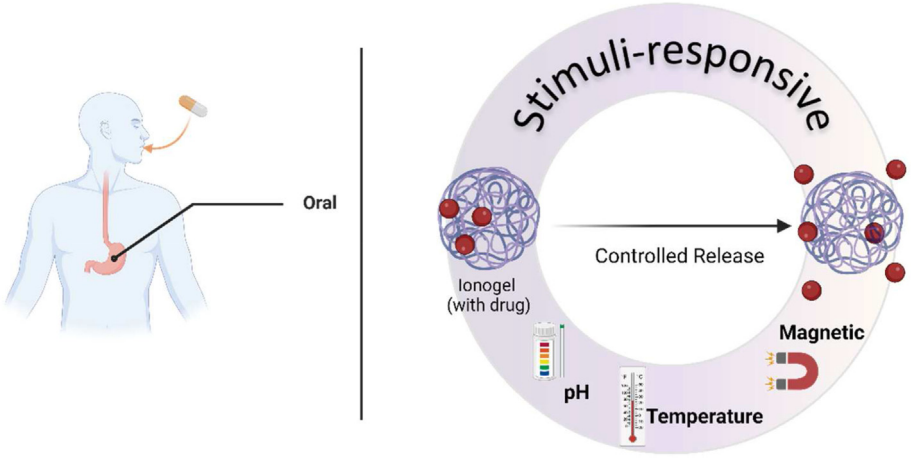

Fig. 8. Illustration on the application of ionogels as oral DDS for targeted and controlled drug delivery with improved solubility. Created with BioRender.com.

Table 5
Summary of the works reported on the use of ionogels for the targeted and controlled delivery of drugs with improved solubility focusing enteral administration.

Goal	Preparation method	Route of administration	Ionic Liquid	Solid support	Biocompatibility studies	Drug
Synthesis of ionogels based on polymerizable ILs with prolonged drug release profiles [154].	*In situ* polymerization.	Oral.	PIL comprising cholinium acrylate and N,N -methylene-bis-acrylamide.	None.	No.	5-fluorouracil.
Preparation of low density tablets based on polysaccharides for gastric-floating drug delivery purposes [155].	Direct mixing.	Oral.	1-ethyl-3-methylimidazolium acetate.	Starch (Gelose 50) and microcrystalline cellulose.	No.	Ranitidine hydrochloride.
Preparation of buccal adhesive patches comprising antibacterial PILs loaded with anti-inflammatory drugs to treat oral aphthous ulcers [112].	*In situ* polymerization.	Oral.	PIL based on a catechol-containing monomer (obtained by dimethylaminoethyl acrylate and 3,4-dihydroxyphenacyl chloride). Chloride exchanged to diclofenac anions afterward.	None.	Cytotoxicity and assessment of *in vivo* therapeutic efficiency.	Diclofenac (anionic form of PIL).
Fabrication of polymeric patches for buccal delivery of insulin using chitosan as the mucoadhesive matrix and ILs as transport facilitators [132].	Direct mixing.	Oral.	Cholinium bicarbonate and geranic acid (CAGE).	PVA and chitosan.	Buccal administration assays in rats.	Insulin.
Development of a mucoadhesive gel designed to adhere the intestine and able to entrap both the IL and therapeutic drug for their controlled and sustained release [80].	Direct mixing.	Oral.	Cholinium bicarbonate and geranic acid (CAGE).	PVA.	Cell viability using CaCo-2 cells.	Insulin.
Preparation of celulose ionogels non- and modified with tannic acid and L-methyonine for sustained release of selenourea [156].	*In situ* polymerization.	Oral.	1-ethyl-3-methylimidazolium acetate.	Cellulose.	No.	Selenourea.
Fabrication and characterization of pH-responsive ionogels using temperature-responsive low molecular weight IL-based gelators [77].	*In situ* gelation.	NR.	Cetylpyridinium salicylate.	NR.	No.	Imatinib mesylate.
Production of thermoresponsive ionogels comprised of silk fibroin and PVP for drug delivery [104].	Direct mixing.	NR.	Choline acetate, choline dihydrogen phosphate, and choline chloride.	Silk fibroin; silk fibroin and PVP.	No.	Phenobarbital.
Preparation of magneto-responsive ionogels by combining a biopolymer and a valine-based magnetic IL surfactant to be applied as drug delivery nanocarriers [93].	*In situ* polymerization.	NR.	$[ValC_{16}][FeCl_4]$.	Gelatin.	Ethidium bromide exclusion assay with salmon DNA.	Ornidazole; 5-fluorouracil.
Preparation of viscoelastic gels using a solution blend approach for the loading and release of an API-IL [28].	Direct mixing.	NR.	1-dodecyl-1-methylpiperidinium acetylsalicylate.	Agar, chitosan with low (L) and medium (M) molar mass.	No.	Acetylsalicylate (API-IL).
Preparation of bioactive linear PILs for the delivery of an antibiotic drug, incorporated as an anion in the PIL [157].	*In situ* polymerization.	NR.	PIL based on [2-(methacryloyloxy) ethyl]trimethylammonium p-aminosalicylate (ChMAPAS).	None.	No.	*p*-aminosalicylate (API-IL).
Sol-gel synthesis of silica-based ionogels comprising ibuprofenate under the form of an API-IL and investigation of their ability to act as DDS with controlled release kinetics [38].	Direct mixing.	NR.	1-methyl-3-butylimidazolium ibuprofenate.	TMOS or TMOS/MTMOS precursor mixtures.	No.	Ibuprofen (API-IL)
Preparation of monolithic ionogels using tetramethoxysilane as the silica source using an API-IL	Solvent exchange.	NR.	1-methyl-3-octyl-imidazolium ibuprofenate.	TMOS.	No.	Ibuprofen (API-IL).

(*continued on next page*)

Table 5 (*continued*)

Goal	Preparation method	Route of administration	Ionic Liquid	Solid support	Biocompatibility studies	Drug
acting both as templating agent and as a catalyst, promoting its own encapsulation [158].						
Encapsulation of a hydrophobic drug in hydrophilic polymeric core, and evaluation of the biocompatibility and anti-cancer activity of the resulting ionogels [40].	Solvent exchange.	NR.	Cholinium formate.	PHEMA.	Toxicity measured against zebrafish embryos.	Curcumin.
Ionogels preparation by self-aggregation of an IL-based surfactant and study of their ability to encapsulate drugs [159].	Direct mixing.	NR.	3- methyl-1-(hexadecyloxycarbonylmethyl) imidazolium bromide.	None.	No.	Imatinib mesylate; diclofenac sodium.

Abbreviations – API-IL – Active pharmaceutical ingredient ionic liquid; CAGE – Cholinium bicarbonate and geranic acid; DDS – Drug delivery system; IL – Ionic liquid; MTMOS – Methyltrimethoxysilane; NR – Not reported; PHEMA – Poly(2-hydroxyethyl methacrylate); PIL – Poly(ionic liquid); PVA – poly(vinyl alcohol); PVP – Polyvinylpyrrolidone; TMOS –Tetramethoxysilane.

high-water solubility, biocompatibility, mechanical strength, and adhesive properties, PVA was selected as the solid network. Chitosan and a mixture of cholinium bicarbonate and geranic acid (CAGE) were applied, respectively, as the mucoadhesive matrix and as the transport facilitator. A 7-fold increase in the cumulative insulin transport across the *ex vivo* porcine buccal tissue was induced by CAGE, confirming its ability as a permeation enhancer and to improve the transport of (bio)molecules across the buccal mucosa. The developed patches were placed in the rat buccal pouch, being observed their ability to lower *in vivo* blood glucose levels in a dose-dependent manner with no obvious lesions at the application site, additionally validating the safety and efficacy of this non-invasive system of administering insulin [132]. Also resorting to CAGE and PVA, the same research group prepared mucoadhesive ionogel patches designed to adhere to the intestine with controlled-release behaviour for both CAGE and insulin [80]. CAGE was encapsulated within PVA gels to form ionogels by two distinct approaches. In the first approach, solutions were left to dry undisturbed, and in the second, PVA solutions were subjected to repeated freeze and thaw cycles (FT-CAGE). FT-CAGE ionogel patches demonstrated mucoadhesive strength, swelling, and controlled release behaviour of both CAGE and insulin. Additionally, the authors reported a 30 % increase in the insulin transport across co-cultures of intestinal cells (Caco-2 and HT29-MTX-E12) when compared with controls, proving that the small intestine's ability to absorb insulin and other poorly soluble medications may be enhanced by CAGE. During oral administration, the ionogel patches could be used in a specific location and prevented long-term damage to the epithelium and drug loss due to epithelial cell uptake, being thus envisaged as effective systems for the oral delivery of biopharmaceuticals [80].

Stimuli-responsive systems respond to specific triggers (*e.g.*, pH, temperature, enzymes, magnetic field, among others) to release their cargo at the target site, enhancing drug efficacy while minimizing potential side effects [160]. For the sustained release of selenourea (SeU), Santra and Ken [156] created pH-responsive cellulose-based ionogels (CSeU) modified with tannic acid (CTSeU) and L-methionine (CMSeU) resorting to the IL 1-ethyl-3-methylimidazolium acetate as the solvent. The loading of SeU was performed in different approaches, namely with and without modification with tannic acid and L-methionine. From CTSeU, SeU release was high (79 %) at the pH 6.65, while only 40 % SeU was released by the same material at pH 2.09. CSeU and CMSeU, however, showed a lower drug release (below 5 %). The amount of SeU released from CTSeU was considerably lower (*ca.* 25 %) in simulated gastric fluid (pH 1.2), indicating that the microstructures of the beads are stable [156]. Furthermore, the tyrosinase inhibitory effect of SeU released from CSeU, CTSeU, and CMSeU materials show that it presents an inhibitory effect on the enzymatic activity of tyrosinase [156]. A pH-responsive ionogel with potential to specifically target cancer cells was developed by Malek and co-authors [77] using temperature-responsive IL-based LMWG, thereafter loaded with imatinib mesylate. Using cetylpyridiniumsalicylate (CetPySal) above its critical micellar concentration, a gel was formed at a physiological pH that was afterward immersed in a solution of imatinib mesylate. The prepared ionogels were able to encapsulate 10.2 % and 33.0 % of imatinib mesylate, respectively, at controlled temperatures of 15 °C and 25 °C for 72 h, with hydrophobic interactions being the dominant factor. The kinetic release profile of imatinib mesylate encapsulated in the designed ionogels was characterized at 37 °C and pH 5, 7.4 and 10 by resorting to different buffer solutions, in which pH 5 was used to mimic the intracellular environment of cancer cells. The imatinib mesylate release profile from the ionogel matrix was studied using a dialysis membrane against Milli-Q water and shown to be pH-dependent at 37 °C. Imatinib mesylate releases very slowly at pH 10 and pH 7.4 from the ionogel matrix. About 53.17 % and 88.3 % imatinib mesylate was released in 330 min at pH 10 and 7.4, respectively. On the other hand, imatinib mesylate release rate was notably enhanced under acidic conditions (pH 5), namely 94.17 % in only 210 min [77]. Temperature-responsive ionogels obtained by stirring a mixture of ILs, PVP and/or silk fibroin at 25 °C, followed by the dropwise addition of different formulations containing traditional pharmaceutical excipients (*e.g.*, trehalose, tween-20, sucrose, glycerol, and histidine) were prepared to encapsulate the model antiepileptic drug phenobarbital [104]. In the absence of ILs, the authors failed to observe the formation of gels over two months; however, ionogel formulations containing cholinium acetate and cholinium dihydrogen phosphate were relatively rapidly formed at 25 °C, contrasting with those comprised of cholinium chloride which required extended formation periods, as long as 32 days. Furthermore, cholinium acetate and cholinium dihydrogen phosphate-ionogels were formed below 37 °C in the absence of PVP, which could be beneficial for local and controlled drug delivery applications. Even though the time-course release of phenobarbital was not addressed, the authors observed the instantaneous solubility of this model drug in the presence of formulations containing cholinium acetate and cholinium dihydrogen phosphate, which is largely insoluble in formulations lacking ILs. Using a combination of experimental assays and density functional theory calculations, the authors attributed the formation of ionogels to macromolecular crowding and confinement effects [104]. Kumar and co-workers [93] prepared magneto-responsive ionogels by combining gelatin and vesicles of valine-based magnetic IL surfactant [$ValC_{16}$][$FeCl_4$], and explored their potential as drug delivery nanocarriers for ornidazole and 5-fluroucacil. After gel preparation, the drug was loaded *in vitro* in a phosphate buffer solution over a period of 24h and its release was also

studied in PBS at 37 °C for 4 and 96h, since after 96h no further release was observed. The encapsulation efficiency of ornidazole and 5-fluorouracil in the magnetic biocomposite gel was found to be 69 % and 78 %, respectively. Results show that lowering the concentration of [$ValC_{16}$][$FeCl_4$] in the magnetic biocomposite gel from the vesicular region to the micellar region, negatively impacts the loading efficiency of 5-fluorouracil and ornidazole to 49 % and 42 %, revealing that the vesicles are more favourable to load hydrophilic drugs. The prepared biocomposite gels show good magnetic behaviour and since they can be manipulated spatiotemporally using an external magnetic field, these gels are promising candidates as active scaffolds for advanced drug delivery applications [93].

Along with specific stimuli-responsiveness behaviour, other factors, including the physical form and composition of DDS, as well as the temperature required for gel formation, will influence both drug encapsulation and release profiles. A solution blend approach was applied for the preparation of viscoelastic gels composed of the API-IL 1-dodecyl-1-methylpiperidinium acetylsalicylate ([C_{12}mpip][AcSa]) in sodium salicylate aqueous media, as well as in agar, and chitosan with low (L) and medium (M) molar mass in aqueous media [28]. The release of the drug anion from gels as well as their dry cast thin films was monitored as a function of time. For gels, the release profiles of the drug anion were of S type and follow the order agar > chitosan (L) > chitosan (M), indicating that chitosan (M) chains hold more amount of drug anions. Also, the higher concentrations of biopolymers, the less the fraction of the drug anion released. At higher biopolymer concentrations, the density of network structures increases and does not allow the drug to dissipate. The release profiles were fitted to the Hixon-Crowell model, suggesting that the release predominantly occurs by simple dissolution of the drug anion upon dilution. For thin films, the release profile was found to be of inverted L type and fitted well with the Ritger-Peppas model, indicating that the drug release depends on complex factors such as diffusion, swelling, dissolution, and surface erosion. Overall, these results show that the mechanism of release can be tuned to desired characteristics by adopting the solution blend-based hybrid systems and also by changing the physical form of the drug carrier system [28]. PILs obtained from the copolymerization of [2-(methacryloyloxy)ethyl]trimethylammonium p-aminosalicylate (ChMAPAS) with methyl methacrylate (MMA) were prepared, containing *p*-aminosalicylate (PAS) as an anion while being an antibiotic effective against *Mycobacterium tuberculosis* [157]. The resultant PIL presented various contents of PAS anions (24–42 %), depending on the initial ratio of ChMAPAS to MMA and conversion degree. Since the drug anion is kept by ionic interactions with the polymer matrix, drug release is based on ion exchange with phosphate anions in the PBS buffer, applied to mimic the natural environment of the physiological fluid. Among the different ratios used of ChMAPAS/MMA, the case where the initial content of PAS monomer was 50 % in the polymerization mixture provided the optimal system, allowing full drug release within 4 h in a more controlled release process [157].

Vioux and co-workers [38] prepared an ionogel with ibuprofen under the form of an API-IL to control the kinetics of release of this drug. To this end, the API-IL 1-methyl-3-butylimidazolium ibuprofenate was synthesized by one-step anion exchange from 1-methyl-3-butylimidazolium chloride and sodium ibuprofenate. The IL was then used in a sol-gel synthesis using pure TMOS or TMOS/methyltrimethoxysilane (MTMOS) precursor mixtures and diluted HCl. Using simulated intestinal media (pH 7.48), the authors have shown that the release kinetics is slower with ionogels than with crystalline ibuprofen and pure ibuprofenate API-IL, demonstrating that ionogels act as drug reservoirs for controlled delivery [38]. Later, the same group [158] investigated the direct sol-gel encapsulation of an API-IL comprising a long alkyl chain imidazolium cation (1-methyl-3-octylimidazolium) and the ibuprofenate anion using TMOS as the silica source. Herein, a triple role was assigned to the IL, namely as an API, a sol-gel catalyst, and a tensioactive templating agent. Using a low IL-to-silica ratio of 0.25 and due to the bulkiness of the cation-anion pairs, materials with surface areas (812 $m^2 g^{-1}$) and pore volumes (1.25 $cm^3 g^{-1}$) higher than other ionogels previously reported in the literature were obtained. Furthermore, the catalytical activity of ibuprofenate led to a relatively high condensation degree (88 %) [158].

To increase the efficacy of curcumin encapsulation, MacFarlane and co-authors [40] investigated hydrophilic polymeric core poly(2-hydroxyethyl methacrylate) ([PHEMA]) nanoparticles from the gelled IL cholinium formate. Afterward, curcumin-loaded PHEMA nanoparticles (C-PHEMA-NPs) were prepared *via* a nano-precipitation method. The authors were able to load 26.4 % of curcumin in the biocompatible hydrophilic polymer. *In vitro* release patterns demonstrated that free curcumin releases more quickly than curcumin bound to nanoparticles. During the first 12h, 10 % of the entrapped curcumin from C-PHEMA-NPs was released slowly, followed by a sustained release pattern of the substance. The slower release in C-PHEMA-NPs compared with free curcumin may be a result of the drug's slow diffusion through the matrix of the polymer. Additionally, the authors tested the C-PHEMA-NPs' anticancer activity in ovarian cancer cells (SKOV-3), showing that it was more effective than free curcumin at regressing tumour cells. With an IC_{50} (Half maximal inhibitory concentration, measured by the cytotoxicity activity against SKOV-3) value of 3.78 μg/ml, C-PHEMA-NPs presented a higher cytotoxic activity than free curcumin, and thus effectively inhibited the proliferation of cancer cells. The toxicity of PHEMA nanoparticles was further investigated in a zebrafish embryo model, confirming that these materials are biocompatible. Overall, the authors demonstrated that PHEMA nanoparticles loaded with curcumin might have therapeutic benefits for the treatment of cancer [40]. To create an ionogel at physiological pH, Malek and co-workers [159] used an IL-based surfactant with an ester (3-methyl-1-(hexadecyloxycarbonylmethyl)imidazolium bromide) that self-aggregates at 8.80 % w/v in aqueous media. At 25 °C, the ionogel was capable of absorbing dyes and drugs like sodium diclofenac and imatinib mesylate. The prepared materials were able to encapsulate both drugs with encapsulation efficiencies of 40.4 % for diclofenac, and 72.3 % for imatinib mesylate. Contrarily, at 50 °C, the gel encapsulates only 1.4 % of diclofenac and 53.59 % of imatinib mesylate. In general, these materials demonstrate that the addition of 3-methyl-1-(hexadecyloxycarbonylmethyl)imidazolium bromide to an aqueous solution is able to form a gel-to-gel reversible transition with a change in temperature, opaque at 25 °C and transparent at 50 °C, ultimately allowing to control the encapsulation efficiency [159].

According to the works reviewed in this sub-section, ionogels are starting to be investigated as DDS for the oral delivery of drugs. Ionogels have been engineered to display improved mechanical properties (*e.g.*, adherence to wet tissues or self-healing properties), favouring their adaptability to complex environments such as the oral cavity. Concerning the solid supports employed in ionogel preparation, there is a preference for polymeric materials, some of them which have been previously reported for drug delivery based on hydrogels, micelles, polyplexes, or polymer-drug conjugates [161]. By carefully selecting the composition of ionogels, materials with the capacity to deliver their cargo in different locations of the gastrointestinal tract and/or with stimuli-responsive behaviour (pH, temperature, and magnetic fields) have been designed. Proof of concept studies have shown that ionogels can be applied as DDS to target the acidic intracellular environment from cancer cells. Nevertheless, the investigation of ionogels able to respond to external stimuli, such as light or electric fields, could guarantee a more sensitive and localized controlled release of pharmaceutical drugs. There has been an effort to study both hydrophobic and hydrophilic drugs/compounds; however, it is noticeable the lack of studies addressing biopharmaceuticals, with only two reports investigating insulin delivery. Considering the rapid growth of the biopharmaceutical market, in the future it would be interesting to understand how ionogels could improve the administration of such biomolecules and the effect on their shelf-life, especially considering their lower stability when compared with traditional pharma products. There has also been a limitation regarding the

type of ILs being studied since most focus on the imidazolium family. Nevertheless, some works already reported cholinium-based ILs, which are often reported to be more biocompatible. Specifically, there is a lack of studies considering API-ILs and mainly restricted to drugs with anti-inflammatory activity as well as for ILs with intrinsic biological activity. Their application would be interesting to explore in the future if the antibacterial, anti-inflammatory, antitumoural, and antioxidant activity could be improved by exploring new ILs, *e.g.*, by resorting to ILs comprising cholinium and anions derived phenolic acids [114,115] or taurine-based ILs [162].

3.2.2. *Ionogels for parenteral administration*

Despite involving injections that can be painful and associated with local reactions, parenteral administration of drugs subcutaneously, intradermally, intravenously, and intramuscularly, among others, represents an effective way of increasing the therapeutic efficiency of drugs since they reach circulation without having to cross the enteral mucosa or the liver [163]. This sub-section resumes the works dealing with the preparation of injectable ionogels for drug delivery applications, as schematized in Fig. 9.

Table 6 summarizes the works reviewed and respective main goals, the IL and solid support used, the ionogel's preparation method, whether biocompatibility studies were performed, and the drug in study.

Oscharz and co-authors [164] combined timolol maleate and polymerized anionic 3-sulfopropylmethacrylate potassium, and ibuprofen combined with poly-[2-(methacryloyloxy) ethyl] trimethylammonium chloride, and addressed the drug release profile of these materials. In PBS at pH 7.4 and 37 °C, the authors noticed that the release is rather dependent on the resulting concentration in solution than the actual release time, thus not being determined by the diffusion speed of the drug in the polymer. The investigated gels functionalized with different ion groups showed the ability to retain a counterion that is released only by ion exchange in contrast to a diffusion-controlled mechanism [164]. These gels are capable to be sterilized by gamma radiation, ensuring sufficient stabilization for medical applications [164]. Furthermore, the excellent biocompatibility of the designed gels had been confirmed in a previous work using *in vitro* cell seeding experiments [168]. Based on these promising properties, the authors identified PILs as very promising systems for drug depot applications in body regions with low flow rates, as is the case of subconjunctival space, accessible by minimally invasive surgeries (*e.g.*, in the treatment of glaucoma) [164].

Malek and co-authors [165] designed a PVA-based hybrid gel consisting of an ester-functionalized morpholinium-based IL (4-(2-(hexadecyloxy)-2-oxoethyl)-4-methylmorpholin-4-ium bromide) and other biocompatible additives. The designed polymeric ionogel responds to intracellular biological conditions, observed to be optimal at 37 °C and pH 5. Furthermore, the gel in the absence of IL showed a low encapsulation efficiency (~52.4 %) and drug loading capacity (~3.2 %) for doxorubicin, whereas the addition of doxorubicin at the same ratio in the presence of IL allowed to obtain higher encapsulation efficiencies, of approximately 79.7 % with a drug loading capacity of nearly 12.3 %. After 50 h, the *in vitro* doxorubicin release experiments show a 82.3 % cumulative release at 37 °C and pH 5.0, while a 53 % release was observed at pH 7.4. Acidic pH accelerates doxorubicin release due to increased hydrophilicity and desolubilization, while 37 °C increases drug release due to the increased permeability. The dual stimuli-responsive nature of the studied smart polymeric gel could be envisaged as a smart drug carrier for the wide-ranging positively charged drugs for cancer therapy, being additionally shown that it displays excellent biocompatibility [165]. Singh and co-workers [166] created an amphiphilic hybrid ionogel composed of poly (ethylene glycol)-block-poly(propyleneglycol)-block-poly(ethylene glycol) (Pluronic P123) using cholinium acetate that was loaded with iron oxide nanoparticles. This ionogel behaves as a highly effective DDS, demonstrated to be stimuli-responsive, biocompatible, and self-healable. Sodium diclofenac was loaded onto the ionogel matrix with and without iron oxide nanoparticles at 37 °C, and the gel was submerged in a liquid solution at 37 °C and 25 °C at 200 rpm to study the controlled release behaviour. Due to the increased thermal conductivity of iron oxide nanoparticles, it was demonstrated that their incorporation significantly improved drug release. At 37 °C and for 15 h, diclofenac showed a sustained release of 50 % for the gel loaded with nanoparticles, which contrasts with only 20 % when nanoparticles were not present. The results show that under physiological temperature conditions, the gel under investigation released diclofenac slowly and consistently [166].

Significant problems in drug delivery applications are also associated with the poor solubility of drugs and their stability over long storage periods [105]. Ionogels using fluorinated ILs for improved drug solubility while envisaging local drug administration through a needle were proposed by Hermida-Merino et al. [105]. The authors prepared mixtures comprising gelatin solutions and 1-ethyl-3-methylpyridinium perfluorobutanesulfonate that were initially heated to 55 °C, after which 1 mg/ml of doxorubicin or mithramycin was added, creating the ionogel. The higher viscosity modulation featured by ionogels with higher IL content indicates the viability of intra-articular injection through a needle diameter of 0.9 mm, ultimately promoting a longer residence after the inoculation inside the human body and hence confirming the feasibility of local administration by a syringe. Afterward, a dialysis membrane was used to test the drug release in the presence of PBS at 37 °C, being observed a burst release both for doxorubicin and mithramycin in the

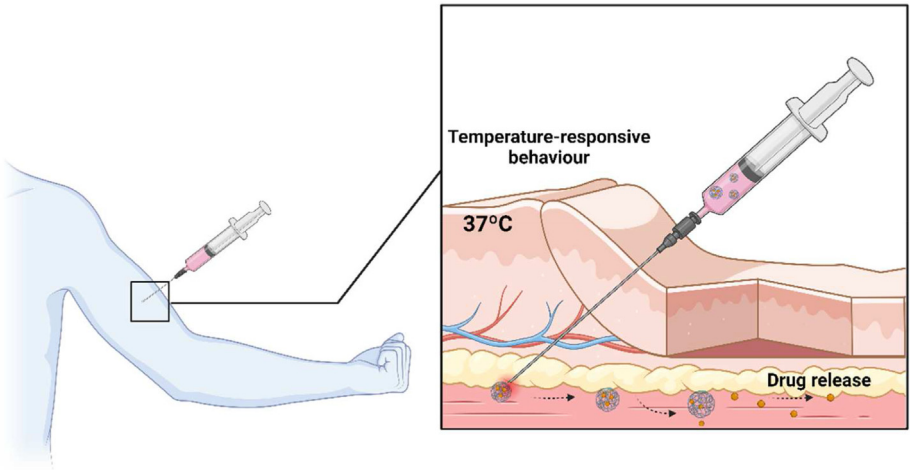

Fig. 9. Illustration on the application of ionogels for parenteral drug administration, overall allowing to overcome first-pass effects on the gastrointestinal tract. Created with BioRender.com.

Table 6
Summary of the works reported on the use of ionogels for the targeted and controlled delivery of drugs with improved solubility focusing parenteral administration.

Goal	Preparation method	Ionic Liquid	Solid support	Biocompatibility studies	Drug
Preparation of injectable gels as DDS demonstrating ion exchange depending release behaviours [164]. *	*In situ* polymerization.	PILs: 3-sulfopropylmethacrylate potassium ($MAESO_3$); 2-(methacryloyloxy) ethyl] trimethylammonium chloride (MAETMA).	None.	No.	Timolol maleate and ibuprofen.
Designing of a stimuli-responsive injectable polymeric gel comprising an ester-functionalized IL, applied as an additive to improve the efficiency of encapsulation and localized delivery of anticancer drugs [165].	Direct mixing.	4-(2-(Hexadecyloxy)-2-oxoethyl)-4-methylmorpholin-4-ium bromide.	PVA.	Cell viability using HeLa and MCF-7 cells.	Doxorubicin.
Preparation of biocompatible, biodegradable, self-healable, and stimuli-responsive gels for drug uptake and delivery [166].	*In situ* polymerization.	Cholinium acetate.	Hybrid – Pluronic P123 and iron oxide nanoparticles.	No.	Sodium diclofenac.
Development of ionogels comprised by perfluorinated ILs to improve the solubility of drugs and promote their local administration by a syringe [105].	*In situ* polymerization.	1-ethyl-3-methylpyridinium perfluorobutanesulfonate.	Gelatin.	No.	Doxorubicin; Mithramycin.
Preparation of multifunctional gels with improved ability to encapsulate a hydrophobic drug and for sustained release [107].	*In situ* polymerization.	Cholinium oleate.	PVA.	Cytotoxicity assays.	Curcumin.
Preparation of dual-responsive gels as local DDS for the treatment of breast cancer [167].	*In situ* polymerization.	Cholinium oleate.	PVA.	Cytotoxicity assays.	5-fluorouracil.

Abbreviations – DDS – Drug delivery system; HA – Hyaluronic acid; IL – Ionic liquid; PIL – Poly(ionic liquid); Pluronic P-123 – Poly(ethylene glycol)-block-poly(propyleneglycol)-block-poly(ethylene glycol); PVA – poly(vinyl alcohol). *Predicted to be injectable and intended for ocular applications.

first 5–6 h of the experiment. Following the burst release of doxorubicin, it was observed a very slow release independent of the composition of the ionogel, which slightly increases after 120 h and suggests a high affinity of doxorubicin for the gelatin interface [105].

A hybrid gel formed by the surface-active IL cholinium oleate and PVA in combination with dextrose, sodium borax and glycerol was fabricated and applied to encapsulate the hydrophobic drug curcumin [107]. The addition of cholinium oleate to the hybrid gel improved the gelation characteristics, allowing to reduce the critical gelation concentration from 16 % to 6 % w/v, as well as the hydrophilicity and water retention ability of the resulting materials. The stability of curcumin in the designed gels was found to be improved after 1 month of incubation, hypothesized to be due to its encapsulation within the most hydrophobic environment, reducing interactions with water. Also, the gel matrix was able to encapsulate 7.3 mg/g curcumin, approximately 12,200 times more than in aqueous solutions. The assessment of curcumin release profiles showed a 85 % cumulative release from the gels after 75 h at 37 °C and pH 5.0, compared to a 69 % at pH 7.4 in the same period, and occurs through surface erosion of the gel. Since the cytotoxicity assays showed that these gels do not significantly impair the viability of a human cell line, they hold promising applications for improving the encapsulation of hydrophobic drugs with sustained release profiles for smart drug delivery [107]. In a different work [167], the authors investigated the same ionogel composition for the targeted delivery of 5-fluouracil, as an approach for breast cancer treatment. Unlike hydrogels formed by PVA (without IL), which are able to encapsulate 80 mM for 5-fluorouracil, ionogels encapsulated 146 mM of 5-fluouracil. Since cholinium-oleate-based gels are degraded at 37 °C and pH 5.0, which are typical biological conditions observed in cancerous cells, they provide site-specific drug release and thus can be preferentially envisaged as drug delivery vehicles for the treatment of cancer. Using a breast cancer cell line (MCF-7), the authors demonstrated that ionogels without 5-fluouracil are biocompatible while their loading with 5-fluorouracil shows cytotoxicity with IC_{50} values of 1.20 ± 0.5 μg/mL at 48 h, overall confirming their effectiveness as a prospective therapeutic option for the treatment of breast cancer [167].

Overall, most of the challenges regarding the use of ionogels for enteral administration identified in the previous sub-section also apply to parenteral administration. Nevertheless, this field is much less developed with just a few studies using ionogels as DDS for parenteral administration. Ionogels with potential application as drug depot in body regions with low flow-rates as well as with stimuli-responsive behaviour over doxorubicin- and diclofenac-controlled release have been reported, with potential application in cancer therapy. In addition to consistent and controlled drug release patterns, some injectable DDS were fabricated, allowing improvements in the solubility of doxorubicin, curcumin, and 5-fluorouracil.

3.2.3. *Ionogels for transdermal administration*

Transdermal drug delivery systems involve the administration of drugs through skin, being the drug absorbed through blood arteries in the skin into the systemic circulation, avoiding invasive approaches [153]. However, some problems prevail using this mode of administration, including side effects such as skin irritation, erythema, and local edema, difficulties in controlling dosage for creams and lotions, and slow permeation of hydrophilic drugs [169]. Transdermal drug delivery using ionogels is overviewed in this sub-section, which can exert localized or systemic effects, as shown in Fig. 10.

The works analysed and respective objectives are described in Table 7, as well as the IL and solid support used, the ionogels' preparation method, whether biocompatibility studies were performed, and the drug under study.

Transdermal drug delivery systems are preferably applied for dermatological diseases since these disorders manifest primarily as skin lesions exposed to the body surface, the local where drugs are directly delivered using this route [173]. For the transdermal delivery of methotrexate (MTX), Wang and co-workers [78] created a thermally responsive gel based on N-isopropylacrylamide (NIPAM) and silk fibroin, thereafter loaded with an IL microemulsion (IL-ME) containing MTX (MTX-ME). Initial observations showed that the IL-ME was able to increase the solubility of MTX up to 9-fold, thereby improving the drug availability. The permeation enhancing effects of the gel loaded with MTX-ME (MTX/ME@Gel) were evaluated using pig skin, being observed a plateau (32 %) for the drug permeability at 16 h, contrasting with 5.1 %

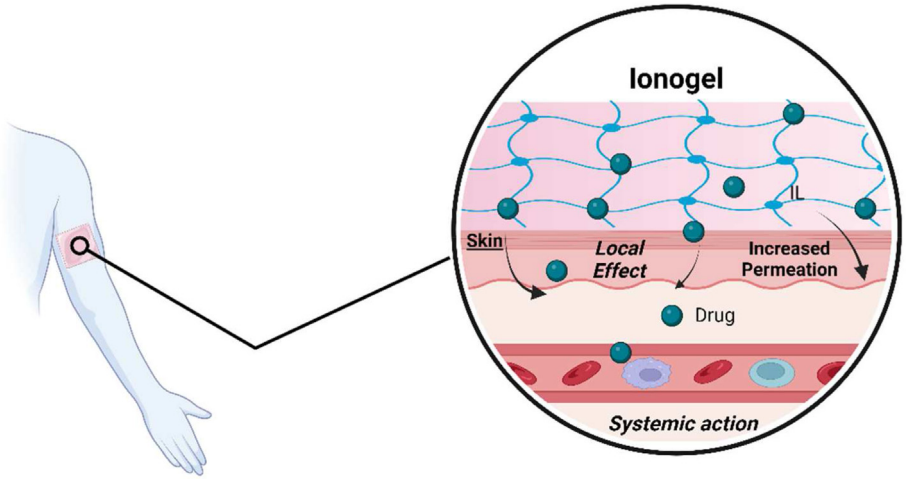

Fig. 10. Illustration on the application of ionogels for transdermal administration. Created with BioRender.com.

for the gel prepared with phosphate-buffered saline (MTX/PBS@Gel). Additionally, the gels release rate nearly doubled at 37 °C with respect to that at 25 °C, causing shrinking of the gel network and the release of the drug. However, the diffusion rate of MTX/ME@Gel was weakened due to high viscosity and hydrogen bonds between the IL-ME and the gel, decreasing the amount of drug released. IL-ME also has potent antibacterial properties, the MTX/ME@Gel killed more than 90 % of *S. aureus* or *E. coli* in 30 min. *In vivo* experiments further demonstrated that the MTX/ME@Gel can effectively treat imiquimod-induced skin inflammation without side effects [78]. Considering the ability of ILs to act as antimicrobial agents and as skin penetration enhancers, gels comprising SEPINEO™ P 600 (Acrylamide/sodium acryloyldimethyl taurate copolymer/isohexadecane/polysorbate 80) or hydroxyethylcellulose were fabricated with hydrophilic ILs, namely hexylpyridinium chloride, cholinium dihydrogenphosphate, and 1-ethyl-3-methylimidazolium ethylsulfate, and investigated as dermal DDS [170]. The influence of the ILs on the antimicrobial properties of the resulting ionogels was determined against Gram-positive (*S. gallinarum*) and Gram-negative bacteria (*E. coli*), as well as one strain of fungi (*K. marxianus*) while *ex vivo* skin permeation studies were performed using two model drugs, the lipophilic testosterone and the hydrophilic caffeine. For hexylpyridinium chloride, a significant drop in turbidity that correlated with the inhibition of microbial growth (survival) was observed. Additional work with formulation G2 (4.0 wt% SEPINEO™ P 600, 5.0 wt% hexylpyridinium chloride, 1.5 wt% cetostearyl alcohol, and 3.0 wt% glycerol 85 %) was performed to evaluate the gels capability to enhance skin permeation for caffeine and testosterone over 24h. These results showed an increase of two-fold in caffeine uptake from the gel formulation containing hexylpyridinium chloride after a 24-h period, compared to the formulation without hexylpyridinium chloride. However, no testosterone was detected in the medium using these conditions [170].

Another work explored the use of cholinium glycolate to manufacture copper-loaded gel with transdermal distribution capability for treating wounds as a dressing [74]. The authors polymerized dopamine *in situ* along a PVA chain and chelated copper ions (Cu^{2+}) to form a mixture. Cholinium glycolate was added to the mixture as a dispersion phase to plasticize the ionic gel, which also promote the transdermal delivery of the Cu^{2+} incorporated in the polymer network. As a result, the production of hydroxyl free radicals (•OH) in the wound is stimulated by chemodynamic treatment, allowing the designed ionogels to exhibit a broad-spectrum antibacterial effect against drug-resistant Gram--positive and Gram-negative bacteria, respectively, MRSA and *E. coli*. Additionally, the IL superior transdermal ability allows the released Cu^{2+} to promote cell migration and quicken the healing process after a wound. The prepared gel displayed good biocompatibility, and it was used to treat mouse skin infections [74].

Along with chemodynamic therapy, ionogels with multiple biological activities, *e.g.*, with antibacterial and angiogenic capabilities, can represent advanced strategies for wound healing. In this regard, Guo and co-workers [171] prepared ionogels loaded with angiogenic deferoxamine using PILs derived from imidazolium- and ε-Poly(lysine)-sulfhydryl containing moieties, synthesized with lysine-grafted maleic anhydride (MAH-Lys) as a cross-linker *via* a "thiol-ene" click reaction. The gels antibacterial activity was tested against *E. coli* and *S. aureus* and after 4h of treatment, they were able to reduce the bacteria by more than 90 %. Moreover, gels containing PILs prevented the formation of biofilms. Since deferoxamine accelerates vessel formation and promotes wound healing and bone regeneration, the gels were designed to release deferoxamine up to 80 % in the first 24 h, thus not only acting as an antibacterial agent but also promoting tissue repair. The addition of deferoxamine to the gels had significant anti-inflammatory activities that inhibited the release of various inflammatory mediators by regulating cell signaling pathways and avoiding an inflammatory cascade reaction as well [171].

The use of combinatorial approaches based on microwave thermal therapy and transdermal enhancers has the merits of combining the delivery of drugs and a strong tissue penetration, which may facilitate the healing of wound infections [94]. To test this hypothesis, Wang and co-workers [94] employed a microwave-responsive IL, vinylbenzyl trimethylammonium chloride ([VBTMA]Cl), and a transdermal enhancer IL, [2-(methacryloyloxy)ethyl]trimethylammonium chloride ([ChMA]Cl), that were copolymerized with acrylic acid to fabricate ionogels named as VACPHs. PVP was incorporated to improve the mechanical properties of the resulting gels and levofloxacin was loaded as a model antibiotic drug. VACPHs loaded with levofloxacin showed great adhesive ability and great stretchability, mechanical properties important to allow the joints to move flexible if wounds appear for instance in the ankle or knee. *In vivo* experiments in a skin infection model of mice confirmed the ability of VACPHs to fight infection by responding to microwave and the ability for transdermal delivery. These assays also confirm the biosafety of the designed ionogels since no differences in the weight of mice nor histological features in major organs indicative of complications after treatment were observed. Overall, VACPHs gels exhibit favourable microwave thermal conversion performance, which may facilitate rapid healing of wound infection [94]. From a different point of view, Dias and co-workers [76] synthesized electro-responsive semi-interpenetrating copolymer networks (semi-IPN) by combining chitosan and poly(1-butyl-3-vinylimidazolium chloride) and poly(2-hydroxymethyl methacrylate-co-1-butyl-3-vinylimidazolium chloride) for the preparation of dressings for specific and controlled drug delivery. The

Table 7
Summary on the works reported on the use of ionogels for controlled delivery of drugs with improved solubility focusing transdermal administration.

Goal	Preparation method	Ionic Liquid	Solid support	Biocompatibility studies	Drug
Construction of thermally-responsive gels based on an IL microemulsion for the transdermal delivery of methotrexate [78].	*In situ* polymerization.	Cholininium bicarbonate and geranic acid (CAGE).	Silk fibroin and N-isopropylacrylamide.	Cytotoxicity and hemolysis experiments.	Methotrexate.
Preparation of dermal DDS comprising ILs and study of their influence on drug penetration, on antimicrobial properties, and on formulation properties [170].	*In situ* polymerization.	Hexylpyridinium chloride – [HPyr]Cl; cholinium dihydrogen phosphate [Ch][DHP]; 1-ethyl-3-methylimidazolium ethyl sulfate [Emim]$EtSO_4$].	SEPINEO™ P 600 or hydroxyethylcellulose.	Skin irritation and corrosion studies.	Testosterone and cafeine.
Develop a Cu^{2+}-loaded gel to promote its release and generate hydroxyl free radicals in the wound through chemodynamic therapy and kill drug-resistant bacteria [74].	*In situ* polymerization.	Cholinium Glycolate.	PVA and PDA.	Cytotoxicity, hemolytic activity and wound healing assays.	Cu^{2+} (as Fenton catalytically active group)
Preparation of antibacterial gels *via* "thiol-ene" click reaction for improving angiogenesis in wound healing [171].	*In situ* polymerization.	PILs: imidazolium (Imidazole-SH) and ε-Poly(lysine) containing sulfhydryl groups. Crosslinked with lysine-grafted maleic anhydride (MAH-Lys).	None.	Cell migration and anti-inflammatory activity.	Deferoxamine.
Preparation of antibacterial gels comprising microwave-responsive-ILs and a transdermal enhancer IL loaded with an antibiotic as antibacterial materials for the treatment of deep tissue infections [94].	*In situ* polymerization.	PIL resulting from copolymerization of acrylic acid and the ILs vinylbenzyl trimethylammonium chloride ([VBTMA]Cl), [2-(methacryloyloxy) ethyl] trimethylammonium chloride ([ChMA]Cl).	PVP.	Cytotoxicity, hemolytic activity and wound healing assays.	Levofloxacin.
Development of electro-responsive ionogels as iontophoretic biomaterials for the controlled release/permeation of charged biomolecules [76].	*In situ* polymerization.	PILs: poly(1-butyl-3-vinylimidazolium chloride) and poly(2-hydroxymethyl methacrylate-*co*-1-butyl-3-vinylimidazolium chloride).	Chitosan.	Hemocompatibility and blood clotting assays.	Lidocaine hydrochloride.
Preparation of a stable and biocompatible bilayer wound dressing material loaded with dual-biological function API-ILs [27].	*In situ* polymerization.	Lidocainium Naproxen; Lidocainium Ibuprofenate; Lidocainium Diclofenac.	PVDF and PVDF/HA.	Cytotoxicity and wound healing assays.	Lidocaine, naproxen, ibuprofen, and diclofenac (API-ILs).
Preparation of a gelatin/PVA transdermal patch using the freeze/thaw method loaded with lidocaine-diclofenac under the form of an API-IL, and evaluation of the *in vitro* release of lidocaine and diclofenac [172].	Direct mixing.	Lidocainium Diclofenac.	Gelatin and PVA	No.	Lidocaine and diclofenac (API-IL).
Preparation of gels able to improve the solubility of poorly soluble drugs as topical formulations for cosmetical applications [79].	Direct mixing.	Cholinium phenylalaninate, cholinium glutamate, and cholinium glycinate.	Propylene glycol and Carbopol® 940.	No.	caffeic and *p*-coumaric acid.

Abbreviations – API-IL – Active pharmaceutical ingredient ionic liquid; CAGE – Cholinium bicarbonate and geranic acid; DDS – Drug delivery system; HA – Hyaluronic acid; IL – Ionic liquid; NR – Not reported; PDA – Polydopamine; PIL – Poly(ionic liquid); PVA – poly(vinyl alcohol); PVDF – Polyvinylidene fluoride; PVP – Poly-vinylpyrrolidone; SEPINEO™ - Acrylamide/sodium acryloyldimethyl taurate copolymer/isohexadecane/polysorbate 80.

electro-assisted iontophoretic permeation/release kinetics of lidocaine hydrochloride (LH) was determined at 32 °C. The effect of the electrical stimulus on LH permeation kinetics through the cationic gels showed that LH permeation rates are significantly higher when the electrical stimulus (0.56 mA/cm^2) is applied. Additionally, it was shown that the designed semi-IPN gels are non-haemolytic (haemolytic index $\leq$0.2 %) and present strong haemostatic activity (blood clotting index of approximately 12 $\pm$ 1 %). These results show that the prepared semi-IPNs can be employed in different biological media for different pharmaceutical and biomedical applications, such as wound healing dressings and iontophoretic patches [76].

In addition to the use of drugs in ionogels, these can be prepared as well with ILs comprising ions derived from APIs [24]. Taking advantage of this possibility, Mehrizi and co-workers [27] prepared dual-biological function ILs made from API-ILs, combining lidocaine and hydrophobic nonsteroidal anti-inflammatory drugs, namely ibuprofen, naproxen and diclofenac. In comparison with noncharged non-steroidal anti-inflammatory drugs (NSAIDs), API-ILs have significantly increased water solubility up to 470-fold, without affecting their cytotoxic profile. These API-ILs were incorporated in polyvinylidene fluoride or poly-vinylidene difluoride/hyaluronic acid (PVDF/HA) membranes, being responsible, respectively, for providing stability for bilayer wound dressings and enhanced fibroblast cell proliferation, migration, and adhesion. The prepared membranes were immunologically safe and biocompatible, with a higher release of API-ILs than of the original NSAIDs, thereby enhancing their analgesic and anti-inflammatory properties relevant in wound healing [27].

Contrarily to previous examples where therapeutic localized effects were aimed, transdermal DDS are also effective for the systemic delivery of drugs. A transdermal patch comprised by gelatin/PVA loaded with 5 wt% of a lidocaine-diclofenac API-IL was prepared by the freeze/thaw method using glycerin as a plasticizer [172]. The lidocaine-diclofenac API-IL was obtained by ion pair reactions between the hydrochloride salts of lidocaine and the sodium salts of diclofenac, ultimately showing

increased water solubility. *In vitro* release experiments using a modified Franz-type diffusion cell and isotonic phosphate buffer pH 7.4 as the receptor medium revealed that the transdermal patch was able to control the drug release of both lidocaine and diclofenac over a 12 h period, with cumulative releases of lidocaine and diclofenac of, respectively, 2.12 ± 0.32 and 2.43 ± 0.28 mg/cm^2. Additional release experiments carried out after the patches had been stored for 3 months at different temperatures, namely 4 °C, ambient temperature – 28 ± 4 °C – and 45 °C, showed that the stability is impaired at 45 °C with a lower amount of drugs being released and with different release patterns [172]. In a different study, ionogels comprising amino-acid-based ILs, namely, cholinium phenylalaninate, cholinium L-glutamate, and cholinium glycinate, propylene glycol and carbopol® 940 were shown to increase the solubility of poorly soluble caffeic and *p*-coumaric acids, as well the amount of drugs incorporated in the materials [79]. Moreover, the addition of ILs increased the viscosity of formulations, bringing another functionality to the synthesized gels by altering the viscosity of topical formulations, which according to the authors may improve the consumer's acceptance of the product [79].

Transdermal drug delivery using ionogels has been successfully applied for the treatment of local skin lesions with emphasis on wound healing as well as for systemic applications. The results obtained thus far have shown that the ability of ILs to act as permeation enhancers is transferred to ionogels, improving the transportation of both hydrophobic and hydrophilic drugs across the skin. An additional feature of ionogels is their ability to increase the solubility and availability of drugs, either by direct solubilization in IL-containing media, exemplified for methotrexate [78], or by combining the ionic forms of lidocaine, ibuprofen, naproxen, and diclofenac as API-ILs [27]. Up to date, ionogels for enhanced wound healing were reported for chemodynamic therapy, and by resorting to the delivery of angiogenic drugs and API-ILs. Also, combinatorial approaches assisted by microwave radiation [94] and electric fields (iontophoresis) [76] using ionogels constituted by ILs that respond to the stimuli may, respectively, increase tissue penetration of the drugs and control their release profile, ultimately boosting the wound healing efficiency. As addressed in more detail in section 3.1 and in addition to the direct antibacterial effect of ionogels, crucial to help reducing the possibility of infections for wound management [74], it is worth noting that PIL-based ionogels [171] also prevent biofilm formation, which pose serious health hazards and tend to be become more difficult to combat than free bacteria [174].

Ionogels for systemic delivery of drugs have also been designed, further allowing enhancements on their solubility. As with enteral and parenteral administration, the application of ionogels loaded with (bio) pharmaceuticals is foreseen to expand the versatility and applicability of ionogels for transdermal administration. Being non-invasive, this mode of administration holds promising potential as a safer approach with high patient adherence for systemic (bio)drug delivery. Further investigations are crucial to reach this goal, which should include continuous improvements on ionogels' formulations to improve drug permeability and stability, as well as deep characterization of drug pharmacokinetic profiles. Overall and among the different modes of administration, transdermal drug delivery using ionogels has already been evaluated *in vivo*, confirming their therapeutic efficiency and biocompatible nature.

4. Current prospects and future directions

Ionogels emerged as high-performance materials for wound healing and drug delivery applications, as reviewed above. According to the works reported in Tables 3–7, approximately 65 % (28 out of 43) were published between 2020 and 2024, indicating the growing interest of the scientific community in this field. However, several issues remain to be solved and concerns about the potential toxicity of ionogels are key barriers to overcome, particularly for enteral and parenteral administration. A SWOT analysis on the application of ionogels in drug delivery and wound healing is sketched in Fig. 11.

Strengths. Ionogels represent nowadays an advanced class of materials with promising potential for improving current wound healing and drug delivery approaches. ILs endow ionogels of several biological activities, including antimicrobial [131,144], anti-inflammatory [117], and antioxidant [39] properties, collectively improving the therapeutic efficiency of these materials. IL chemical properties offer an additional way to tailor ionogel characteristics for specific requirements, improving their mechanical properties, increasing viscosity of topical formulations while contributing to improve consumer's acceptance, or by providing stimuli-responsiveness (*e.g.*, ionic conductivity for iontophoresis applications, magnetic behaviour and temperature/pH-responsiveness for targeted drug delivery). Since ionogels' synthetic route can be prepared without a crosslinker, the use of potentially harmful chemicals can be avoided [175]. ILs and the corresponding ionogels also represent potential alternatives to toxic organic solvents, allowing remarkable enhancements in the solubility and bioavailability of hydrophobic [40], and hydrophilic drugs [93,170], acting as well as permeation enhancers [132].

Weaknesses. Despite the efforts to use ion constituents of ILs derived from natural sources as is the case of choline, most studies still employ imidazolium-based ILs (mainly as PILs monomers) whereas the high diversity of IL chemical structures available remains largely unexplored. Furthermore, the number of API-ILs has been mostly restricted to drugs with anti-inflammatory properties, and little is known about the pharmacokinetic profiles of drug ions as API-ILs. Up to date, there is still limited knowledge about the cradle to grave life cycle of ILs and, consequently, of ionogels [175]. In fact, finding the ideal balance between cost, performance and biocompatibility will be crucial for large-scale health-related applications [118]. Due to their high affinity for water, additional processing steps required for drying ILs can increase their cost. On the other hand, the impact of trace impurities of ILs on the biological efficacy of ionogels still deserves further exploration. The regulatory uncertainty regarding the toxicology of ILs remains a key hurdle for adoption and hence for commercialization. Multi-level and comprehensive safety evaluations of ILs are crucial to assess their toxicological behaviour. Afterward, further research and clinical trials are needed to realize the full potential of ionogels for human-related applications, particularly in relation to the ILs applied and their long-term effects on human health. The use of ILs derived from natural sources (*e.g.*, cholinium-based ILs) and solid networks previously applied in clinically approved formulations are good candidates for these investigations.

Opportunities. As a result of the chemical and biological properties of ILs and the synergistic properties of ILs and the solid networks, novel applications of ionogels are envisaged. By expanding the number of chemical structures of ILs, novel biological functionalities are expected to be introduced in the ensuing ionogels, as well as improvements on ionogels' mechanical properties favouring even more their application as dressings. Aiming at moving towards more biocompatible ionogels, the use of naturally-occurring components with favourable cytotoxic profiles such as choline, glycine-betaine, or carboxylic acids as ion constituents of ILs must be considered [176,177]. Throughout this process and in line with recent developments, the application of artificial intelligence and machine learning techniques may streamline the design of ILs with improved therapeutic effectiveness in a shortened drug development time [118] while allowing their use in mining and modeling toxicity data to make meaningful predictions [142]. In addition to improving the solubility and bioavailability of hydrophilic and hydrophobic synthetic pharmaceutical drugs, ILs enhance or maintain biopharmaceutical's (proteins, antibodies, DNA, RNA) thermal and chemical stabilities, inhibiting their aggregation, denaturation and enzymatic degradation [99]. This opens good perspectives towards the application of ionogels for the delivery of biopharmaceuticals with improved stability. Moreover, the development of smart ionogels for drug delivery responsive either to internal (temperature, pH, redox, enzymatic reactions) and external stimuli (ultrasounds, light, among others) will allow for more

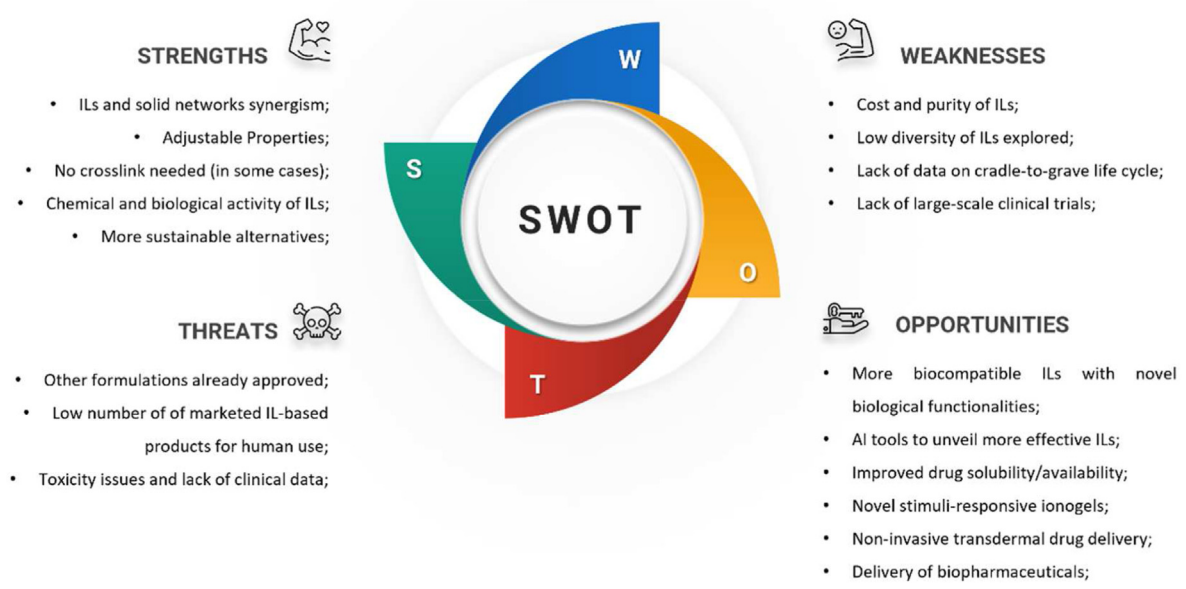

Fig. 11. SWOT analysis on the application of ionogels for wound healing and drug delivery.

precise and targeted drug delivery systems. Due to the ability of ionogels to increase the permeation of drugs across the skin (*e.g.*, in Refs. [76,78]), transdermal drug delivery represents a non-invasive approach with high patient compliance with promising potential to be further investigated.

Threats. As we previously highlighted [175], marketed wound dressings and formulations already approved by regulatory agencies for drug delivery will continue to dominate the market in coming years. If on one hand the information herein reviewed provides compelling evidence about the potential performance benefits brought by the use of ionogels for pharmaceutical applications, economical and commercially viable alternative solutions using ILs have been proposed in other fields [178]. Nevertheless, uncertainties around the safety profile of ILs and ionogels still require further investigations. Recently, the U.S. Food and Drug Administration (FDA) has accepted the New Drug Application (NDA) for MRX-5LBT, jointly developed in U.S. by the MEDRx group and D. Western Therapeutics Institute, Inc [179]. MRX-5LBT consists of a medicated path with lidocaine resorting to the Ionic Liquid Transdermal System (ILTS®) designed to increase the transdermal permeability of targeted drugs [179]. In addition to MEDRx, other companies such as CAGE Bio Inc [180] and i2o Therapeutics [181] are exploiting the use of IL-based technologies for drug delivery. CAGE Bio Inc [180]. is a clinical-stage startup exploiting its proprietary deep eutectic IL platform to develop novel products for dermatology, inflammation, and immunology. This company is taking advantage of the ability of ILs to deliver small molecules, peptides, proteins and nucleic acids across the stratum corneum following topical administration. According to the company [180], the topical gel CGB-400 is being investigated in two clinical trials for the treatment of inflammatory lesions of Rosacea (NCT04886739) and for fungal infections (NCT05202366). On the other hand, the biotech company i2o Therapeutics [181] seeks to use IL-based technologies to transform injectable biologics and peptides into oral therapies. Although some challenges remain to be surpassed, the promising outcomes obtained with the application of IL platforms for transdermal drug delivery are undoubtedly a milestone in ionogels' roadmap toward their commercialization in human-related applications.

5. Conclusions

Ionogels offer tremendous potential in the pharmaceutical field, gaining traction to address some of the unmet needs that this industry faces nowadays in wound healing management and drug delivery applications. Although recent studies using *in vivo* mouse models generally demonstrate that, if properly engineered, ionogels can be biocompatible and therapeutically efficient, the lack of safety data and uncertainty regarding their long-term effects on human health still present significant obstacles to clinical translation and regulatory approval. Our SWOT analysis showed that this challenge persists over the last few years and has not been yet entirely addressed. An exception to this trend is the niche of transdermal drug delivery, in which the NDA of MRX-5LBT® was already accepted by FDA, realizing pharmaceutical sales and marketing of IL platforms for drug delivery applications. In addition, due to the chemical and biological activity of ILs, promising applications are envisaged using non-invasive approaches, novel stimuli-responsive systems, in biopharmaceuticals delivery, and to improve drug pharmacokinetic profiles. As this field evolves and novel and improved ionogels for pharmaceutical applications are being developed, a comprehensive and multi-level safety data of ILs and ionogels must be performed to address their feasibility for human applications. To reach these goals, a proeminent role may be attributed to artificial intelligence tools, both to design ionogels with enhanced therapeutic efficiency as well as to better understand ILs toxicity profiles to fabricate materials with biocompatible and biodegradable nature.

Declaration of competing interest

The authors declare no competing interests.

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References

[1] S. Sharifi, M.J. Hajipour, L. Gould, M. Mahmoudi, Nanomedicine in healing chronic wounds: opportunities and challenges, Mol. Pharm. 18 (2) (2021) 550–575, https://doi.org/10.1021/acs.molpharmaceut.0c00346.

[2] X. Ding, Q. Tang, Z. Xu, Y. Xu, H. Zhang, D. Zheng, S. Wang, Q. Tan, J. Maitz, P.K. Maitz, et al., Challenges and innovations in treating chronic and acute wound infections: from basic science to clinical practice, Burns Trauma 10 (2022) tkac014, https://doi.org/10.1093/burnst/tkac014.

[3] T. Shi, Y. Liu, D. Wang, D. Xia, B. Li, R. Xu, N. Li, C. Liang, M. Chen, Spatially engineering tri-layer nanofiber dressings featuring asymmetric wettability for wound healing, Nano Materials Science (2024), https://doi.org/10.1016/j.nanoms.2024.01.008.

[4] M. Abrigo, S.L. McArthur, P. Kingshott, Electrospun nanofibers as dressings for chronic wound care: advances, challenges, and future prospects, Macromol. Biosci. 14 (6) (2014) 772–792, https://doi.org/10.1002/mabi.201300561.

[5] C. Stamoran, The golden age of drug delivery, in: themedicinemaker.com/discovery-development/opportunities-and-challenges-in-drug-delivery-in-2023, 2023, 13th November 2023.

[6] W.H. Organization, Antibiotic resistance, in: who.int/news-room/fact-sheets/detail/antibiotic-resistance, 2020, 19th October 2023.

[7] T.K. Sastri, V.N. Gupta, S. Chakraborty, S. Madhusudhan, H. Kumar, P. Chand, V. Jain, B. Veeranna, D.V. Gowda, Novel gels: an emerging approach for delivering of therapeutic molecules and recent trends, Gels 8 (5) (2022), https://doi.org/10.3390/gels8050316.

[8] B. Homayun, X. Lin, H.-J. Choi, Challenges and recent progress in oral drug delivery systems for biopharmaceuticals, Pharmaceutics 11 (3) (2019) 129, https://doi.org/10.3390/pharmaceutics11030129.

[9] N. Singh, A. Joshi, A.P. Toor, G. Verma, Drug delivery: advancements and challenges, in: E. Andronescu, A.M. Grumezescu (Eds.), Nanostructures for Drug Delivery, Elsevier, 2017, pp. 865–886.

[10] H. Kamali, R. Nosrati, B. Malaekeh-Nikouei, Nanostructures and their associated challenges for drug delivery, in: P. Kesharwani, N.K. Jain (Eds.), Hybrid Nanomaterials for Drug Delivery, Woodhead Publishing, 2022, pp. 1–26.

[11] R. Md Moshikur, M.R. Chowdhury, M. Moniruzzaman, M. Goto, Biocompatible ionic liquids and their applications in pharmaceutics, Green Chem. 22 (23) (2020) 8116–8139, https://doi.org/10.1039/D0GC02387F.

[12] K. Pathak, S. Raghuvanshi, Oral bioavailability: issues and solutions via nanoformulations, Clin. Pharmacokinet. 54 (4) (2015) 325–357, https://doi.org/10.1007/s40262-015-0242-x.

[13] M. Wang, J. Hu, M.D. Dickey, Tough ionogels: synthesis, toughening mechanisms, and mechanical properties-A perspective, JACS Au 2 (12) (2022) 2645–2657, https://doi.org/10.1021/jacsau.2c00489.

[14] J. Le Bideau, L. Viau, A. Ionogels Vioux, Ionic liquid based hybrid materials, Chem. Soc. Rev. 40 (2) (2011) 907–925, https://doi.org/10.1039/C0CS00059K.

[15] K. Wang, J. Wang, L. Li, L. Xu, N. Feng, Y. Wang, X. Fei, J. Tian, Y. Li, Synthesis of a novel anti-freezing, non-drying antibacterial hydrogel dressing by one-pot method, Chem. Eng. J. 372 (2019) 216–225, https://doi.org/10.1016/j.cej.2019.04.107.

[16] P. Monika, M.N. Chandraprabha, A. Rangarajan, P.V. Waiker, K.N. Chidambara Murthy, Challenges in healing wound: role of complementary and alternative medicine, Front. Nutr. 8 (2022) Review, https://doi.org/10.3389/fnut.2021.791899.

[17] I. Klojdova, T. Milota, J. Smetanova, C. Stathopoulos, Encapsulation: a strategy to deliver therapeutics and bioactive compounds? Pharmaceuticals 16 (3) (2023) https://doi.org/10.3390/ph16030362.

[18] M.A. Kuzina, D.D. Kartsev, A.V. Stratonovich, P.A. Levkin, Organogels versus hydrogels: advantages, challenges, and applications, Adv. Funct. Mater. 33 (27) (2023) 2301421, https://doi.org/10.1002/adfm.202301421.

[19] M. Sivapragasam, M. Moniruzzaman, M. Goto, Recent advances in exploiting ionic liquids for biomolecules: solubility, stability and applications, Biotechnol. J. 11 (8) (2016) 1000–1013, https://doi.org/10.1002/biot.201500603.

[20] S.P.M. Ventura, F.A. e Silva, M.V. Quental, D. Mondal, M.G. Freire, J.A.P. Coutinho, Ionic-liquid-Mediated extraction and separation processes for bioactive compounds: past, present, and future trends, Chem. Rev. 117 (10) (2017) 6984–7052, https://doi.org/10.1021/acs.chemrev.6b00550.

[21] J. Huang, Z. Yu, P. Wu, 3D printing of ionogels with complementary functionalities enabled by self-regulating ink, Adv. Sci. 10 (24) (2023) 2302891, https://doi.org/10.1002/advs.202302891.

[22] R. Freer, A. Curzons, The pros and cons of using ionic liquids in the pharmaceutical industry, in: R.D. Rogers, K.R. Seddon, S. Volkov (Eds.), Green Industrial Applications of Ionic Liquids, Springer Netherlands, 2002, pp. 129–136.

[23] R.M. Moshikur, M.K. Ali, M. Goto, Ionic liquids for increasing the solubility of sparingly soluble drug molecules, in: M. Goto, M. Moniruzzaman (Eds.), Application of Ionic Liquids in Drug Delivery, Springer Singapore, 2021, pp. 51–70.

[24] J.L. Shamshina, R.D. Rogers, Ionic liquids: new forms of active pharmaceutical ingredients with unique, tunable properties, Chem. Rev. 123 (20) (2023) 11894–11953, https://doi.org/10.1021/acs.chemrev.3c00384.

[25] I.M. Marrucho, L.C. Branco, L.P.N. Rebelo, Ionic liquids in pharmaceutical applications, Annu. Rev. Chem. Biomol. Eng. 5 (1) (2014) 527–546, https://doi.org/10.1146/annurev-chembioeng-060713-040024.

[26] K.S. Egorova, E.G. Gordeev, V.P. Ananikov, Biological activity of ionic liquids and their application in pharmaceutics and medicine, Chem. Rev. 117 (10) (2017) 7132–7189, https://doi.org/10.1021/acs.chemrev.6b00562.

[27] A. Abednejad, A. Ghaee, E.S. Morais, M. Sharma, B.M. Neves, M.G. Freire, J. Nourmohammadi, A.A. Mehrizi, Polyvinylidene fluoride–Hyaluronic acid wound dressing comprised of ionic liquids for controlled drug delivery and dual therapeutic behavior, Acta Biomater. 100 (2019) 142–157, https://doi.org/10.1016/j.actbio.2019.10.007.

[28] N.V. Sastry, D.K. Singh, P.A. Trivedi, Hybrid hydrogel systems of micelles of drug anion containing ionic liquid and biopolymers: rheological behavior and drug release, Colloids Surf. A Physicochem. Eng. Asp. 555 (2018) 668–678, https://doi.org/10.1016/j.colsurfa.2018.07.047.

[29] C. Zhao, C. Sheng, C. Zhou, Fast gelation of poly(ionic liquid)-based injectable antibacterial hydrogels, Gels 8 (1) (2022) 52, https://doi.org/10.3390/gels8010052.

[30] J. Guo, Y. Qian, B. Sun, Z. Sun, Z. Chen, H. Mao, B. Wang, F. Yan, Antibacterial amino acid-based poly(ionic liquid) membranes: effects of chirality, chemical bonding type, and application for MRSA skin infections, ACS Appl. Bio Mater. 2 (10) (2019) 4418–4426, https://doi.org/10.1021/acsabm.9b00619.

[31] M. Zakrewsky, K.S. Lovejoy, T.L. Kern, T.E. Miller, V. Le, A. Nagy, A.M. Goumas, R.S. Iyer, R.E. Del Sesto, A.T. Koppisch, et al., Ionic liquids as a class of materials for transdermal delivery and pathogen neutralization, Proc. Natl. Acad. Sci. USA 111 (37) (2014) 13313–13318, https://doi.org/10.1073/pnas.1403995111.

[32] S.N. Pedro, R.F. CS, A.J.D. Silvestre, M.G. Freire, The role of ionic liquids in the pharmaceutical field: an overview of relevant applications, Int. J. Mol. Sci. 21 (21) (2020), https://doi.org/10.3390/ijms21218298.

[33] C.-C. Yan, W. Li, Z. Liu, S. Zheng, Y. Hu, Y. Zhou, J. Guo, X. Ou, Q. Li, J. Yu, et al., Ionogels: preparation, properties and applications, Adv. Funct. Mater. 34 (17) (2024) 2314408, https://doi.org/10.1002/adfm.202314408.

[34] L. Zhang, D. Jiang, T. Dong, R. Das, D. Pan, C. Sun, Z. Wu, Q. Zhang, C. Liu, Z. Guo, Overview of ionogels in flexible electronics, Chem. Rec. 20 (9) (2020) 948–967, https://doi.org/10.1002/tcr.202000041.

[35] Z. Luo, W. Li, J. Yan, J. Sun, Roles of ionic liquids in adjusting nature of ionogels: a mini review, Adv. Funct. Mater. 32 (32) (2022) 2203988, https://doi.org/10.1002/adfm.202203988.

[36] R. Sahrash, A. Siddiqa, H. Razzaq, T. Iqbal, S. Qaisar, PVDF based ionogels: applications towards electrochemical devices and membrane separation processes, Heliyon 4 (11) (2018) e00847, https://doi.org/10.1016/j.heliyon.2018.e00847.

[37] J.W. Suen, N.K. Elumalai, S. Debnath, N.M. Mubarak, C.I. Lim, M.M. Reddy, The role of interfaces in ionic liquid-based hybrid materials (ionogels) for sensing and energy applications, Adv. Mater. Interfac. 9 (34) (2022) 2201405, https://doi.org/10.1002/admi.202201405.

[38] L. Viau, C. Tourné-Péteilh, J.-M. Devoisselle, A. Vioux, Ionogels as drug delivery system: one-step sol–gel synthesis using imidazolium ibuprofenate ionic liquid, Chem. Commun. 46 (2) (2010) 228–230, https://doi.org/10.1039/B913879J.

[39] Y. Zhang, B. Yuan, Y. Zhang, Q. Cao, C. Yang, Y. Li, J. Zhou, Biomimetic lignin/poly(ionic liquids) composite hydrogel dressing with excellent mechanical strength, self-healing properties, and reusability, Chem. Eng. J. 400 (2020) 125984, https://doi.org/10.1016/j.cej.2020.125984.

[40] S.S.D. Kumar, M. Surianarayanan, R. Vijayaraghavan, A.B. Mandal, D.R. MacFarlane, Curcumin loaded poly(2-hydroxyethyl methacrylate) nanoparticles from gelled ionic liquid – in vitro cytotoxicity and anti-cancer activity in SKOV-3 cells, Eur. J. Pharmaceut. Sci. 51 (2014) 34–44, https://doi.org/10.1016/j.ejps.2013.08.036.

[41] E. Andrzejewska, A. Marcinkowska, A. Zgrzeba, Ionogels – materials containing immobilized ionic liquids, Polimery 62 (5) (2021) 344–352, https://doi.org/10.14314/polimery.2017.344, acccessed 2023/11/13.

[42] J. Xie, X. Li, Z. He, L. Fan, D. Yao, Y. Zheng, Preparation of tough and stiff ionogels via phase separation, Mater. Horiz. 11 (1) (2024) 238–250, https://doi.org/10.1039/D3MH01587D, 10.1039/D3MH01587D.

[43] A. Lewandowska, P. Gajewski, K. Szcześniak, A. Marcinkowska, The influence of monomer structure on the properties of ionogels obtained by thiol–ene photopolymerization, Gels 7 (4) (2021) 214, https://doi.org/10.3390/gels7040214.

[44] V. Patel, E. Das, A. Bhargava, S. Deshmukh, A. Modi, R. Srivastava, Ionogels for flexible conductive substrates and their application in biosensing, Int. J. Biol. Macromol. 254 (2024) 127736, https://doi.org/10.1016/j.ijbiomac.2023.127736.

[45] M. Bielejewski, Effect of self-assembly aggregation on physical properties of non-aqueous ionogels based on LMWG, J. Sol. Gel Sci. Technol. 88 (3) (2018) 671–683, https://doi.org/10.1007/s10971-018-4831-7.

[46] M. Wang, J. Hu, M.D. Dickey, Tough ionogels: synthesis, toughening mechanisms, and mechanical Properties—A perspective, JACS Au 2 (12) (2022) 2645–2657, https://doi.org/10.1021/jacsau.2c00489.

[47] M. Salsamendi, L. Rubatat, D. Mecerreyes, Polymeric ion gels: preparation methods, characterization, and applications, in: A.A.J. Torriero (Ed.), Electrochemistry in Ionic Liquids: Volume 1: Fundamentals, Springer International Publishing, 2015, pp. 283–315.

[48] Y. Yu, Z. Yang, S. Ren, Y. Gao, L. Zheng, Multifunctional hydrogel based on ionic liquid with antibacterial performance, J. Mol. Liq. 299 (2020) 112185, https://doi.org/10.1016/j.molliq.2019.112185.

[49] S. Shimano, H. Zhou, I. Honma, Preparation of nanohybrid solid-state electrolytes with liquidlike mobilities by solidifying ionic liquids with silica particles, Chem. Mater. 19 (22) (2007) 5216–5221, https://doi.org/10.1021/cm0707814.

[50] A. Guyomard-Lack, P.E. Delannoy, N. Dupré, C.V. Cerclier, B. Humbert, J. Le Bideau, Destructuring ionic liquids in ionogels: enhanced fragility for solid devices, Phys. Chem. Chem. Phys. 16 (43) (2014) 23639–23645, https://doi.org/10.1039/C4CP03187C.
[51] F. Wu, N. Chen, R. Chen, L. Wang, L. Li, Organically modified silica-supported ionogels electrolyte for high temperature lithium-ion batteries, Nano Energy 31 (2017) 9–18, https://doi.org/10.1016/j.nanoen.2016.10.060.
[52] S.M. Kamal Mohamed, R. Murali Sankar, M.S. Kiran, S.N. Jaisankar, B. Milow, A.B. Mandal, Facile preparation of biocompatible and transparent silica aerogels as ionogels using choline dihydrogen phosphate ionic liquid, Appl. Sci. 11 (1) (2021) 206, https://doi.org/10.3390/app11010206.
[53] M.J. Lo Faro, A.A. Leonardi, D. Morganti, S. Conoci, B. Fazio, A. Irrera, Hybrid platforms of silicon nanowires and carbon nanotubes in an ionic liquid bucky gel, Molecules 27 (14) (2022) 4412, https://doi.org/10.3390/molecules27144412.
[54] R. Sumitani, T. Mochida, Switchable ionic conductivity and viscoelasticity of ionogels containing photo- and thermo-responsive organometallic ionic liquids, J. Mol. Liq. 342 (2021) 117510, https://doi.org/10.1016/j.molliq.2021.117510.
[55] Y. Ishioka, N. Minakuchi, M. Mizuhata, T. Maruyama, Supramolecular gelators based on benzenetricarboxamides for ionic liquids, Soft Matter 10 (7) (2014) 965–971, https://doi.org/10.1039/C3SM52363B.
[56] N. Minakuchi, K. Hoe, D. Yamaki, S. Ten-no, K. Nakashima, M. Goto, M. Mizuhata, T. Maruyama, Versatile supramolecular gelators that can harden water, organic solvents and ionic liquids, Langmuir 28 (25) (2012) 9259–9266, https://doi.org/10.1021/la301442f.
[57] F. Billeci, F. D'Anna, H.Q.N. Gunaratne, N.V. Plechkova, K.R. Seddon, "Sweet" ionic liquid gels: materials for sweetening of fuels, Green Chem. 20 (18) (2018) 4260–4276, https://doi.org/10.1039/C8GC01615A.
[58] X. Wang, J. Hao, Ionogels of sugar surfactant in ethylammonium nitrate: phase transition from closely packed bilayers to right-handed twisted ribbons, J. Phys. Chem. B 119 (42) (2015) 13321–13329, https://doi.org/10.1021/acs.jpcb.5b07712.
[59] N. Kimizuka, T. Nakashima, Spontaneous self-assembly of glycolipid bilayer membranes in sugar-philic ionic liquids and formation of ionogels, Langmuir 17 (22) (2001) 6759–6761, https://doi.org/10.1021/la015523e.
[60] X. Fan, S. Liu, Z. Jia, J.J. Koh, J.C.C. Yeo, C.-G. Wang, N.E. Surat'man, X.J. Loh, J. Le Bideau, C. He, et al., Ionogels: recent advances in design, material properties and emerging biomedical applications, Chem. Soc. Rev. 52 (7) (2023) 2497–2527, https://doi.org/10.1039/D2CS00652A.
[61] J. Jiang, D. Gao, Z. Li, G. Su, Gel polymer electrolytes prepared by in situ polymerization of vinyl monomers in room-temperature ionic liquids, React. Funct. Polym. 66 (10) (2006) 1141–1148, https://doi.org/10.1016/j.reactfunctpolym.2006.02.004.
[62] A. Marcinkowska, A. Zgrzeba, G. Lota, K. Kopczyński, E. Andrzejewska, Ionogels by thiol-ene photopolymerization in ionic liquids: formation, morphology and properties, Polymer 160 (2019) 272–281, https://doi.org/10.14314/polimery.2017.344.
[63] Y.-R. Gao, J.-F. Cao, Y. Shu, J.-H. Wang, Research progress of ionic liquids-based gels in energy storage, sensors and antibacterial, Green Chemical Engineering 2 (4) (2021) 368–383, https://doi.org/10.1016/j.gce.2021.07.012.
[64] S. Sen, S.E. Goodwin, P.V. Barbará, G.A. Rance, D. Wales, J.M. Cameron, V. Sans, M. Mamlouk, K. Scott, D.A. Walsh, Gel–polymer electrolytes based on poly(ionic liquid)/ionic liquid networks, ACS Appl. Polym. Mater. 3 (1) (2021) 200–208, https://doi.org/10.1021/acsapm.0c01042.
[65] J.H. Lee, A.S. Lee, S.M. Hong, S.S. Hwang, C.M. Koo, Hybrid ionogels derived from polycationic polysilsesquioxanes for lithium ion batteries, Polymer 117 (2017) 160–166, https://doi.org/10.1016/j.polymer.2017.03.085.
[66] F. Yang, D. Wu, Z. Luo, B. Tan, Z. Xie, Hybrid organic-inorganic dyeionogels: reversibly pH-responsive materials based dye-ionic liquids with improved structural stability and flexibility, Sensor. Actuator. B Chem. 249 (2017) 486–492, https://doi.org/10.1016/j.snb.2017.04.133.
[67] K. Liu, J. Lv, G. Fan, B. Wang, Z. Mao, X. Sui, X. Feng, Flexible and robust bacterial cellulose-based ionogels with high thermoelectric properties for low-grade heat harvesting, Adv. Funct. Mater. 32 (6) (2022) 2107105, https://doi.org/10.1002/adfm.202107105.
[68] L. Zhang, K. Jia, J. Wang, J. Zhao, J. Tang, J. Hu, Stretchable and transparent ionogel-based heaters, Mater. Horiz. 9 (7) (2022) 1911–1920, https://doi.org/10.1039/D1MH01775F.
[69] J.H. Park, H.H. Rana, J.S. Kim, J.W. Hong, S.J. Lee, H.S. Park, Inorganic–organic double network ionogels based on silica nanoparticles for high-temperature flexible supercapacitors, ACS Appl. Mater. Interfaces 15 (31) (2023) 37344–37353, https://doi.org/10.1021/acsami.3c05254.
[70] M.A. Alaei Shahmirzadi, A. Kargari, T. Matsuura, One-pot synthesis of inorganic-organic hybrid ionogel membrane for propylene/propane separation via olefin-facilitated transport, Sep. Purif. Technol. 300 (2022) 121845, https://doi.org/10.1016/j.seppur.2022.121845.
[71] Y. Ding, J. Zhang, L. Chang, X. Zhang, H. Liu, L. Jiang, Preparation of high-performance ionogels with excellent transparency, good mechanical strength, and high conductivity, Adv. Mater. 29 (47) (2017) 1704253, https://doi.org/10.1002/adma.201704253.
[72] T.B.V. Dinis, F.A. e Silva, F. Sousa, M.G. Freire, Advances brought by hydrophilic ionic liquids in fields involving pharmaceuticals, Materials 14 (21) (2021) 6231, https://doi.org/10.3390/ma14216231.
[73] P.C. Marr, A.C. Marr, Ionic liquid gel materials: applications in green and sustainable chemistry, Green Chem. 18 (1) (2016) 105–128, https://doi.org/10.1039/C5GC02277K.
[74] Y.-R. Gao, W.-X. Zhang, Y.-N. Wei, Y. Li, T. Fei, Y. Shu, J.-H. Wang, Ionic liquids enable the preparation of a copper-loaded gel with transdermal delivery function for wound dressings, Biomater. Sci. 10 (4) (2022) 1041–1052, https://doi.org/10.1039/D1BM01745D.
[75] H. Wang, J. Xu, K. Li, Y. Dong, Z. Du, S. Wang, Highly stretchable, self-healable, and self-adhesive ionogels with efficient antibacterial performances for a highly sensitive wearable strain sensor, J. Mater. Chem. B 10 (8) (2022) 1301–1307, https://doi.org/10.1039/D2TB00041E.
[76] A.F. Kanaan, A.P. Piedade, H.C. de Sousa, A.M.A. Dias, Semi-interpenetrating chitosan/ionic liquid polymer networks as electro-responsive biomaterials for potential wound dressings and iontophoretic applications, Mater. Sci. Eng. C 121 (2021) 111798, https://doi.org/10.1016/j.msec.2020.111798.
[77] M. Kuddushi, N.K. Patel, S. Rajput, O.A. El Seoud, J.P. Mata, N.I. Malek, Temperature-responsive low molecular weight ionic liquid based gelator: an approach to fabricate an anti-cancer drug-loaded hybrid ionogel, ChemSystemsChem 2 (5) (2020) e1900053, https://doi.org/10.1002/syst.201900053.
[78] Y. Shu, R. Xue, Y. Gao, W. Zhang, J. Wang, A thermo-responsive hydrogel loaded with an ionic liquid microemulsion for transdermal delivery of methotrexate, J. Mater. Chem. B 11 (24) (2023) 5494–5502, https://doi.org/10.1039/D2TB02189G.
[79] A.J. Almeida, Ionic liquids as tools to improve gel formulations containing sparingly soluble phenolic acids, Biomedical and Biopharmaceutical Research 19 (1) (2022) 153–167, https://doi.org/10.19277/bbr.19.1.
[80] K. Peng, Y. Shi, A. LaBarbiera, S. Mitragotri, Mucoadhesive ionic liquid gel patches for oral delivery, ACS Biomater. Sci. Eng. 9 (6) (2023) 2838–2845, https://doi.org/10.1021/acsbiomaterials.0c01024.
[81] X. He, X. Sun, H. Meng, S. Deng, T. He, H. Zang, D. Wei, Self-healing polymeric ionic liquid hydrogels with high mechanical strength and ionic conductivity, J. Mater. Sci. 56 (17) (2021) 10231–10248, https://doi.org/10.1007/s10853-021-05930-1.
[82] M. Wang, J. Hu, M.D. Dickey, Emerging applications of tough ionogels, NPG Asia Mater. 15 (1) (2023) 66, https://doi.org/10.1038/s41427-023-00514-8.
[83] B. Yiming, X. Guo, N. Ali, N. Zhang, X. Zhang, Z. Han, Y. Lu, Z. Wu, X. Fan, Z. Jia, et al., Ambiently and mechanically stable ionogels for soft ionotronics, Adv. Funct. Mater. 31 (33) (2021) 2102773, https://doi.org/10.1002/adfm.202102773.
[84] X. Fan, W. Feng, S. Wang, Y. Chen, W.J. Zheng, J. Yan, Fluorine-containing ionogels with stretchable, solvent-resistant, wide temperature tolerance, and transparent properties for ionic conductors, Polymers 16 (7) (2024), https://doi.org/10.3390/polym16071013.
[85] X. Lyu, H. Zhang, S. Yang, W. Zhan, M. Wu, Y. Yu, Z. Shen, Z. Zou, Strain-stiffening ionogel with high-temperature tolerance via the synergy of ionic clusters and hydrogen bonds, ACS Appl. Mater. Interfaces 15 (26) (2023) 31888–31898, https://doi.org/10.1021/acsami.3c05802.
[86] Y. Ren, J. Guo, Z. Liu, Z. Sun, Y. Wu, L. Liu, F. Yan, Ionic liquid–based click-ionogels, Sci. Adv. 5 (8) (2019) eaax0648, https://doi.org/10.1126/sciadv.aax0648.
[87] H. Zhi, F. Wang, X. Zhang, Q. Cai, M. Chen, Y. Shi, L. Feng, Green, pH-sensitive, highly stretchable, and hydrogen bond-dominated ionogel for wound healing activity, ACS Appl. Bio Mater. 7 (1) (2024) 498–507, https://doi.org/10.1021/acsabm.3c01146.
[88] W. Li, W. Xiao, Q. Luo, J. Yan, G. Zhang, L. Chen, J. Sun, Ionic liquids promoted synthesis, enhanced functions, and expanded applications of porous organic frameworks, Coord. Chem. Rev. 493 (2023) 215304, https://doi.org/10.1016/j.ccr.2023.215304.
[89] Y. Wang, H. Haick, S. Guo, C. Wang, S. Lee, T. Yokota, T. Someya, Skin bioelectronics towards long-term, continuous health monitoring, Chem. Soc. Rev. 51 (9) (2022) 3759–3793, https://doi.org/10.1039/D2CS00207H.
[90] X. Wan, Y. He, Z. Xu, C. Li, C. Yang, Progress of hydrophobic ionogels: a review, Macromol. Rapid Commun. 44 (12) (2023) e2200957, https://doi.org/10.1002/marc.202200957.
[91] H. Zhang, X. Yu, Y. Wang, X. Fan, Y.-E. Miao, X. Zhang, T. Liu, Mechanically robust, stretchable, recyclable, and biodegradable ionogels reinforced by polylactide stereocomplex nanocrystals, Compos. Sci. Technol. 230 (2022) 109740, https://doi.org/10.1016/j.compscitech.2022.109740.
[92] X. Ju, J. Kong, G. Qi, S. Hou, B. Wang, X. Diao, S. Dong, Y. Jin, Photoelectric-driven conductive composite ionogel patch for effective wound healing, eScience 4 (2) (2024) 100223, https://doi.org/10.1016/j.esci.2023.100223.
[93] A. Kulshrestha, S. Sharma, K. Singh, A. Kumar, Magnetoresponsive biocomposite hydrogels comprising gelatin and valine based magnetic ionic liquid surfactant as controlled release nanocarrier for drug delivery, Materials Advances 3 (1) (2022) 484–492, https://doi.org/10.1039/D1MA00758K.
[94] Y. Gao, Y. Hao, W. Zhang, Y. Wei, Y. Shu, J. Wang, Microwave-triggered ionic liquid-based hydrogel dressing with excellent hyperthermia and transdermal drug delivery performance, Chem. Eng. J. 429 (2022) 131590, https://doi.org/10.1016/j.cej.2021.131590.
[95] A. Ghoussoub, J.-M. Lehn, Dynamic sol–gel interconversion by reversible cation binding and release in G-quartet-based supramolecular polymers, Chem. Commun. 46 (2005) 5763–5765, https://doi.org/10.1039/B512527H.
[96] M.M. Perera, N. Ayres, Dynamic covalent bonds in self-healing, shape memory, and controllable stiffness hydrogels, Polym. Chem. 11 (8) (2020) 1410–1423, https://doi.org/10.1039/C9PY01694E.
[97] Y. Gao, W. Zhang, L. Li, Z. Wang, Y. Shu, J. Wang, Ionic liquid-based gels for biomedical applications, Chem. Eng. J. 452 (2023) 139248, https://doi.org/10.1016/j.cej.2022.139248.

[98] J. Xu, H. Wang, X. Du, X. Cheng, Z. Du, H. Wang, Self-healing, anti-freezing and highly stretchable polyurethane ionogel as ionic skin for wireless strain sensing, Chem. Eng. J. 426 (2021) 130724, https://doi.org/10.1016/j.cej.2021.130724.
[99] C. Almeida, A.Q. Pedro, A.P.M. Tavares, M.C. Neves, M.G. Freire, Ionic-liquid-based approaches to improve biopharmaceuticals downstream processing and formulation, Front. Bioeng. Biotechnol. 11 (2023) Review, https://doi.org/10.3389/fbioe.2023.1037436.
[100] M. Guncheva, P. Ossowicz, E. Janus, S. Todinova, D. Yancheva, Elucidation of the effect of some cholinium amino acid ionic liquids on the thermal and the conformational stability of insulin, J. Mol. Liq. 283 (2019) 257–262, https://doi.org/10.1016/j.molliq.2019.03.074.
[101] R.R. Mazid, R. Vijayaraghavan, D.R. MacFarlane, C. Cortez-Jugo, W. Cheng, Inhibited fragmentation of mAbs in buffered ionic liquids, Chem. Commun. 51 (38) (2015) 8089–8092, https://doi.org/10.1039/C5CC01877C.
[102] A.Q. Pedro, P. Pereira, M.J. Quental, A.P. Carvalho, S.M. Santos, J.A. Queiroz, F. Sousa, M.G. Freire, Cholinium-based Good's buffers ionic liquids as remarkable stabilizers and recyclable preservation media for recombinant small RNAs, ACS Sustain. Chem. Eng. 6 (12) (2018) 16645–16656, https://doi.org/10.1021/acssuschemeng.8b03900.
[103] X. Lin, Y. Yang, S. Li, Y. Song, G. Ma, Z. Su, S. Zhang, Unique stabilizing mechanism provided by biocompatible choline-based ionic liquids for inhibiting dissociation of inactivated foot-and-mouth disease virus particles, RSC Adv. 9 (24) (2019) 13933–13939, https://doi.org/10.1039/C9RA02722J.
[104] T.A. Shmool, L.K. Martin, A. Jirkas, R.P. Matthews, A.P. Constantinou, D.M. Vadukul, T.K. Georgiou, F.A. Aprile, J.P. Hallett, Unveiling the rational development of stimuli-responsive silk fibroin-based ionogel formulations, Chem. Mater. 35 (15) (2023) 5798–5808, https://doi.org/10.1021/acs.chemmater.3c00303.
[105] C. Hermida-Merino, D. Cabaleiro, C. Gracia-Fernández, J. Valcarcel, J.A. Vázquez, N. Sanz, M. Pérez-Rodríguez, M. Arenas-Moreira, D. Banerjee, A. Longo, et al., Ionogels derived from fluorinated ionic liquids to enhance aqueous drug solubility for local drug administration, Gels 8 (9) (2022) 594, https://doi.org/10.3390/gels8090594.
[106] G. Chantereau, M. Sharma, A. Abednejad, B.M. Neves, G. Sèbe, V. Coma, M.G. Freire, C.S.R. Freire, A.J.D. Silvestre, Design of nonsteroidal anti-inflammatory drug-based ionic liquids with improved water solubility and drug delivery, ACS Sustain. Chem. Eng. 7 (16) (2019) 14126–14134, https://doi.org/10.1021/acssuschemeng.9b02797.
[107] R. Pansuriya, S. Mehra, A. Kumar, O. El Seoud, S. Kumar Kailasa, N. Malek, Two birds with one stone: multifunctional ionic liquid based polymeric hydrogel as decontaminant and vehicle for drug delivery, J. Mol. Liq. 382 (2023) 121857, https://doi.org/10.1016/j.molliq.2023.121857.
[108] M.M. Fernandes, E.O. Carvalho, D.M. Correia, J.M.S.S. Esperança, J. Padrão, K. Ivanova, J. Hoyo, T. Tzanov, S. Lanceros-Mendez, Ionic liquids as biocompatible antibacterial agents: a case study on structure-related bioactivity on Escherichia coli, ACS Appl. Bio Mater. 5 (11) (2022) 5181–5189, https://doi.org/10.1021/acsabm.2c00615.
[109] Z. Fang, X. Zheng, L. Li, J. Qi, W. Wu, Y. Lu, Ionic liquids: emerging antimicrobial agents, Pharm. Res. (N. Y.) 39 (10) (2022) 2391–2404, https://doi.org/10.1007/s11095-022-03336-5.
[110] N. Nikfarjam, M. Ghomi, T. Agarwal, M. Hassanpour, E. Sharifi, D. Khorsandi, M. Ali Khan, F. Rossi, A. Rossetti, E. Nazarzadeh Zare, et al., Antimicrobial ionic liquid-based materials for biomedical applications, Adv. Funct. Mater. 31 (42) (2021) 2104148, https://doi.org/10.1002/adfm.202104148.
[111] A.M.O. Azevedo, S.P.F. Costa, A.F.V. Dias, A.H.O. Marques, P.C.A.G. Pinto, K. Bica, A.K. Ressmann, M.L.C. Passos, A.R.T.S. Araújo, S. Reis, et al., Anti-inflammatory choline based ionic liquids: insights into their lipophilicity, solubility and toxicity parameters, J. Mol. Liq. 232 (2017) 20–26, https://doi.org/10.1016/j.molliq.2017.02.027.
[112] Z. Zhang, Q. Zhang, S. Gao, H. Xu, J. Guo, F. Yan, Antibacterial, anti-inflammatory and wet-adhesive poly(ionic liquid)-based oral patch for the treatment of oral ulcers with bacterial infection, Acta Biomater. 166 (2023) 254–265, https://doi.org/10.1016/j.actbio.2023.05.017.
[113] Y. Hu, H. Zhou, J. Huang, T. Wang, H. Wang, D. Wu, C. Yu, G. Pan, L. Zhang, L. Zhang, et al., Multifunctional IL-based hydrogel modulator for the synergistic acceleration of wound healing: optimizing drug solubility, antioxidant, and anti-inflammatory effects, ACS Sustain. Chem. Eng. 11 (13) (2023) 5122–5134, https://doi.org/10.1021/acssuschemeng.2c07172.
[114] T.E. Sintra, A. Luís, S.N. Rocha, A.I.M.C. Lobo Ferreira, F. Gonçalves, L.M.N.B.F. Santos, B.M. Neves, M.G. Freire, S.P.M. Ventura, J.A.P. Coutinho, Enhancing the antioxidant characteristics of phenolic acids by their conversion into cholinium salts, ACS Sustain. Chem. Eng. 3 (10) (2015) 2558–2565, https://doi.org/10.1021/acssuschemeng.5b00751.
[115] E.S. Morais, N.H.C.S. Silva, T.E. Sintra, S.A.O. Santos, B.M. Neves, I.F. Almeida, P.C. Costa, I. Correia-Sá, S.P.M. Ventura, A.J.D. Silvestre, et al., Anti-inflammatory and antioxidant nanostructured cellulose membranes loaded with phenolic-based ionic liquids for cutaneous application, Carbohydrate Polym. 206 (2019) 187–197, https://doi.org/10.1016/j.carbpol.2018.10.051.
[116] J.M. Gomes, S.S. Silva, L.C. Rodrigues, R.L. Reis, Alginate/acemannan-based beads loaded with a biocompatible ionic liquid as a bioactive delivery system, Int. J. Biol. Macromol. 242 (2023) 125026, https://doi.org/10.1016/j.ijbiomac.2023.125026.
[117] G.C. Luque, M. Moya, M.L. Picchio, V. Bagnarello, I. Valerio, J. Bolaños, M. Vethencourt, S.H. Gamboa, L.C. Tomé, R.J. Minari, et al., Polyphenol iongel patches with antimicrobial, antioxidant and anti-inflammatory properties, Polymers 15 (5) (2023), https://doi.org/10.3390/polym15051076.
[118] Y. Hu, Y. Xing, H. Yue, T. Chen, Y. Diao, W. Wei, S. Zhang, Ionic liquids revolutionizing biomedicine: recent advances and emerging opportunities, Chem. Soc. Rev. 52 (20) (2023) 7262–7293, https://doi.org/10.1039/d3cs00510k.
[119] J.L. Shamshina, P. Berton, Ionic liquids as designed, multi-functional plasticizers for biodegradable polymeric materials: a mini-review, Int. J. Mol. Sci. 25 (3) (2024) 1720, https://doi.org/10.3390/ijms25031720.
[120] S.S. de Jesus, R. Maciel Filho, Are ionic liquids eco-friendly? Renew. Sustain. Energy Rev. 157 (2022) 112039 https://doi.org/10.1016/j.rser.2021.112039.
[121] M.M. Bailey, P.L. Jernigan, M.B. Henson, J. Sturdivant, J.F. Rasco, A.N. Lovich, J.E. Lockhard, W.L. Hough, K.R. Di Bona, J. Beaird, et al., A comparison of the effects of prenatal exposure of CD-1 mice to three imidazolium-based ionic liquids, Birth Defects Res. Part B Dev. Reproductive Toxicol. 89 (3) (2010) 233–238, https://doi.org/10.1002/bdrb.20251.
[122] T.D. Landry, K. Brooks, D. Poche, M. Woolhiser, Acute toxicity profile of 1-butyl-3-methylimidazolium chloride, Bull. Environ. Contam. Toxicol. 74 (3) (2005) 559–565, https://doi.org/10.1007/s00128-005-0620-4.
[123] M. Musiał, E. Zorębski, K. Malarz, M. Kuczak, A. Mrozek-Wilczkiewicz, J. Jacquemin, M. Dzida, Cytotoxicity of ionic liquids on normal human dermal fibroblasts in the context of their present and future applications, ACS Sustain. Chem. Eng. 9 (22) (2021) 7649–7657, https://doi.org/10.1021/acssuschemeng.1c02277.
[124] S.A. Pérez, M.G. Montalbán, G. Carissimi, P. Licence, G. Víllora, In vitro cytotoxicity assessment of monocationic and dicationic pyridinium-based ionic liquids on HeLa, MCF-7, BGM and EA.hy926 cell lines, J. Hazard Mater. 385 (2020) 121513, https://doi.org/10.1016/j.jhazmat.2019.121513.
[125] J.H. Hwang, H. Park, D.W. Choi, K.T. Nam, K.M. Lim, Investigation of dermal toxicity of ionic liquids in monolayer-cultured skin cells and 3D reconstructed human skin models, Toxicol. Vitro 46 (2018) 194–202, https://doi.org/10.1016/j.tiv.2017.09.025.
[126] B. Kanjilal, Y. Zhu, V. Krishnadoss, J.M. Unagolla, P. Saemian, A. Caci, D. Cheraghali, I. Dehzangi, A. Khademhosseini, I. Noshadi, Bioionic liquids: enabling a paradigm shift toward advanced and smart biomedical applications, Advanced Intelligent Systems 5 (5) (2023) 2200306, https://doi.org/10.1002/aisy.202200306.
[127] I. Noshadi, B.W. Walker, R. Portillo-Lara, E. Shirzaei Sani, N. Gomes, M.R. Aziziyan, N. Annabi, Engineering biodegradable and biocompatible bio-ionic liquid conjugated hydrogels with tunable conductivity and mechanical properties, Sci. Rep. 7 (1) (2017) 4345, https://doi.org/10.1038/s41598-017-04280-w.
[128] M.V. Quental, A.Q. Pedro, P. Pereira, M. Sharma, J.A. Queiroz, J.A.P. Coutinho, F. Sousa, M.G. Freire, Integrated extraction-preservation strategies for RNA using biobased ionic liquids, ACS Sustain. Chem. Eng. 7 (10) (2019) 9439–9448, https://doi.org/10.1021/acssuschemeng.9b00688.
[129] L.R. Jorge, L.K. Harada, E.C. Silva, W.F. Campos, F.C. Moreli, G. Shimamoto, J.F.B. Pereira, J.M. Oliveira, M. Tubino, M.M.D.C. Vila, et al., Non-invasive transdermal delivery of human insulin using ionic liquids: in vitro studies, Front. Pharmacol. 11 (2020), https://doi.org/10.3389/fphar.2020.00243. Original Research.
[130] K. Kuroda, A simple overview of toxicity of ionic liquids and designs of biocompatible ionic liquids, New J. Chem. 46 (42) (2022) 20047–20052, https://doi.org/10.1039/D2NJ02634A.
[131] Q. Xu, Z. Zheng, B. Wang, H. Mao, F. Yan, Zinc ion coordinated poly(ionic liquid) antimicrobial membranes for wound healing, ACS Appl. Mater. Interfaces 9 (17) (2017) 14656–14664, https://doi.org/10.1021/acsami.7b01677.
[132] A. Vaidya, S. Mitragotri, Ionic liquid-mediated delivery of insulin to buccal mucosa, J. Contr. Release 327 (2020) 26–34, https://doi.org/10.1016/j.jconrel.2020.07.037.
[133] A. Jordan, N. Gathergood, Biodegradation of ionic liquids – a critical review, Chem. Soc. Rev. 44 (22) (2015) 8200–8237, https://doi.org/10.1039/C5CS00444F.
[134] D. Coleman, N. Gathergood, Biodegradation studies of ionic liquids, Chem. Soc. Rev. 39 (2) (2010) 600–637, https://doi.org/10.1039/B817717C.
[135] S. Stolte, S. Steudte, A. Igartua, P. Stepnowski, The biodegradation of ionic liquids - the view from a chemical structure perspective, Curr. Org. Chem. 15 (12) (2011) 1946–1973, https://doi.org/10.2174/138527211795703603.
[136] J. Flieger, M. Flieger, Ionic liquids toxicity—benefits and threats, Int. J. Mol. Sci. 21 (17) (2020) 6267, https://doi.org/10.3390/ijms21176267.
[137] A.-K. Amsel, O. Olsson, K. Kümmerer, Inventory of biodegradation data of ionic liquids, Chemosphere 299 (2022) 134385, https://doi.org/10.1016/j.chemosphere.2022.134385.
[138] I.P.E. Macário, T. Veloso, J.L. Pereira, S.P.M. Ventura, J.A.P. Coutinho, Potential threats of ionic liquids to the environment and ecosphere, in: S. Zhang (Ed.), Encyclopedia of Ionic Liquids, Springer Singapore, 2020, pp. 1–17.
[139] A.Y. Yuen, L. Porcarelli, R.H. Aguirresarobe, A. Sanchez-Sanchez, I. Del Agua, U.G. Ismailov, G. Malliaras, D. Mecerreyes, E. Ismailova, H. Sardon, Biodegradable polycarbonate iongels for electrophysiology measurements, Polymers 10 (9) (2018) 989, https://doi.org/10.3390/polym10090989.
[140] C.A. Smith, V.A. Cataldo, T. Dimke, I. Stephan, R. Guterman, Antibacterial and degradable thioimidazolium poly(ionic liquid), ACS Sustain. Chem. Eng. 8 (22) (2020) 8419–8424, https://doi.org/10.1021/acssuschemeng.0c02666.
[141] S. Ostadjoo, P. Berton, J.L. Shamshina, R.D. Rogers, Scaling-up ionic liquid-based technologies: how much do we care about their toxicity? Prima facie information on 1-ethyl-3-methylimidazolium acetate, Toxicol. Sci. 161 (2) (2017) 249–265, https://doi.org/10.1093/toxsci/kfx172, 5/15/2024.
[142] P. Wei, X. Pan, C.-Y. Chen, H.-Y. Li, X. Yan, C. Li, Y.-H. Chu, B. Yan, Emerging impacts of ionic liquids on eco-environmental safety and human health, Chem. Soc. Rev. 50 (24) (2021) 13609–13627, https://doi.org/10.1039/D1CS00946J.

[143] V. Brumberg, T. Astrelina, T. Malivanova, A. Samoilov, Modern wound dressings: hydrogel dressings, Biomedicines 9 (9) (2021) 1235, https://doi.org/10.3390/biomedicines9091235.
[144] H. Fang, J. Wang, L. Li, L. Xu, Y. Wu, Y. Wang, X. Fei, J. Tian, Y. Li, A novel high-strength poly(ionic liquid)/PVA hydrogel dressing for antibacterial applications, Chem. Eng. J. 365 (2019) 153–164, https://doi.org/10.1016/j.cej.2019.02.030.
[145] E.R.D. Seiler, K. Koyama, T. Iijima, T. Saito, Y. Takeoka, M. Rikukawa, M. Yoshizawa-Fujita, Simple and fast one-pot cellulose gel preparation in aqueous pyrrolidinium hydroxide solution–cellulose solvent and antibacterial agent, Polymers 13 (12) (2021) 1942, https://doi.org/10.3390/polym13121942.
[146] Z. Luo, H. Cui, J. Guo, J. Yao, X. Fang, F. Yan, B. Wang, H. Mao, Poly(ionic liquid)/Ce-based antimicrobial nanofibrous membrane for blocking drug-resistance dissemination from MRSA-infected wounds, Adv. Funct. Mater. 31 (23) (2021) 2100336, https://doi.org/10.1002/adfm.202100336.
[147] V. Puca, R.Z. Marulli, R. Grande, I. Vitale, A. Niro, G. Molinaro, S. Prezioso, R. Muraro, P. Di Giovanni, Microbial species isolated from infected wounds and antimicrobial resistance analysis: data emerging from a three-years retrospective study, Antibiotics 10 (10) (2021), https://doi.org/10.3390/antibiotics10101162.
[148] B. Liu, R. Fu, Z. Duan, C. Zhu, J. Deng, D. Fan, Ionic liquid-based non-releasing antibacterial, anti-inflammatory, high-transparency hydrogel coupled with electrical stimulation for infected diabetic wound healing, Compos. B Eng. 236 (2022) 109804, https://doi.org/10.1016/j.compositesb.2022.109804.
[149] G. Tao, Y. Wang, R. Cai, H. Chang, K. Song, H. Zuo, P. Zhao, Q. Xia, H. He, Design and performance of sericin/poly(vinyl alcohol) hydrogel as a drug delivery carrier for potential wound dressing application, Mater. Sci. Eng. C 101 (2019) 341–351, https://doi.org/10.1016/j.msec.2019.03.111.
[150] S. Gilotra, D. Chouhan, N. Bhardwaj, S.K. Nandi, B.B. Mandal, Potential of silk sericin based nanofibrous mats for wound dressing applications, Mater. Sci. Eng., C 90 (2018) 420–432, https://doi.org/10.1016/j.msec.2018.04.077.
[151] N. Lammari, M. Tarhini, K. Miladi, O. Louaer, A.H. Meniai, S. Sfar, H. Fessi, A. Elaissari, Chapter 14 - encapsulation methods of active molecules for drug delivery, in: E. Chappel (Ed.), Drug Delivery Devices and Therapeutic Systems, Academic Press, 2021, pp. 289–306.
[152] S.K. Bardal, J.E. Waechter, D.S. Martin, in: Applied Pharmacology, S.K. Bardal, J.E. Waechter, D.S. Martin (Eds.), Chapter 2 - Pharmacokinetics, W.B. Saunders, 2011, pp. 17–34.
[153] D. Ramadon, M.T.C. McCrudden, A.J. Courtenay, R.F. Donnelly, Enhancement strategies for transdermal drug delivery systems: current trends and applications, Drug Deliv Transl Res 12 (4) (2022) 758–791, https://doi.org/10.1007/s13346-021-00909-6.
[154] C. Mukesh, J. Bhatt, K. Prasad, A polymerizable bioionic liquid based nanogel: a new nanocarrier for an anticancer drug, Macromol. Chem. Phys. 215 (15) (2014) 1498–1504, https://doi.org/10.1002/macp.201400269.
[155] J. Xu, X. Tan, L. Chen, X. Li, F. Xie, Starch/microcrystalline cellulose hybrid gels as gastric-floating drug delivery systems, Carbohydrate Polym. 215 (2019) 151–159, https://doi.org/10.1016/j.carbpol.2019.03.078.
[156] D. Santra, K. Sen, Ionic liquid–modified cellulosic hydrogels for loading and sustained release of selenourea: an ensuing inhibition of tyrosinase activity, Mater. Today Chem. 18 (2020) 100365, https://doi.org/10.1016/j.mtchem.2020.100365.
[157] S. Keihankhadiv, D. Neugebauer, Synthesis and characterization of linear copolymers based on pharmaceutically functionalized monomeric choline ionic liquid for delivery of p-aminosalicylate, Pharmaceutics 15 (3) (2023) 860, https://doi.org/10.3390/pharmaceutics15030860.
[158] D. Brevet, C. Jouannin, C. Tourné-Péteilh, J.-M. Devoisselle, A. Vioux, L. Viau, Self-encapsulation of a drug-containing ionic liquid into mesoporous silica monoliths or nanoparticles by a sol–gel process, RSC Adv. 6 (86) (2016) 82916–82923, https://doi.org/10.1039/C6RA17431K.
[159] M. Kuddushi, N.K. Patel, S. Rajput, A. Shah, O.A. El Seoud, N.I. Malek, Thermo-Switchable de Novo Ionic Liquid-Based Gelators with Dye-Absorbing and Drug-Encapsulating Characteristics, ACS Omega 3 (9) (2018) 12068–12078, https://doi.org/10.1021/acsomega.8b01984.
[160] M.A. Rahim, N. Jan, S. Khan, H. Shah, A. Madni, A. Khan, A. Jabar, S. Khan, A. Elhissi, Z. Hussain, et al., Recent advancements in stimuli responsive drug delivery platforms for active and passive cancer targeting, Cancers 13 (4) (2021) 670, https://doi.org/10.3390/cancers13040670.
[161] W.B. Liechty, D.R. Kryscio, B.V. Slaughter, N.A. Peppas, Polymers for drug delivery systems, Annu. Rev. Chem. Biomol. Eng. 1 (2010) 149–173, https://doi.org/10.1146/annurev-chembioeng-073009-100847.
[162] B. Lu, M. Yi, S. Hu, D. Wu, Z. Zhu, C. Wu, Z. Wang, Y. Li, J. Zhang, Taurine-based ionic liquids for transdermal protein delivery and enhanced anticancer activity, ACS Sustain. Chem. Eng. 9 (17) (2021) 5991–6000, https://doi.org/10.1021/acssuschemeng.1c01064.
[163] A. Arivazhahan, Principles and modes of drug administration, in: G.M. Raj, R. Raveendran (Eds.), Introduction to Basics of Pharmacology and Toxicology: Volume 1: General and Molecular Pharmacology: Principles of Drug Action, Springer Singapore, 2019, pp. 69–79.
[164] J. Claus, T. Eickner, N. Grabow, U. Kragl, S. Oschatz, Ion exchange controlled drug release from polymerized ionic liquids, Macromol. Biosci. 20 (9) (2020) 2000152, https://doi.org/10.1002/mabi.202000152.
[165] M. Kuddushi, D. Ray, V. Aswal, C. Hoskins, N. Malek, Poly(vinyl alcohol) and functionalized ionic liquid-based smart hydrogels for doxorubicin release, ACS Appl. Bio Mater. 3 (8) (2020) 4883–4894, https://doi.org/10.1021/acsabm.0c00393.
[166] D.K. Pandey, M. Kuddushi, A. Kumar, D.K. Singh, Iron oxide nanoparticles loaded smart hybrid hydrogel for anti-inflammatory drug delivery: preparation and characterizations, Colloids Surf. A Physicochem. Eng. Asp. 650 (2022) 129631, https://doi.org/10.1016/j.colsurfa.2022.129631.
[167] R. Pansuriya, T. Patel, S. Mehra, A. Kumar, O.A. El Seoud, S. Kumar, V.K. Aswal, S.K. Kailasa, N.I. Malek, A dual responsive ionic liquid-based polymeric hydrogel: a promising drug delivery vehicle for the treatment of breast cancer, New J. Chem. 47 (30) (2023) 14261–14272, https://doi.org/10.1039/D3NJ01914D.
[168] J. Claus, A. Brietzke, C. Lehnert, S. Oschatz, N. Grabow, U. Kragl, Swelling characteristics and biocompatibility of ionic liquid based hydrogels for biomedical applications, PLoS One 15 (4) (2020) e0231421, https://doi.org/10.1371/journal.pone.0231421.
[169] N. Raina, R. Rani, V.K. Thakur, M. Gupta, New insights in topical drug delivery for skin disorders: from a nanotechnological perspective, ACS Omega 8 (22) (2023) 19145–19167, https://doi.org/10.1021/acsomega.2c08016.
[170] D. Dobler, T. Schmidts, C. Zinecker, P. Schlupp, J. Schäfer, F. Runkel, Hydrophilic ionic liquids as ingredients of gel-based dermal formulations, AAPS PharmSciTech 17 (4) (2016) 923–931, https://doi.org/10.1208/s12249-015-0421-y.
[171] C. Sheng, X. Tan, Q. Huang, K. Li, C. Zhou, M. Guo, Antibacterial and angiogenic poly(ionic liquid) hydrogels, Gels 8 (8) (2022) 476, https://doi.org/10.3390/gels8080476.
[172] P. Maneewattanapinyo, A. Yeesamun, F. Watthana, K. Panrat, W. Pichayakorn, J. Suksaeree, Controlled release of lidocaine–diclofenac ionic liquid drug from freeze-thawed gelatin/poly(vinyl alcohol) transdermal patches, AAPS PharmSciTech 20 (8) (2019) 322, https://doi.org/10.1208/s12249-019-1545-2.
[173] T. Cheng, Z. Tai, M. Shen, Y. Li, J. Yu, J. Wang, Q. Zhu, Z. Chen, Advance and challenges in the treatment of skin diseases with the transdermal drug delivery system, Pharmaceutics 15 (8) (2023) 2165, https://doi.org/10.3390/pharmaceutics15082165.
[174] Y.K. Mohanta, K. Biswas, S.K. Jena, A. Hashem, E.F. Abd_Allah, T.K. Mohanta, Anti-biofilm and antibacterial activities of silver nanoparticles synthesized by the reducing activity of phytoconstituents present in the Indian medicinal plants, Front. Microbiol. 11 (2020), https://doi.org/10.3389/fmicb.2020.01143. Original Research.
[175] B. Kopilovic, F.A. e Silva, A.Q. Pedro, J.A.P. Coutinho, M.G. Freire, Ionogels for biomedical applications, in: S. Gopi, P. Balakrishnan, N.M. Mubarak (Eds.), Nanotechnology for Biomedical Applications, Springer Singapore, 2022, pp. 391–425.
[176] A.M. Ferreira, E.S. Morais, A.C. Leite, A. Mohamadou, B. Holmbom, T. Holmbom, B.M. Neves, J.A.P. Coutinho, M.G. Freire, A.J.D. Silvestre, Enhanced extraction and biological activity of 7-hydroxymatairesinol obtained from Norway spruce knots using aqueous solutions of ionic liquids, Green Chem. 19 (11) (2017) 2626–2635, https://doi.org/10.1039/C7GC01091E.
[177] S. Magina, A. Barros-Timmons, S.P.M. Ventura, D.V. Evtuguin, Evaluating the hazardous impact of ionic liquids – challenges and opportunities, J. Hazard Mater. 412 (2021) 125215, https://doi.org/10.1016/j.jhazmat.2021.125215.
[178] H.K. Timken, H. Luo, B.-K. Chang, E. Carter, M. Cole, ISOALKY™ technology: next-generation alkylate gasoline manufacturing process technology using ionic liquid catalyst, in: M.B. Shiflett (Ed.), Commercial Applications of Ionic Liquids, Springer International Publishing, 2020, pp. 33–47.
[179] MEDRx Co., Ltd. https://www.medrx.co.jp/english/business/iltspipeline/index.html (accessed 24th February 2024).
[180] CAGE Bio Inc. https://cagebio.com/(accessed 25th February 2024).
[181] i2o Therapeutics. https://i2obio.com/(accessed 25th February 2024).