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TUTORIAL REVIEWS

Ionic liquids for preparation of biopolymer materials for drug/gene delivery: A review

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Biopolymers are particularly suitable for drug applications due to their biocompatibility, biodegradability, and low immunogenicity. There has been growing interest in using biopolymers to achieve the controlled release of therapeutics. However, the solubility and processability of biopolymers remain to be challenging due to their structural heterogeneity and dense networks of inter- and intramolecular interactions. Fortunately, ionic liquids (ILs), regarded as green solvents, have been increasingly appreciated for their unparalleled power for biopolymer processing. By dissolution of biopolymers in ILs, various materials including sponges, films, microparticles (MPs), nanoparticles (NPs), and aerogels can be generated as potential drug delivery carriers. Besides, ILs can be used as reaction mediums and/or catalysts for biopolymer chemical reactions, which shows enhanced reaction efficiencies. In addition, because of their unique physicochemical (*e.g.*, polarity, hydrophobicity, amphipathicity and miscibility) and biological properties (*e.g.*, antibacterial activity), ILs can assist or participate in the formation of drug delivery carriers. To cover all these aspects of research, this review provides an overview of the recent progress in using ILs for the engineering of next-generation drug/gene delivery carrier materials. The tunable properties of ILs as affected by their structures are highlighted. Also, the key principles, challenges and prospects in this area are presented.

1 Introduction

During the past decades, considerable progress has been made in therapeutics and pharmaceutics for treating various diseases. Stimulus-responsive and target-specific delivery systems are the two most outstanding examples, which take advantage of the physiological and pathological bases of humans for delivering bioactive compounds to the site of interest with the maximized therapeutic potential and minimized toxicity.[1] However, it is noteworthy that the toxicity of drug delivery systems (DDSs) could not only be attributed to the unwanted drug release, but also the low biocompatibility and degradability of the drug carrier materials. Materials for drug applications need to minimize the possibilities of hypersensitivity reactions and afford excellent tissue compatibility.[2] Thus, owing to the unique properties of biopolymers such as versatility, biocompatibility, and bioabsorbability, numerous efforts have been undertaken to prepare drug/gene delivery systems from biopolymers. Moreover, biopolymers, either intrinsically or via modification, can exhibit antibacterial activity and suitable mechanical and adhesive properties,[3, 4] making them ideal for biomedical applications.

Although biopolymers serve as abundant, diverse, and renewable sources, their low solubility in conventional solvents makes it rather challenging to prepare materials from biopolymers or undertake the chemical derivatization of biopolymers. This is especially the case for polysaccharides, which have a sophisticated native structure combining amorphous and crystalline regions with strong hydrogen bonds between the molecular chains. Only certain polysaccharides can be dissolved and/or modified in selected polar solvents (*e.g.*, water, pyridine, formamide, dimethylformamide (DMF), and dimethylsulfoxide (DMSO)).[5-8] For example, due to the supramolecular structure,[9] starch exhibits low solubility in almost any solvent except DMSO.[10] However, these polar solvents except water are either flammable, toxic or corrosive, or have difficulty in solvent recovery,[11] which may cause safety issues to humans and the environment. Furthermore, to fully dissolve biopolymers, multi-step pretreatment is often needed, followed by prolonged mechanical stirring, which will cause intensive energy consumption. With consideration of these limitations, it is highly desirable to find potential green solvents for biopolymers. Recently, ILs have shown huge potential to

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address the issues mentioned above. ILs are a group of salts formed from bulky, unsymmetrical ions with a delocalized charge, which make them as a liquid at relatively low temperatures (<100 °C). Especially, those ILs having a melting point below room temperature are called room-temperature ionic liquids (RTILs).[12] Since most ILs are nonvolatile, recyclable, nonexplosive, thermally robust, they can be used as more environmentally friendly solvents compared to conventional organic liquids.[13] The most common examples of ILs include salts of organic cations, such as imidazolium, pyridinium, ammonium, or phosphonium,[13] and the derivatives of these salts with different lengths of side alkyl chains and structural functionalities. On the other hand, anions vary from organic ions such as lactate (Lac)[14] and formate,[15] to inorganic ions such as hexafluorophosphate (PF_6), tetrafluoroborate (BF_4), and then to chloride (Cl) and bromide (Br) in several low-melting salts.[13]

Interestingly, the variety of possible combinations of anions and cations can, in principle, generate a wide spectrum of excellent and recyclable media with extensive tuneable properties.[16] These solvents present unusual solubility and miscibility properties, attractive electric conductivity with a wide electrochemical stability window, interesting polarity nucleophilicity for catalysis, and remarkable tribological properties.[17] These features endow them with a diversified range of applications including the processing of biopolymers. The application of ILs allows the comprehensive utilization of biopolymers by combining two major green chemistry principles: using environmentally preferable solvents (ILs) and biorenewable feedstock (biopolymers). Motivated by the excellent solubility of biopolymers in ILs, the application of ILs offers opportunities of not only the *in-situ* functionalization of biopolymer materials,[18-21] but also the creation of novel hybrid materials, such as ionogels.[22-24] For instance, guar gum has been exploited as a biosource to generate highly conductive and elastic ionogels with ILs.[25, 26] The combined presence of guar gum and poly(ionic liquid) (P(IL)) conferred excellent dimensional stability to the ionogels with no IL exudation combined with high thermal properties (up to 310 °C).[25] Confinement of ILs in gel matrices makes them suitable for an array of applications. These could include soft matter electronic devices such as quasi-solid dye-sensitized solar cells,[27] actuators,[28] sensors[29] or electrochromic displays,[30] as well as biomedical applications such as electrical-sensitive matrices[31] and DNA ionogels.[32] Nonetheless, the green aspects of ILs was often over-exaggerated and their effects upon exposure to the environment and in the human body have not been well understood.[33-35] Despite their extremely low vapour pressure that prevents IL evaporation to the atmosphere, they will inevitably end up in the aqueous and soil environments. Thus, it is vital to consider the impact of ILs with regard to their ecotoxicity and biodegradability, since it may damage the greenness of biopolymers, especially concerning the safe drug/gene delivery applications.

ILs have been increasingly demonstrated to be able to dissolve various biopolymers,[36-40] and to serve as green reaction media for catalysis processes[41] and the derivatization of biopolymers[42-46] for the promotion of 2D- and 3D-based

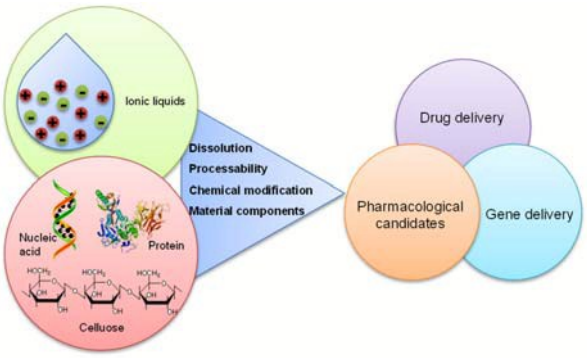


Fig. 1. Overview of the strategies and pharmaceutical applications of biopolymer-based materials prepared in ionic liquids.

biopolymer matrices in pharmaceutical applications (Fig. 1). Moreover, some new applications such as pharmaceutical ILs are emerging.[47] Being very effective at dissolving many types of biologically active compounds (*e.g.*, proteins, nucleosides, and amino acids)[32, 48] and the formation of drug/gene delivery carriers,[49] ILs are considered highly useful for the pharmaceutical industry. In recent years, there have been several reviews documenting the advances in using ILs for pharmaceuticals,[47] the application of ILs for biodegradable composite materials,[50] or chitin and chitosan materials for biomedical applications.[51] To the best of our knowledge, no application of ILs in the development of biopolymer-based DDSs have been systematically reviewed. Trends are continuing through the rapid development of new technologies involving the use of ILs for the processing of biopolymers and the fabrication of IL-based drug formulations and biopolymer-based DDSs. In this review, the role of ILs in the fabrication of carrier materials are particularly focused. The cations and anions constituting ILs considered in this review are listed in Table 1 and Table 2. We will discuss the strategies and principles to create carrier materials that are effective in drug delivery and drug formulations, and illustrate how these principles are underpinning the development of biopolymer-based DDSs.

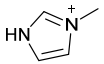
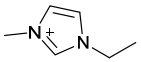
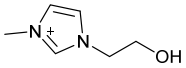
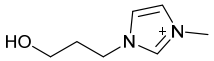
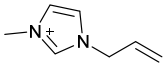
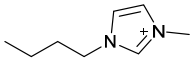
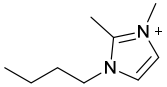
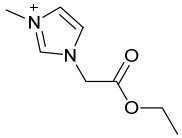
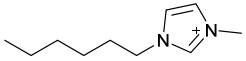
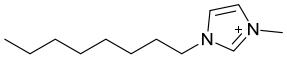
2 ILs and their significance in biopolymer materials

The studies of biopolymer materials with the use of ILs have demonstrated huge opportunities for clean processes for biopolymers and for the creation of new functional IL-biopolymer complexes thanks to the favourably tailor-made chemical, physical and biological properties of ILs (Fig. 2). Thus, in this section, considering the core solvent properties of ILs, we will discuss the structural factors of biopolymers and ILs, the physicochemical properties of ILs, and the dissolution process of biopolymers in ILs that could be applicable to biomedical applications especially drug/gene delivery.

2.1 Biopolymers

Nowadays, a diversity of naturally occurring polymers derived from renewable resources are available for material

Table 1 List of cations of ionic liquids presented in this work

Name	Abbreviation	Structure
Imidazolium cations		
1-Methylimidazolium	HMIM	
1,2-Dimethylimidazolium	1,2-M_2IM	
1-Ethyl-3-methylimidazolium	EMIM	
1-(2-hydroxyethyl)-3-methylimidazolium	C_2OHMIM	
1-(3-hydroxypropyl)-3-methylimidazolium	C_3OHMIM	
1-Allyl-3-methylimidazolium	AMIM	
1-Butyl-3-methylimidazolium	BMIM	
1-Butyl-2,3-dimethylimidazolium	DMBIM	
3-Methyl-1-(ethylacetyl)imidazolium	EtMIM	
1-Hexyl-3-methylimidazolium	C_6MIM	
1-Octyl-3-methylimidazolium	OMIM	

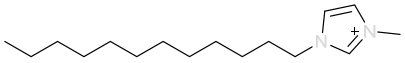
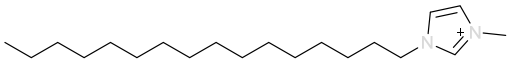
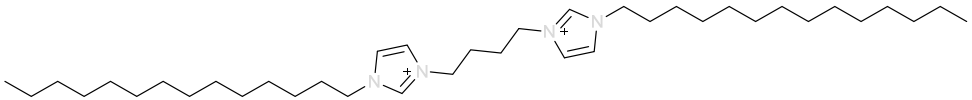
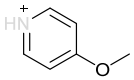
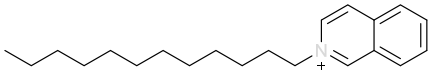
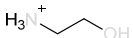
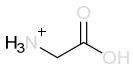
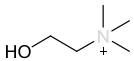
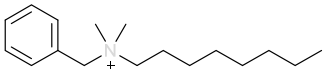
1-Dodecyl-3-methylimidazolium	C_{12}MIM	
1-Hexadecyl-3-methylimidazolium	C_{16}MIM	
Imidazolium Gemini surfactant	[C_{14}-4-C_{14}IM]	
Pyridinium cations		
4-Methoxypyridinium	[4-MeOPy]	
Quinolinium cations		
Lauryl isoquinolinium	C_{12}iQuin	
Ammonium cations		
Hydroxylammonium	[NH_3OH]	
2-Hydroxyethylammonium	[$NH_3(CH_2)_2OH$]	
Glycine	Gly	
Choline	Ch	
Benzyl dimethyl octyl ammonium	BDOA	

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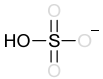
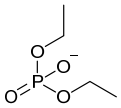
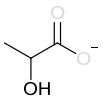
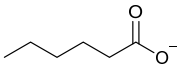
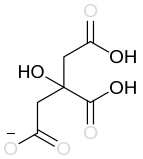
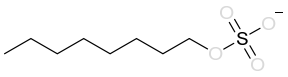
Table 2 List of anions of ionic liquids presented in this work

Name	Abbreviation	Structure
Chloride	Cl	
Bromide	Br	
Acetate	Ac	
Benzoate	Ba	
Hexafluorophosphate	PF_6	
Tetrafluoroborate	BF_4	
Hydrogen sulphate	HSO_4	
Dihydrogen phosphate	DHP	
Methylphosphonate	MP	
Diethyl phosphate	DEP	
Thiocyanate	SCN	
Formate	Formate	
Lactate	Lac	
Hexanoate	Hex	
Citrate	Cit	
Octylsulfate	C_8OSO_3	

applications to decrease our dependency on fossil fuel and increase the biodegradability and biocompatibility of the materials.[52] These biopolymers are produced from living organisms and can be classified into three main groups, namely polysaccharides, proteins, and nucleic acids. Biopolymers can perform a diverse set of functions in their native settings. For example, proteins can function as structural materials as the quintessential part of motility, stabilization, elasticity, scaffolding, and the protection of cells, tissues, and organisms.[53] Thus, the increased understanding of the biopolymer structure

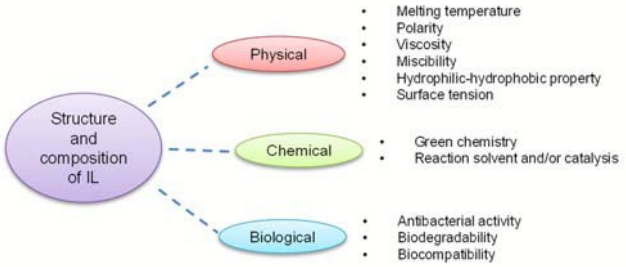


Fig. 2. Physicochemical and biological considerations of ionic liquids (ILs) for processing of biopolymers in drug application.

and how they function in biology is the key step for the success of biopolymer materials.[53, 54]

Being applied in material science, structural proteins are mostly studied for biomedical applications due to its easy processing and impressive mechanical strength,[55, 56] such as silk.[57] The interest in silk as a biomedical material is due to its enhanced environmental stability, significant crystallinity, impressive combination of strength and toughness, high elasticity, and resistance to failure in compression.[57] Typical examples of these proteins also include collagen and gelatin. Collagen is a long and fibrous structural protein and multiple collagen fibrils can form into collagen fibres, which are the major components of the extracellular matrix and support most tissue and cell structures because of the great tensile strength.[58] Being partially hydrolyzed under mild conditions, the three collagen strands separate into globular, random coils and produce gelatin. In contrast with collagen, gelatin has relatively lower antigenicity and may promote cell adhesion, differentiation, and proliferation, which is particularly attractive in the application of multifunctional vehicles for cell and growth factor delivery in regeneration research.[59]

Polysaccharides are long carbohydrate molecules of repeated monosaccharide units joined together by glycosidic bonds. Cellulose, chitin, starch, and chitosan are the most common examples of polysaccharides. They are naturally derived from various sources and have complex crystalline and amorphous structures caused by strong intra- and intermolecular hydrogen bonds within the polysaccharides. For example, starch can be extracted from plant roots, stalks, and crop seeds (*e.g.*, rice, corn, wheat, tapioca, and potato).[60] Starch is made up of two polymers of anhydrous glucose units, namely the unbranched amylose (with α-(1-4) linkage), and the highly branched amylopectin (with α-(1-4)- and α-(1-6)- linkages). The ratio between these two starch macromolecules and the way they organized within the granule give rise to several ordered size scales: intact granules (1–100 μm), growth rings of alternating crystalline and amorphous regions (100–500 nm), alternating crystalline and amorphous lamellae (9–11 nm).[61] While linked by β-(1-4)-D-glucose units, cellulose consists of linear chains and is the most abundant polysaccharide on earth.[62] These chains are hydrogen-bonded in both parallel and antiparallel manners, which impart more rigidity to the structure, and the subsequent packaging of bound-chains into microfibrils (highly structured crystalline regions). Thus, cellulose has high chemical and mechanical stability. The

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molecular structural difference usually affects the way of arrangement of molecular chains and contributes to the supramolecular structures of different biopolymers. As the second most abundant polysaccharide, chitin shares the structural similarity to cellulose (both having β-(1-4)-glycosidic linkages). Nevertheless, because of an additional acetamide group in its structural unit,[63, 64] chitin forms more complex inter- and intramolecularly hydrogen-bonded networks. After partially or completely deacetylation of chitin,[65, 66] chitosan is produced, which has -NH_2 functionality on the C-2 of the D-glucosamine repeat unit.[67] As a result, chitosan possesses many important properties including low toxicity, high adsorption capacities, film-forming ability, and bacteriostatic action.[65, 66, 68] Still, chitosan presents a highly ordered structure (the presence of amorphous and crystalline regions because of strong hydrogen bonding). This highly ordered structure of biopolymers makes it challenging to find suitable solvents for its dissolution and derivatization.[69] As an attempt, the biopolymer-ILs science is thriving quickly.

2.2 ILs and their related properties for biopolymer materials

ILs are ionic compounds with immeasurable combinations of anions and cations and the resultant far-ranging properties (Fig. 2). More importantly, influences such as the strength of charges between the cation and the anion, and the polarity and the hydrophilicity/hydrophobicity of the molecules, all contribute to the manifestation of the structure and the nature of substituent groups. To optimize the application of ILs in carrier materials, it is essential to understand the physicochemical properties of ILs. Here, the key parameters of ILs that affect the formation of carrier materials are addressed, especially those related to the solvation capabilities of ILs for biopolymers, which is the prerequisite for the fabrication of carrier materials.

The polarity and viscosity of ILs are the prime parameters for the solvation capability. Generally, ILs are classified as highly polar solvents on account of their ionic nature.[16, 70] It was observed that ILs have polarity close to short- to medium-chain alcohols or formamide.[71] The polarity of ILs depends mainly on the anion. The nature of the anion determines the polarity thus the resulting hydrogen-bond basicity of ILs,[72, 73] which favours the dissolution of biopolymers. While a high viscosity exerts an opposite effect, ILs with a low viscosity are more efficient in dissolving biopolymers.[74, 75] The viscosity of ILs is higher than that of water and similar to that of oils, which decreases with increasing temperature.[76, 77] Moreover, like polarity, the viscosity depends primarily on the anion type. Moreover, the viscosity of ILs is highly sensitive to cosolvents. For example, the presence of water in ILs can decreases viscosity sharply.[78] The presence of cosolvents seems to decrease the aggregation of the ions in the liquid, resulting in a reduced viscosity.

Due to the nature of high polarity, ILs are usually miscible with polar solvents such as ketones, lower alcohols and dichloromethane, but immiscible with nonpolar organic solvents including ethers and alkanes.[79] Based on their water miscibility, ILs can be classified into hydrophilic (water miscible) and hydrophobic (forming a biphasic system with water) ones. Considering the hydrophilic nature and the hydrogen bonding ability of biopolymers, the hydrophilicity of ILs promote the dissolution process. The hydrophilicity/hydrophobicity of ILs can be adjusted by the introduction of structural functionality on the cationic or anionic part. For example, armed with long chain alkyl chains in their cation, ILs show amphipathicity and behave like surfactants in aqueous solutions.[80] Moreover, owing to their strong and directional polarizability and excellent water solubility, surfactant ILs were observed to self-assemble into highly structured forms, useful for the preparation of a variety of nanomaterials.[81] Particularly, this self-assembly behaviour can be adjusted just by changing the ion type and the alkyl chain length of ILs.[82]

2.3 Dissolution of biopolymers in ILs

Owing to the capability of forming a broad range of intermolecular interactions such as hydrogen bonds, dipolar, dispersive and ionic interactions,[83, 84] ILs have been shown to be excellent solvents for a vast array of biopolymer compounds, such as proteins (*e.g.*, silks,[85] collagen,[86] and gelatin,[87] and zein[88]), DNA,[32, 89] polysaccharides (*e.g.*, cellulose,[62] chitosan,[90] chitin,[91] heparin,[38] starch,[92] and guar gum[93]). Up to date, most of the work has focused on the dissolution of polysaccharides in ILs (Table 3). Remarkably, it has also been reported that ILs can be employed for the selective dissolution and extraction of desired components from raw biomass without the need of purification,[94] such as wood,[95] cellulose-rich pulp,[21] and crab and shrimp shells.[95-100] Take chitin as an example, most of the current industrial extraction of chitin involves multiple processes with the use of harsh acids and caustic soda at elevated temperatures,[66] which are waste- and energy-intensive. Besides, degradation of the chitin structure often occurred during the process, leading to a reduced molecular mass (*M*) and degree of acetylation (DA), thus changing the properties of the biopolymer.[101] When 1-ethyl-3-methylimidazolium acetate ([EMIM][Ac]) was used, 94% of the available chitin in shrimp shells can be extracted in a single step and recovered with high weight-average molecular mass (M_w) and purity.[96] Moreover, this less chemical- and energy-intensive process can retain the acetylation of chitin, indicating that chitin is not deacetylated into chitosan during the dissolution process.[98] During the dissolution, ILs can hold higher concentrations of biopolymers compared to other solvents, which enhances the process efficiency.[102, 103] For example, chitosan with a high *M* can be dissolved by 1-butyl-3-methylimidazolium acetate ([BMIM][Ac]) to achieve up to 50 wt% concentration by completely disrupting the hydrogen bonds in the structure of chitosan, suggesting excellent dissolution.[104] Nonetheless, since excessively high concentrations of biopolymers are not suitable for the handleability and processability,[105] in this part, only the dissolution of biopolymers used for the process of potential biomedical application (including drug/gene delivery system) is discussed.

All ILs reported in the literature for the dissolution of biopolymers are hydrophilic and polar ILs, especially those with 1-alkyl-3-methylimidazolium cations (mostly used) (Table 3).

Table 3 Application of ionic liquids as the dissolution media for biopolymer-based materials

Biopolymers	Sources and Features	ILs	Dissolutions	Process parameters	Matrices	Refs
Chitin	α-chitin from shrimp shell; DA>90%	[EMIM][Ac]	10 wt%	100 °C, 6 h	Film	103
	Shrimp shell	[EMIM][Ac]	0.67 wt%	Microwave irradiation	Nanofibre	39
	α-chitin from crab shell; DP = 2000–4000; DA = 94.6%	[AMIM][Br]	5%, 7% (w/w)	100 °C, 48 h	Gel	106
	α-chitin from crab shell; η = 35 cp and DA = 99% β-chitins from squid-pen; η = 15 cp and η = 278 cp	[BMIM][Ac] [BMIM][Cl]	α-chitin: 4 wt%; β-chitin: 1 wt% α-chitin: 1 wt%; β-chitin: 1 wt%	110 °C, 2 h	Film	91
CEL	Cotton linter	[AMIM][Cl]	2, 4, 6 wt%	90 °C	Scaffold	107
	Microcrystalline CEL; DP = 196	[BMIM][Cl]	1–4 wt%	130 °C, 3.5 h	Nanoporous foam	108
	Holocellulose	[BMIM][Cl]	2, 5, 10 wt%	130 °C, 30 min; microwave heating	Film	109
	cotton fabrics, DP = 850	[AMIM][Cl]	3.0 wt%	110 °C; 30 min	Sponge	110
CS	η = 60–100 cps and DA = 90-95%	[BMIM][Cl] [EtMIM][Cl]	0.2–0.8 wt% 0.4–3.2 wt%	70–110 °C 50–110 °C	Nd	111
Silk fibroin	Non-mulberry and mulberry silkworm	[BMIM][Ac]	10 wt%	95 °C, 8h	Hydrogel	112
	Mulberry silkworm	[BMIM][Cl] [DMBIM][Cl] [EMIM][Cl] [BMIM][Br]	13.2 wt% 8.3 wt% 23.3 wt% 0.7 wt%	100 °C	Film	85
Guar gum	Seeds of *Cyamopsis tetragonolobus*; M_w = 126, 299, 566 kDa	[AMIM][Cl] [BMIM][Cl] [EMIM][MP]	19–24 wt%	[AMIM][Cl] and [EMIM][MP]: 50 °C [BMIM][Cl]: 80 °C	Gelled film	113
Chitin CEL	Chitin: shrimp shells CEL: wood biomass	[EMIM][Ac]	Chitin: 1.3 g/63.7 g IL CEL: 0.5 g/10 g IL	Chitin: microwave irradiation CEL: 175 °C, 30 min	Hydrogel	95
CS/CEL	CS: Brookfield viscosity of 200,000 cps CEL: pulp powder with a DP of 670	[BMIM][Ac]	Total: 6% wt% CS/CEL: 5/95, 10/90, 25/75, and 50/50 w/w	85–95 °C, CS: 3–4 days and CEL: 12 h	Film	104
CS/CEL	CS: DD = 75%; M_w = 310–375 kDa CEL: microcrystalline powder	[BMIM][Cl]	CS: up to 4% wt% CEL: up to 10% wt%	100 °C, 6–8 h	Antibacterial film	114
Chitin/CEL	Chitin: α-chitin; DA = 94.6% Microcrystalline CEL	[AMIM][Br] [BMIM][Cl]	Chitin: 5% w/w CEL: 10% w/w	100 °C, 24 h	Gel and film	115

Chitin/calcium alginate	Chitin: shrimp shell Calcium alginate: Nd	[EMIM][Ac]	High M_w extracted chitin: 2.75 wt% Alginate acid: up to 20 wt%	100 °C, 2 h	Composite fibre	116
CS/silk fibroin	CS: DD = 91.6%; M_w = 92 kDa Silk fibroin: cocoons of *Bombyx mori*	[BMIM][Ac]	CS: 4 wt% Silk fibroin: 4 wt%	95 °C	Hydrogel	48
CEL/CS CEL/agar CEL/carrageenan	CEL: microcrystalline CEL CS: DD = 75%; high *M* Carrageenan: Type I (more κ- and less λ-carrageenan) Agar: gel strength 500–1000 g/cm^2	[EMIM][Ac]	CEL: 5, 6, and 7 wt% CS: 4 wt% Agar: 3 wt% Carrageenan: 2 wt%	80 °C, 3 h	Composite hydrogel bead	37
CEL/CS/keratin	CEL: microcrystalline CEL; DP = 300 CS: DD = 84%; M_w=310–375 kDa Keratin: Nd	[BMIM][Cl]	Total: 6% wt% CS/keratin/CEL: 10/50/40, 20/40/40, 30/30/40, 40/20/40 and 50/10/40 w/w	Keratin: 125–130 °C, 6-8h CEL and CS: 90–105 °C, 6-8h	Film	117
CEL/zeolite	CEL: microcrystalline CEL; DP = 350 Zeolite: 300nm and surface area of >362m^2/g	[AMIM][Cl]	CEL: 6 wt% Zeolite: 2, 4, 6 and 8 wt% to CEL	90 °C, 24h	Bionanocomposite film	118
CEL/HAP CEL/SiO_2	CEL: soft pulp; DP = 1283 HAP: ~100 nm SiO_2: ~14 nm	[AMIM][Cl]	CEL: 1.5, 1.73 and 2.86 wt% CEL/HAP: ~30% HAP and 70% CEL (1.5 wt%) CEL/SiO_2: ~28% SiO_2 and 72% CEL (1.5 wt%)	80–90 °C, 5 h	Micro- and nanoporous composite aerogel	20
CEL/magnetite powder	CEL: microcrystalline CEL; DP = 270 Pulp 1, DP = 487 and pulp 2, DP = 1056 Peach pulp, DP = 687 Magnetite powder: ≤5 µm	[AMIM][Cl]	Microcrystalline CEL: 11.5 wt% Pulp 1: 4.3 wt% and pulp 2: 8.7 wt% Peach pulp: 3.8 wt% Magnetite powder: 10, 20, or 30 wt% to total composites	80±5 °C, 1.5 min; microwave heating	Magnetite-embedded fibre	21
Chitin/CNTs	Chitin: M_w=100 000 kDa MWCNTs	[EMIM][Ac]	Chitin: 0.015g /5g IL MWNTs: 0.01, 0.03, 0.07, 0.1g /5g IL	130 °C, 3 h	Nanocomposite scaffold	119, 120
Chitin/PLA	Chitin: shrimp shell PLA: M_w =700 000 g/mol	[EMIM][Ac]	Chitin: 2.75 wt % Poly(lactic acid): 0.175–1.75 wt %/1.75 wt % chitin	Chitin: microwave irradiation	Spinning composite fibre	121
Guar gum/CNTs	Guar gum: *Cyamopsis tetragonoloba*, M = 4.22 × 10^6 Da MWNTs: diameter: 30–50 nm; length: 10–30 µm	[BMIM][Cl]	Guar gum: 10% w/v MWNTs: 0.2% w/v	80–100 °C, 2 h	Nanocomposite gel	93, 122

Nd: not defined

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Only a few other ILs such as choline hexanoate ([Ch][Hex]) and choline citrate ([Ch][Cit])[123] have been explored to promote the development of ILs with the outstanding ability to dissolve biopolymers and raw biomass. For instance, inexpensive ILs such as 2-hydroxyethylammonium acetate ($[NH_3(CH_2)_2OH][Ac]$) and hydroxylammonium acetate ($[NH_3OH][Ac]$) can be used to pulp shrimp shells with high chitin yields and purity at up to ten times the biomass loading, although these ILs could potentially result in lower M_W chitin.[97] In addition to the green aspects, ILs can dissolve these biopolymers under relatively mild operating conditions and at normal atmospheric pressure.[36-38] Yet, to complete dissolve a biopolymer, an IL must diffuse into the molecular structure to disentangle molecular chains and to disrupt the amorphous and the ordered regions.[3] Thus, the dissolution of biopolymers usually occurs at moderately higher temperatures (80 °C – 130 °C) (Table 3). Besides, for imidazolium ILs which are solid or a sticky paste at room temperature,[17] high temperatures are often needed to make them become liquid. Nevertheless, the total energy required for the processing of biopolymers should be low according to the green chemistry principles. Thus, for more efficient energy production from biomass, heating should be avoided as much as possible to reduce the energy costs. To overcome this drawback, microwave irradiation[39] or sonication[40] has been applied to assist the dissolution process, which can reduce the dissolution time and energy consumption compared with those required when only thermal heating is used. However, these techniques may cause polymer decomposition or incomplete dissolution due to the excessive, localized overheating.[124] This drawbacks should be taken into consideration for practical applications.

Compared with the cation, the disruption of hydrogen bonding is believed to be highly dependent on the interactions between the anion and the functional groups (*e.g.*, $-NH_2$ and -OH) of biopolymers.[125] Thus, ILs with coordinating anions[72, 73] can effectively dissolve biopolymers (Table 3). Among halide ions, chloride ion has been demonstrated to be strong hydrogen bond acceptor and one of the most effective anions in dissolving biopolymers.[126] For example, cellulose was soluble in 1-butyl-3-methylimidazolium bromide ([BMIM][Br]) and 1-butyl-3-methylimidazolium thiocyanate ([BMIM][SCN]) but presents less than half a degree of solubility in 1-butyl-3-methylimidazolium chloride ([BMIM][Cl]).[102] However, the *M* of biopolymers was often significantly reduced during such processing, which is related to the acidic hydrolysis of, for example, the glycosidic bonds of polysaccharide.[127-129] Instead, ILs with acetate anion were found to be much less aggressive for degrading biopolymers.[130] Owing to its lower viscosity, higher polarity, and stronger basicity for hydrogen bonds than chloride anion,[131] acetate ILs can surpass chloride-based ILs with a higher dissolved biopolymer concentration[91] or a lower dissolving temperature for the same amount of polysaccharides.[131] For example, high *M* chitosan with a Brookfield viscosity of 200,000 cps only swelled in [BMIM][Cl], and no complete dissolution was observed at 100 °C even after 4 days.[104] In contrast, [BMIM][Ac] was capable of completely dissolving chitosan. Moreover, acetate ILs are distinctly better than those chlorinated ILs in dissolving various chitin materials with different origins.[91, 132] Results showed that [EMIM][Ac] can dissolve significantly higher amounts of the shrimp shell samples (46.0 wt%) than 1-ethyl-3-methylimidazolium chloride ([EMIM][Cl]) (9.7 wt%) or [BMIM][Cl] (10.0 wt%).[96] Furthermore, with the assistance of microwave treatment, 73.5 wt% shrimp shell sample (at least 94 wt% of the available chitin) can be dissolved in [EMIM][Ac] with a total irradiation time of 2 min.[96] Despite the predominant role of the anion, the chemical structure of cations does affect the biopolymer dissolution. Compared to [EMIM][Cl], [BMIM][Cl] gives better dissolution for all the chitinous samples[96] and cellulose materials.[133] Although the effect of cation ions is not entirely understood yet, the alkyl chain length[75, 102] or the functional groups of side chain[134, 135] in the cation may exert their influences on the solubility of biopolymers. Still, additional experimental and theoretical studies are needed to fully elucidate the effect of the nature of specific anions and cations on the solvation ability.

Various biopolymers present different dissolution behaviours in the same IL. For example, cellulose was readily soluble in [EMIM][Ac] (with a polymer content up to 12 wt%) whilst chitin can only be dissolved up to 4 wt% under the same process condition.[136] Besides, the difference in dissolution can also be reflected by the dissolution time. When adding cellulose or chitosan to [BMIM][Ac], the dissolution time to achieve a 6 wt% concentration of chitosan was 3–4 days at 85–95 °C while the time for the same weight percentage for cellulose was 12 h.[104] All these differences in dissolution arises from the different biopolymer structures, for example, the crystallinity and polymorphic form. Compared with the amorphous regions, the dissolution of the ordered structure is much more difficult in ILs. [BMIM][Cl] was found to only dissolve the noncrystal domains of a native chitin, leaving compact crystal domains unaltered.[91] Yet, the solubility of [BMIM][Ac] shows less difference between the crystal forms (i.e., α-or β-crystal) of chitin, but strongly depends on their *M*.[91] Chitin with lower *M* can be readily dissolved in 1-allyl-3-methylimidazolium chloride ([AMIM][Cl]) with increased solubility, whereas those with higher *M* cannot be dissolved at 110 °C and form liquid crystals at room temperature.[137] This indicates the importance of molecular features, especially *M*, for the dissolution of biopolymers. Another example lies in the dissolution of wood pulping. Low *M* of biopolymers leads to high solubility. Different dissolved concentrations were found in [EMIM][Cl] linked to the various degree of polymerization (DP) of lignocellulosic polymers, that is, 11.5 wt% for microcrystalline cellulose (DP = 270), 8.7 wt% for pulp sheet 1 (DP = 487), 4.3 wt% for pulp sheet 2 (DP = 1056) and 3.8 wt% for peach pulp (DP = 687).[21] Moreover, the functional groups of biopolymer molecules also affect the dissolution behaviour. Results showed that chitins with DAs of 38.1%, 23.8% and 18.1% were soluble in [AMIM][Cl] at maxima of 3, 5, and 8 wt% concentrations, respectively. However, chitins with DAs of > 50% could only be dissolved in [AMIM][Cl] below 1 wt%, suggesting that the existence of acetamide groups could hinder the dissolution of chitin.[138]

Because of the high tendency of water absorption of ILs, water is often found in ILs as the impurity or cosolvent. Yet,

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water is found to strongly influence the solubility of biopolymers, especially for carbohydrates. Results have shown that water can significantly modify the solvation ability of ILs by linking the glycosidic units causing aggregation and decreasing the accessibility of ILs to carbohydrates.[139] This effect may vary for different polysaccharides. For example, water was capable of acting as a good cosolvent, alongside [EMIM][Ac], to further improve the dissolution of starch, whereas the opposite was observed for cellulose.[127, 140] Thus, it could be difficult to predict the behavior of a biopolymer in a given IL due to the significant structural variations of ILs and biopolymers.[141]

3 Application of ionic liquids for preparation of biopolymer materials for drug/gene delivery

Motivated by the remarkable benefits of using ILs in the dissolution of biopolymers, IL have been exploited to prepare matrices, scaffolds, and composite materials (Table 3), or to functionalize biopolymers for desirable attractive physicochemical, mechanical and biological properties useful for drug/gene delivery (Fig. 3). Besides, ILs can be used as a component polymer interacting with biopolymers to form nanocomposite for drug/gene delivery systems or directly involving in the biopharmaceutical formulations. In this section, the role and application of ILs in carrier materials for potential drug/gene delivery systems and active pharmaceutical formulations will be discussed.

3.1 Regeneration and processability of biopolymers in ILs

The biopolymer dissolution in ILs offers huge potential for the formation of biopolymer-based materials. Allegedly, those dissolved materials can be easily regenerated without derivatization, thus producing sustainable materials that can overcome the complexities pertaining to the processing techniques encountered in the case of organic polymer gels.[30] For instance, based on the excellent miscibility of ILs in organic solvents, the addition of various antisolvents, such as water,[115, 142] acetone,[45] methanol,[143] and ethanol,[144] allows the regeneration of biomatrices. Due to the strong interactions of ILs with biopolymer molecules, a homogeneous sol of the biopolymer often exists in ILs. Then, by addition of, for example, water into the biopolymer/IL solution, ionogels with physically or chemically crosslinked networks can be formed. Those ionogels can absorb large amounts of water without being dissolved,[145] and act as the original template to promote the biopolymer matrix formation by the following reconstitution. For example, chitin could be dissolved in 1-allyl-3-methylimidazolium bromide ([AMIM][Br]) at concentrations up to 5% w/w and form ion gels at higher concentrations (7% w/w). Then, this chitin ionogel was regenerated using methanol to produce a chitin nanofibre dispersion, which was used to construct a film with a highly entangled nanofibre morphology by filtration.[146] By reducing the number of chemicals needed for this process to as low as two (IL and antisolvent), the potential losses of chemicals can be reduced. During these processes, ILs can be recycled upon removal of the antisolvents through

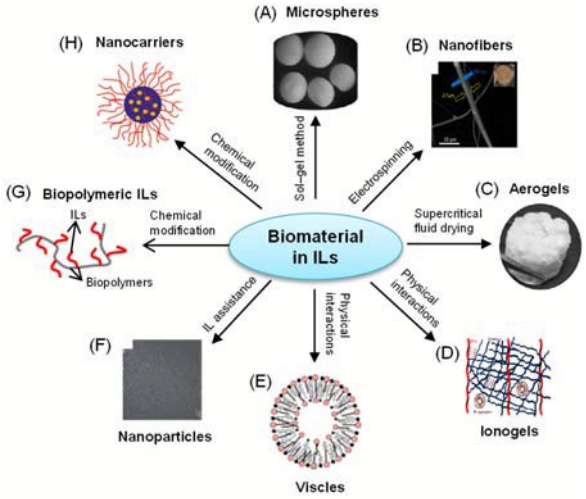

Fig. 3. Schematic illustrations of biopolymer-based carrier materials and technologies generated from biopolymers dissolved in ionic liquids (ILs). (A) Chitin microparticle matrices. Reproduced from Ref.163 with permission of The Royal Society of Chemistry; (B) Cellulose–Fe_3O_4 core–shell nanofibre with internal Fe_3O_4 nanoparticles core and cellulose shell with covalently immobilized heparin. Adapted with permission from Ref.149. Copyright (2016) American Chemical Society; (C) Chitin aerogels produced in [BMIM][Ac]. Reproduced from Ref.163 with permission of The Royal Society of Chemistry; (D) DNA-gelatin ionogels. Adapted with permission from Ref.89. Copyright (2012) American Chemical Society; (E) Unilamellar vesicles of 1-hexadecyl-3-methylimidazolium chloride ([C_{16}MIM][Cl]) and cholesterol. Adapted with permission from Ref.159. Copyright (2014) American Chemical Society; (F) Octenyl succinic anhydride starch nanoparticles. Reproduced from Ref.157 with permission of The Royal Society of Chemistry; (G) Biopolymer-IL conjugates. (H) Self-assembled Poly(*N*-isopropylacrylamide) (PNIPAM)-chitosan-Lilial nanocarriers. Adapted with permission from Ref.153. Copyright (2011) American Chemical Society.

evaporation,[42, 147] conforming to the green processing of biopolymers. The efficient recycling and reuse of ILs are indeed critical to overcoming the high prices of the ILs as well as to realize the environmental benefits of ILs. In previous studies, no appreciable changes in the physical properties of the recovered ILs were observed and the recovered ILs could be reused at least four times without loss of their purity.[42, 114] If there was no derivatization, which is the common case, minor waste and no byproducts would be produced in this process. However, it has also been reported that when bases such as imidazole or 1-methylimidazole are present (*e.g.*, as unreacted starting materials), 1-alkyl-3-methylimidazolium cations can react at the C2 position with cellulose at its reducing end, forming a carbon–carbon bond.[148] Luckily, this unwanted side reaction can be suppressed by the absence of bases and reaction or contact times of less than 2 h.

For pharmaceutical purposes, promising delivery carriers have been reported involving films, fibres, aerogels and composites obtained from various biopolymer/IL (Table 4). Often, an adequate processing technique is needed to form a proper matrix for a drug/gene delivery system, such as the application of wet-wet electrospinning followed by an aqueous coagulation bath to prepare heparin-immobilized cellulose-Fe_3O_4 nanofibre composites from [EMIM][Ac].[149] Notably, the application of ILs together with supercritical fluid drying (SCF) without the collapsing of the gel structure has demonstrated

Table 4 Processability of biopolymers in different ionic liquids and their potential pharmaceutical applications

Materials	ILs	Matrix	Strategy	Relevant properties	Application	Refs
Regeneration and processability						
Chitin	[EMIM][Ac]	Film	Solution casting and SCF	- Porous, sticky film structure - A burst release of ~80% caffeine in the first 20 min, followed by slow release over 20 h	Topical drug delivery	105
Locust bean gum CEL	[BMIM][Cl] [C_2OHMIM][Cl] [EMIM][Ac] [EMIM][DEP] [AMIM][Cl]	Aerogel	SCF	- SCF drug impregnation and highly porous structure - High drug loading content (*ca.* 50% w/w) - Sustained release: ~63% ibuprofen released after 60 min and 91% after 120 min	Potential drug delivery	62, 150 62 150
CS	[Ch][Cl] [Ch][DHP]	Doped film	Solvent casting	- The conductivity of CS films was enhanced by ILs and further increased at acidic condition when using [Ch][DHP] - [Ch][DHP] hindered the DXA release - pH-sensitive release: a less amount DXA released at pH 4 than at pH 7 and pH 10	Electrical and pH-sensitive drug delivery	31
CEL/CS/KER	[BMIM][Cl]	Film	Solvent casting	- The mechanical strength and thermal stability of KER was enhanced by CEL or CS - KER retarded the drug release - CS endowed the film with haemostasis and a bactericide effect	Bandage to treat chronic and ulcerous wounds	117
CEL/MNPs (Fe_3O_4)/heparin	[EMIM][Ac]	Nanofibre	Wet-wet and coaxial electrospinning	- Similar diameter of monofilament fibres (304 nm) as core-shell fibers (302 nm) - All nanofibres showed anticoagulant activity (heparin) and magnetic responsiveness (MNPs)	Magnetically responsive drug delivery	149
Chemical modification						
Linoleic acid-*g*-CS oligosaccharide	[BMIM][Ac]	Nanomicelle	Grafting reaction	- High yield (89%) and DS (36.8%) of copolymer - Good surface activity (CMC: 1.1×10^{-4} g·mL^{-1}) - Spherical shape and a narrower particle size distribution (30–40 nm) - Drug-loaded nanomicelles: less than 200 nm	Intravenous administration	42
CEL-*g*-poly(ε-caprolactone)	[BMIM][Cl]	Nanomicelle	ROP	- Well controlled DS with the range of 0.09–2.41 - CMC (5.86–78.80 μg/mL) and size (18.81–102.00 nm) changed with DS	Potential drug delivery	44
Long-chain fatty acyl-*g*-CS	[AMIM][Cl]	Nanomicelle	Grafting reaction	- CMC: 0.042–0.081 mg/mL and size: 122–295 nm - Low CMC and small sized achieved with high grafting degree	Potential drug delivery	43

CEL-*g*-PNIPAM	[AMIM][Cl]	Nanomicelle	ATRP using CEL macroinitiator (DS: ~0.91)	- High MS_{PNIPAM} (>18.3) made the copolymers water soluble - Temperature-sensitive behaviour: size increased from 200 to 620 nm with increasing temperature (from 33 °C to 50 °C)	Temperature-sensitive drug delivery	46
CEL-*g*-PLA	[BMIM][Cl]	Nanomicelle	Grafting polymerization	- CMC (47.1 and 58.1 mg/L) and size: 30–80 nm - Sustained drug release: 40% of drug released on the first day, then 20% amount released in the next 2 days, with the left released in next 7 days	Intravenous administration	147
	[AMIM][Cl]		ROP	- Controlled size: 64.72 to 169.91 nm and ζ-potential: 31.2 to 23.8 mV - The micelle showed high protection of β-carotene with high stability and enhanced antioxidant activity	Potential drug delivery	151
CEL-*g*-PDMAEMA	[AMIM][Cl]	Nanoparticle	ATRP using CEL macroinitiator (DS: ~0.70)	- PDMAEMA endowed the copolymer with pH- and temperature-responsive properties	Potential temperate and pH-sensitive drug delivery	152
PNIPAM-CS-drug (Lilial) conjugates	[BMIM][Cl]	Nanomicelle	Chemical modification of Lilial with CS in [BMIM][Cl], then grafting reaction with PNIPAM in dimethylformamide	- High grafting content of PNIPAM (154.2%) and drug loading content (35.8 wt%) - Temperature and pH-sensitive size change of micelles and drug release behaviour at the mimicking lysosomal uptake	Temperate- and pH-sensitive drug delivery/cellular-targeting delivery	153
ILs assisted the formation of biopolymer matrixes						
Acid-treated granular starch	[BMIM][PF_6] [C_{16}MIM][Br]	Nanoparticle	Microemulsion crosslinking reaction using [BMIM][PF_6] as the oil phase, or [C_{16}MIM][Br] as the surfactant	- Spherical with a narrow size distribution (91.4 and 94.3 nm) - Aggregation of nanoparticles occurred - A burst release followed by a sustained release in the following 10 h	Potential drug delivery	154, 155
OSA starch	[C_{16}MIM][Br] [OMIM][Ac] [C_3OHMIM][Ac]	Nanoparticle	Microemulsion crosslinking reaction using [OMIM][Ac] and [C_3OHMIM][Ac] as the water phase, or [C_{16}MIM][Br] as the surfactant	- Reduced size distribution (80.5 and 86.69 nm), compared with using acid-treated granular starch - No aggregation formation - A burst release followed by a sustained release in the following 10 h	Potential drug delivery	156, 157
Physical interaction with ILs						
CS	[BMIM][C_8OSO_3] [OMIM][Cl]	Nanocomplex	Electrostatic, ion dipole, and hydrophobic forces	- [BMIM][C_8OSO_3]: 450 nm and 58.5 mV; [OMIM][Cl]: 560 nm and 87 mV - [BMIM][C_8OSO_3]/CS complex had better sphericity and lesser agglomeration	Potential vaccine delivery and antitumor activity	158
Cholesterol	[C_{16}MIM][Cl]	Spherical unilamellar vesicle	Hydrogen bonds and hydrophobic interactions	- The micelles transformed into unilamellar vesicles upon the increased content of cholesterol - Size of vesicles with an average diameter of 150 nm	Controlled release and drug delivery	159

DNA	[C_{12}iQuin][Br]	Ionogel	Electrostatic and hydrophobic interactions	- The size of DNA decreased to 100 nm when the IL concentration reached 0.50 mM - The zeta potential of DNA itself (–29 mV) decreased to a minimum value (–67 mV) at 0.22 mM IL	Photodynamic therapy and gene transportation	[160]
Gelatin /DNA	[OMIM][Cl]	Complex coacervate Ionogel	Hydrogen bonds, ionic interactions, van der Waal and hydrophobic interactions	- The optimum IL concentration (=0.05% (w/v)) was required to maximize the interactions - By heating (50 °C) and cooling (to 20 °C), the coacervate samples transited to ionogel	Potential gene delivery	[89]
Biopolymeric ILs						
Cholesterol /L-glycine	[Cholesterol-Glycine][AOT]	Synthesized AOT based SAILs	Chemical modification	- Act as a surfactant in the formation of IL-in-oil microemulsions - Self-assembled in water to form aggregates with two sizes (120 and 750 nm)	Good biomimicking models and possible drug carrier	[161]
HEC-*g*-poly(1-(11-acryloyloxyundecyl)-3-methylimidazolium bromide	P(IL)s	Grafted HEC copolymer based on P(IL)s	Grafting copolymerization	- Comparable antibacterial activities to ampicillin, increased with the increased grafted P(IL)s - More effective antibacterial against *E. coli* than *S. aureus*	Potential antibacterial pharmaceutical ingredients	[162]

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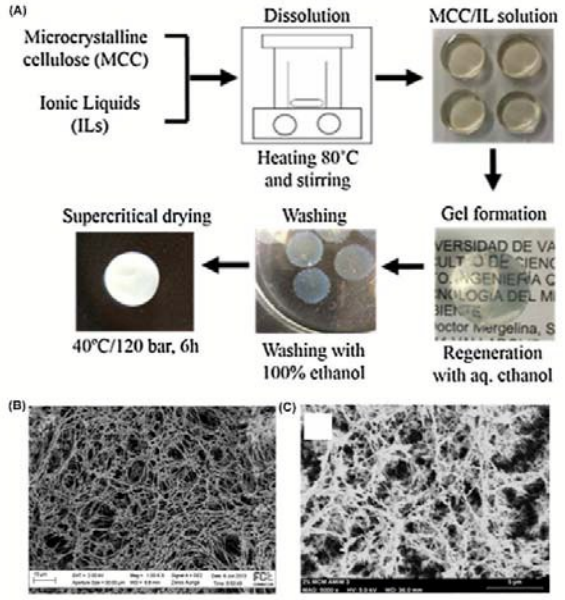

Fig. 4. Preparation process and features of biopolymer-based aerogels in ionic liquids (ILs) using supercritical fluid drying technology (SCF). (A) Scheme of cellulose aerogel preparation in ILs and SCF. Reprinted from Ref.62, Copyright (2017), with permission from Elsevier; (B) SEM image for the cross-section of the locust bean gum gel produced through the dissolution into 1-butyl-3-methylimidazolium chloride ([BMIM][Cl]). Ref.150 -Reproduced by permission of The Royal Society of Chemistry; (C) Non-impregnated cellulose aerogels regenerated from 2% cellulose solution in 1-allyl-3-methylimidazolium chloride ([AMIM][Cl]). Reprinted from Ref.62, Copyright (2017), with permission from Elsevier.

the possibility of developing chitin-, locust bean gum-, and cellulose-based aerogels (Table 4). In order to prepare an aerogel, an ionogel was firstly prepared by the interaction of a biopolymer with an IL. The ionogel was then treated with an alcohol to obtain an alcogel, followed by SCF to remove the alochol (Fig. 4A). Compared with traditional drying methods (freeze- or vacuum-drying), the application of SCF prevented the shrinkage of the matrix, resulting in a porous interconnected structure (Fig. 4B and Fig. 4C), low densities (*e.g.*, 0.15 to 0.41 g·cm^{-3}[150]) and high surface areas (*e.g.*,154 to 434 m^2·g^{-1}[62]). These features make them as ultralight and highly porous DDSs with a topical drug release behaviour.[105, 150] Additionally, SCF allows high drug saturation (*e.g.*, about 50% w/w) and the drying of the gel in a one-pot process.[62] For example, the incorporation of drugs (dexamethasone) into chitin-based microsphere scaffolds could be achieved by drying the matrices for supercritical-assisted agglomeration. Results showed that, by the controlled DDSs prepared in this way, dexamethasone could be sustainably released for a time period of up to 21 days.[163] Furthermore, related to the recycling of ILs, SCF technology can exceed traditional methods by its low cost, nontoxic nature, recoverability and ease of separation from the products.[164] Admittedly, the recovery of ILs often involves the use of conventional organic solvents, which may affect the "green" aspects in their usage due to the cross-contamination. Water as a solvent would seem safe, environmentally benign, and inexpensive. Yet, the greenness of recovering the ILs from

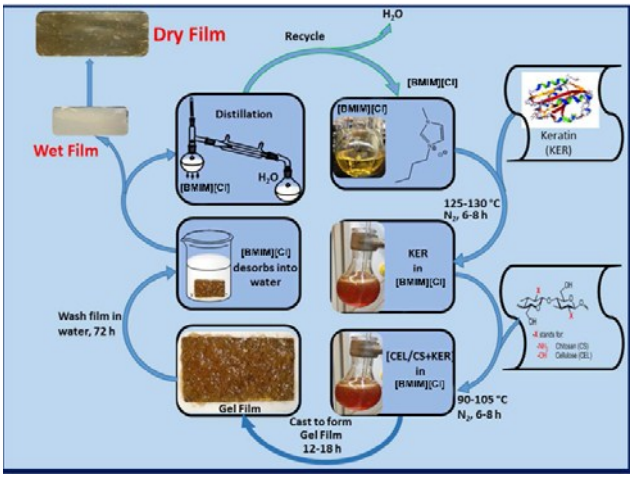

Fig. 5.Procedure used to prepare the [cellulose/chitosan+keratin] composite materials in 1-butyl-3-methylimidazolium chloride ([BMIM][Cl]). Adapted from Ref.117, Copyright (2015) American Chemical Society.

water for reuse must also be considered and this is currently energy intensive.[114] Up to date, the IL extractions, in particular, are energy-consuming, particularly for the direct vacuum distillation protocol.[42] Thus, SCFs may solve these problems by combining the green solvent (IL) with the clean technology (SCF).[165] Nonetheless, the application of SCF for the recovery of ILs from biopolymer materials have scarcely reported, which should be focused on in future studies.

Because of the extensive solvation ability of ILs, the resulting biopolymer/IL solutions can be used for the fabrication of composite materials, which are engineered materials based on two or more constituents (*e.g.*, matrix and/or reinforcement[166]). For example, chitin nanofibres (20–30 nm) regenerated at the optimized concentration of 10% (wt/wt) in several acidic ILs have been used to enhance elasticity and retard the drug release of Ca-alginate beads.[167] In particular, the composite maintains distinct characteristics of every constituent within the finished structure,[168] therefore exhibiting combined properties of its individual components. This is a promising approach to the use of natural biopolymers (Fig. 5), which can overcome the difficulty of chemically synthesizing such composites in a solution medium. For example, cellulose and chitosan were added to keratin/IL solution to enable [cellulose/chitosan+keratin] composites with the aim of overcoming relatively poor mechanical properties of keratin.[117] Besides, due to the comparatively ordered structure (lower content of α-helix and higher β-sheet) of keratin retained in the composite,[142] keratin can retard the drug release compared with cellulose and chitosan (random form).[117] Consequently, increasing the portion of keratin in the composite led to a substantial decrease in the release kinetics (a 41% decrease in the release rate by an increased concentration of keratin from 10% to 30%).[117] Moreover, chitosan was believed to possess not only strong mechanical properties but also additional properties including its ability to stop bleeding (haemostasis), heal wounds, and kill bacteria.[114, 169] Thus, the [cellulose/chitosan+keratin] composite had

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combined properties of its components, namely, superior mechanical strength (cellulose), haemostasis and bactericide (chitosan), and controlled drug release (keratin).

Along with the advances in stimulus-responsive biopolymer-based DDSs, the demand for developing such biopolymer composite in ILs has gained worldwide attention recently. In the case of regenerated biopolymer matrices by ILs without chemical modification, the incorporation of functional components into biopolymer matrices has been proved to be powerful to endow stimulus-responsive properties. Due to the comparatively high viscosity of ILs,[76, 77] a huge advantage of this method is the nanometre size and uniform distribution of the functional component in the biopolymer matrix.[40] ILs are known to be effective in the dissolution of biopolymer and the suspension of functional particulates in the same IL medium.[170] For example, superparamagnetic NPs (Fe_3O_4) (5 nm in diameter, 30 emu/g magnetization) were impregnated into cellulose nanofibre in [EMIM][Ac] to enable the manipulation of both dry and wet nanofibre membranes with an external magnetic field.[149] Results showed that Fe_3O_4 NPs distributed throughout the interior of the fibres with only a small portion of Fe_3O_4 NPs on the fibre surface. Besides, these cellulose nanofibre composites were further functionalized by heparin (an anticoagulant[171]), physically or covalently immobilized on the fibre surface, to reduce the thrombogenicity of blood-contacting devices.[149]

The unique combination of the physicochemical properties of ILs with biopolymers can provide the opportunities of not only *in-situ* processability but also functionalization of materials (ionogels). One of the typical applications was bringing electrical conductivity to biopolymer materials because of the wide electrochemical window of ILs. For example, electrically sensitive chitosan films have been developed by doping with two ammonium-based ILs (choline chloride ([Ch][Cl]) and choline dihydrogen phosphate ([Ch][DHP])) for multi-responsiveness.[31] These IL-based chitosan films can overcome the low electrical sensitivity and conductivity and the intrinsic "soft-material" characters of chitosan-based electrically responsive carrier materials.[172] Compared with [Ch][Cl], the enhanced electrical conductivity with the use of [Ch][DHP] was shown (at the same loaded amount, 75%).[31] The reason for this phenomenon may relate to the solid–solid phase transition characteristic of the former.[173, 174] Moreover, when compared with chitosan films, 75% [Ch][DHP]-loaded chitosan composites showed a clear decrease in the water swelling capacity at pH 4 (~80%) while a small increase observed at pH 7 (~7%) and at pH 10 (~10%).[31] This can be explained by the "shielding" effect of [DHP] in the protonated amino groups in the acidic medium, which consequently decreased the electrostatic repulsions that would favour the swelling capacity. In contrast, at pH 7 or pH 10, the presence of [DHP] can increase the charge density inside the polymer and the osmotic charge gradient, thus increasing the swelling ability. Based on that, an ionic drug (sodium phosphate dexamethasone (DXA)) was encapsulated in 75%[Ch][DHP]-loaded chitosan composites, which showed a pH-sensitive drug release behavior (~62% of the total loaded DXA at acidic pH compared to the DXA release values at pH 7 (~95%) and at pH 10 (~90%)).[31] Besides, the amount of DXA released from films doped with [Ch][DHP] was always lower than for the films without IL, indicating a dual effect of ILs on the conductivities/impedances of the films.

Apart from delivering drugs with high efficiency, biopolymer-IL composites have benefited drug detoxification, which aims at the inhibition of the side effects (*e.g.*, toxicity, anti-inflammatory response) of drugs in their clinical applications. Heparin/cellulose/charcoal composites (2% cellulose solution of [BMIM][Cl] and 1% heparin in 1-ethyl-3-methylimidazolium benzoate ([EMIM][Ba]) have been prepared to enhance the biocompatibility and blood compatibility of activated charcoal beads,[175] and further to inhibit the thromboresistance caused by uncoated activated charcoal.[176, 177] This coating (heparin/cellulose) decreased the active pore size of the activated charcoal, thus diminishing its rate of protein adsorption (a 9% decrease in the amount of bovine serum albumin (BSA) for coated composite, while 27% decrease for uncoated charcoal composites), without decreasing the effective removal of free-diluted and protein-bound small drug molecules.[175] These composites are useful for the rapid and safe removal of small, hydrophobic protein-bound drug molecules from the digestive system or from the blood of overdose patients in an extracorporeal circuit.

3.2 Chemical modifications of biopolymers in ILs

The existence of diverse functional groups allows a wide range of chemical modifications of biopolymers, leading to tailor-made matrices with different shapes, sizes and specific functionalities.[4] Nevertheless, most chemical reactions performed in conventional organic solvents have limitations such as the complexity and heterogeneity of the synthesis process, limited efficiency, long reaction time, serious corrosion, and environmental pollution.[178, 179] These issues would restrict the widespread application and large-scale production of biopolymer materials. Remarkably, these features have stimulated the use of ILs to promote homogeneous reactions and improve the reaction efficiencies (Table 4), thus creating more options to induce novel functional groups and opening up the opportunity to control the total degree of substitution (DS).[18] For example, ILs were exploited as reaction media in which tailor-made guar gum derivatives were synthesized through a direct and homogeneous esterification route with a variety of acid chlorides.[180] Results showed that the DSs (0.12–2.70) of guar gum could be easily varied by experimental conditions (*e.g.*, reaction time),[180] which could overcome the problems of low and uncontrolled substitution reactions of guar gum.[19] These superiorities of ILs as reaction media are much prominent in the chemical modification of cellulose. Due to the extremely poor solubility of cellulose in most aqueous and organic solvents and the difficulty in cellulose processing, most cellulose-based materials can only be prepared from soluble cellulose derivatives such as ethyl cellulose,[181] hydroxypropyl cellulose,[182] and hydroxyethyl cellulose.[183] However, these soluble derivatives could increase the risk of toxicity and the costs of the products. On the other hand, the application of ILs as reaction medium allows the

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homogeneous reactions with unmodified cellulose,[44, 46, 184] such as the generation of biopolymer macroinitiators by esterification for further grafted biopolymer derivatives.[185] Cellulose chloroacetate with the highest DS of 1.87, as a macroinitiator, can be easily synthesized by direct acylation of cellulose with chloroacetyl chloride without any catalysts under mild conditions in [BMIM][Cl].[186] This will provide an effective solution to the problems of soluble cellulose derivatives. However, it should be noted that when ILs are used as reaction media to esterify cellulose, [EMIM][Ac] is not suitable since this IL can lead to unexpected side reactions. Specifically, unexpected pure cellulose acetate samples (DS: 0.55-1.86) were found in any case of homogeneous conversion of cellulose in [EMIM][Ac] with 2-furoyl chloride, *p*-toluenesulfonyl chloride, and triphenylmethyl chloride.[187]

The high reaction efficiency achieved with ILs as media are attributed to their capability to disrupt the biopolymer structure through weakening the inter- and intramolecular hydrogen bonds between biopolymer chains. These interactions lead to the separation of functional groups of different biopolymer chains, resulting in a homogeneous solution and facilitating the interactions between the biopolymer and external catalysts or reactants in the IL.[42] In particular, in the case of grafting reactions of chitosan using ILs,[46, 181] both the functional groups of chitosan (-OH and -NH_2) were found to participate in the reactions, which increased the grafted content and grafting efficiency. For example, high grafting content (630%) of polycaprolactone (PCL) to chitosan was achieved by ROP in [EMIM][Ac] using stannous octoate as the catalyst,[45] suggesting imidazolium-based ILs are excellent chemical media. During chemical processes such as ring-opening polymerization (ROP),[44, 45, 188] reversible addition-fragmentation chain transfer polymerization (RAFT)[185] and atom transfer radical polymerization (ATRP),[46, 186] imidazolium-based ILs have been proved to be excellent media with huge advantages. For example, ILs can reduce the extent of side-reactions in ATRP, thus to obtain grafted biopolymer chains with well-controlled *M* and polydispersity in a mild reaction medium.[186] By applying ATRP reactions, chitin-*g*-polystyrene from a chitin macroinitiator (DS > 1.66) was synthesized in [AMIM][Br] at 60 °C for 10 h with controlled number-average molecular mass (M_n) by adjusting the feed ratios of styrene to the initiating site of chitin macroinitiator.[18] These grafted copolymers could aggregate and self-assembly into a sphere-like polymeric structure,[18, 186] which is highly potential to be applied in DDSs. Moreover, studies suggested that the use of ILs as media could enhance the nucleophilicity of amines of chitosan and increase the stability of the reagent-activated complexes, thus accelerating nucleophilic substitution reactions. It would shorten the reaction time and benefit the grafting control, such as chitosan-graft-polyethylenimine (CS-*g*-PEI) synthesized with a high grafting degree (GD) (maximum: 8.1%) in [BMIM][Ac].[189] It was turned out that the grafting reaction rate was greatly accelerated by 6–30 times and the reaction time was largely shortened from 5 days or 24 h to 4 h.[189] The buffering capacity of chitosan was improved by PEI grafts and increased with the GD. These CS-*g*-PEI/DNA complexes were stable in blood serum with suitable particle sizes (250-270 nm) and proper surface charge (higher than 40 mV).[189] Moreover, for gene transfection performance, the CS-*g*-PEI copolymer with a medium GD of 4.3% showed low cytotoxicity and conferred the best gene transfection with the transfection efficiency 44 times that of chitosan and 38 times that of PEI-1.8 (1.8 kDa of PEI), indicating excellent potential as an efficient and safe nonviral gene vector.[189]

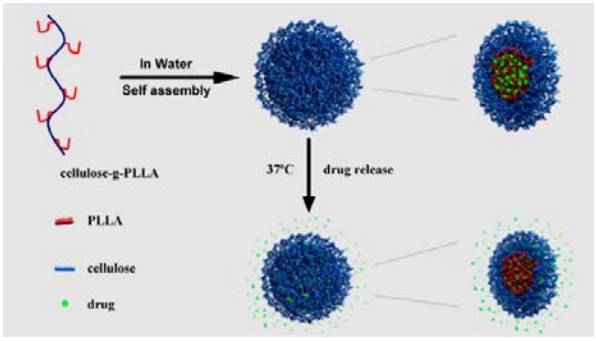

Fig. 6. Schematic illustration to describe self-assembly of cellulose-*g*-poly(L-lactide) (PLA) graft copolymer and drug release of drug loaded (prednisone acetate) micelles at 37 °C. Reprinted from Ref.147, Copyright (2008), with permission from Elsevier.

Because of the diversity and complicacy of reactions, in some cases, ILs can be designed to endow the chemical processes with inherent task-specific properties. For example, instead of the protection and deprotection of amino groups before and after the synthesis of chitosan copolymer in [BMIM][Ac] to obtain amino-reserved chitosan-*g*-PCL,[188] ILs can restrain the reaction of the amino groups of chitosan, rendering the alkylation selectively to occur on hydroxyl groups of chitosan in [BMIM][Cl] without the protection of amino groups.[190] Thus, this *O*-alkylated chitosan can be potentially used as gene delivery carriers. For this, it was hypothesized that the nitrogen atoms of imidazolium-based ILs can be in the electron deficiency environment, hampering the nucleophilic reaction of amino groups. Moreover, in the same chemical process, ILs can serve as a catalyst in addition to a dissolution and reaction medium. For example, ammonium-based ILs, especially choline-based ones, have been exploited to be a catalytic medium without the necessity of basic or acid catalysts. The hydrophobic silanization reaction of cellulose nanocrystals was achieved in choline lactate ([Ch][Lac]) without the addition of an external catalyst,[191] which is a must as it can accelerate the hydrolysis of alkoxy groups to yield silanol groups to further react with -OH groups present on cellulose nanocrystal surfaces.[192]

Among all modifications, grafting hydrophobic polymers onto biopolymers to acquire amphipathic property is regarded as the most effective method to extend the applications of functional carrier materials (*e.g.*, nanomicelles) (Table 4). Cellulose-graft-poly(L-lactide) (CEL-*g*-PLA) was designed and synthesized in [BMIM][Cl],[147] which could self-assemble into micelles in water with the hydrophobic PLA segments as the cores and the hydrophilic cellulose segments as the outer shells (Fig. 6). These drug-loaded micelles showed sustained drug release, which indicates their potential applicability as DDSs.[147]

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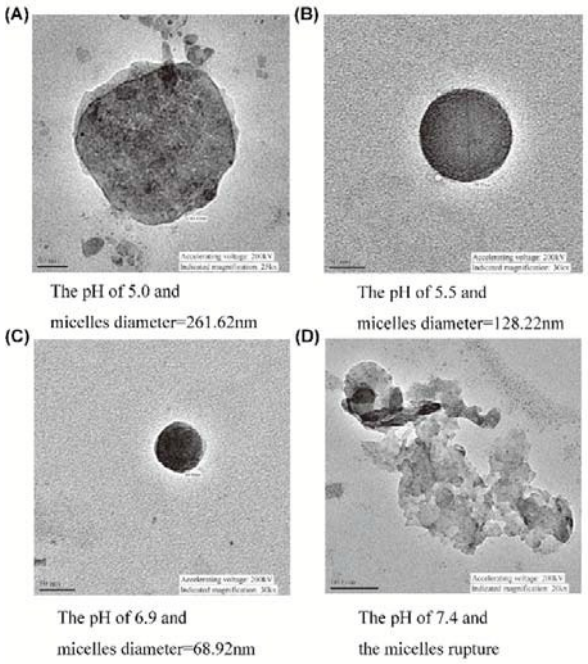

Fig. 7. Cellulose-*g*-poly[2-(diethylamino)-ethyl methacrylate] (PDEAEMA) micelles solutions photographs at different pH values. Reprinted from Ref.184, Copyright (2015), with permission from Elsevier.

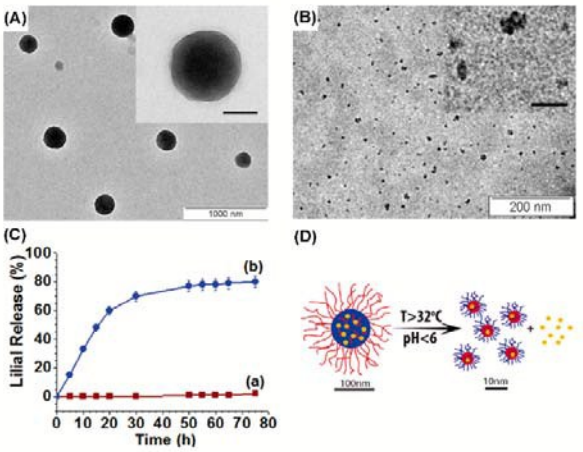

Fig. 8. Smart chitosan (CS)-based stimulus-responsive nanocarriers for the controlled delivery of hydrophobic pharmaceuticals. TEM images of self-assembled poly(*N*-isopropylacrylamide) (PNIPAM)-CS-Lilial nanocarriers (PNIPAM graft content = 154.2%) in dilute H_2O dispersion (0.2 mg/mL) at (A) pH = 7.4 and 37 °C and (B) pH = 4.5 and 37 °C (for 3 days), Individual nanocarriers at higher magnification are shown as the inset in (A) and (B). (C) Lilial release profile at simulated storage stage (25 °C, pH = 7.4) (a) and endosomal/lysosomal uptake stage (37°C, pH = 4.5) (b). (D) Schematic representation of the dual responsive behaviour of self-assembled PNIPAM-CS-Lilial nanocarriers. The PNIPAM and CS are represented in red and blue, respectively. Lilial is represented in yellow. Reprinted with permission from Ref.153. Copyright (2011) American Chemical Society.

In addition, chemical modifications can not only control the physical and delivery properties of biopolymer derivatives (*e.g.*, solubility, hydrophilicity/hydrophobicity, and drug releasing ability), but also provide new functions by grafting functional polymers. For the development of stimulus-responsive DDSs in ILs, the incorporation of stimulus-sensitive polymer units into the biopolymer is an easy way to combine biopolymers with responsiveness. In turn, the addition of biopolymer could enhance the biodegradability and biocompatibility of its copolymers. Such grafted copolymers have been developed by grafting poly(*N*-isopropylacrylamide) (PNIPAM) onto cellulose to prepare thermosensitive biopolymers in [AMIM][Cl][46] or poly[2-(diethylamino)-ethyl methacrylate] (PDEAEMA) onto cellulose (CEL-*g*-PDEAEMA) to prepare pH-sensitive biopolymers by homogeneous ATRP in [AMIM][Cl].[184] The as-prepared copolymers were found to have similar responsiveness to the stimulus-sensitive polymer units with minor modulation. For example, in the case of CEL-*g*-PDEAEMA, the hydrophilic PDEAEMA side chains resided mainly in the corona of the micelles, whereas the hydrophobic backbone of cellulose was mainly in the core of the micelles.[184] At pH values below 6.9, the diameters of the micelles were small (Fig. 7A-C). This reduction was due to the hydrophilic tertiary amine groups of the PDEAEMA structure. At acidic condition (pH 5.0), the *N*,*N*'-dimethylaminoethyl groups were protonated.[181] Then, at higher pH, the deprotonation of the tertiary amine groups led to a contraction of the PDEAEMA brushes, reducing the diameter of the micelles to the minimum value at pH 6.9 (Fig. 7C). However, at pH 7.4, the CEL-*g*-PDEAEMA side chains collapsed in the shell of micelles, leading to micelle rupture (Fig. 7D). All these results imply its potential application as pH-sensitive biomedical materials.

Stimulated by the advances in drug-polymer conjugates in DDSs, such as the high drug loading contents and the minimum side effects of drugs,[1] drug-biopolymer conjugates are also exploited in ILs. Chitosan-Lilial conjugates has been prepared by combining hydrophobic payloads (Lilial as a prototype) efficiently with chitosan via Schiff base bond formation in [BMIM][Cl].[153] The Schiff base bond (stable at neutral pH, but progressively hydrolyzed to break apart when the pH drops below 6)[193] endowed the pH-dependent dissolution-coagulation transition of chitosan.[194] This feature of the chitosan-Lilial conjugate would especially benefit for cellular DDS design since the endosomal or lysosomal uptake is a gradually acidified compartmentalization process (pH = ~6.5–4).[195] Further functional modification was carried out by grafting thermoresponsive PNIPAM to the chitosan-drug conjugate (Fig. 8D). The graft copolymer was observed to self-assemble in water at neutral pH into core-shell nanocarriers with a size distribution of ~ 142 ± 60 nm (Fig. 8A). At 37 °C, zero release of Lilial was observed at neutral pH. While, at pH 4.5 (the conditions mimicking endosomal or lysosomal uptake), the nanocarriers formed reversed micelles (~8 ± 3 nm) (Fig. 8B) and 70% of the drug was liberated within 30 h through the hydrolytic cleavage of the Schiff base conjugation. Based on the smart drug release profile (Fig. 8C), this strategy was deemed viable for the intravenous administration of hydrophobic drugs carried by chitosan-based vehicles.

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3.3 IL-assisted formation of biopolymer matrices

Modern material technology offers an intelligent approach for pharmaceutics by encapsulating drugs to carrier particles such as MPs, NPs, and liposomes, which can modulate the delivery characteristics of drugs and provide controlled release or target specificity.[196] With high surface-to-volume ratios, micro-/nanoparticles can significantly increase their cellular contact, thus increasing the bioavailability of drugs. A well-designed nanoparticulate system is able to preferentially accumulate drugs at the site of interest, such as tumor[1] or M cells of Peyer's patches,[197] and avoid nonspecific distribution. However, its delivery performance is strongly dependent on the characteristics of the produced particles. Technical issues, such as the oversized particles, the heterogenetic distribution of particles,[198] and the lack of balance between hydrophilic/hydrophobic modification of the particle surface,[199] hinder the development of these biopolymer-based carriers. For example, for intravascular administration, the large size and broad size distribution of obtained NPs may induce the clearance by reticuloendothelial system (RES) organs,[1] resulting in a short blood half-life and low efficiency of drug delivery. Therefore, there is a strong incentive to develop new methods for the synthesis of micro-/nanoparticles. Recently, the versatile features of ILs draw attention to address such challenges of biopolymer-based carriers. ILs can be used in the preparation of advanced biopolymer-based DDSs for better particle properties, especially via the suspension polymerization reactions.[200]

With the extensive choice of polarity and miscibility, ILs can be a good alternative as the polar phase (hydrophilic ILs) or nonpolar phase (hydrophobic ILs) in the microemulsion process.[201, 202] These IL-microemulsions have been tested successfully to prepare biopolymer-based NPs (Table 4), which can overcome the size issue of NPs prepared by traditional water (W)/oil (O) microemulsion-crosslinking technique.[203] In these microemulsions, ILs played an indispensable role in the formation of NPs, since such stable microemulsions were not obtainable with common organic solvents.[204] Results showed that starch NPs can be prepared with epichlorohydrin as the crosslinker through an IL/O (1-octyl-3-methylimidazolium acetate ([OMIM][Ac]) as the polar phase (Fig. 9A)) or an W/IL (1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) as the oil phase[154]) microemulsion-crosslinking reaction. The obtained starch NPs were spherical with a small mean diameter (*e.g.*, 91.4 nm[154] and 96.9 nm[205]) and a narrow size distribution. The drug release tests showed an initial burst release followed by a sustained release of 79.95% of the model drug within 10 hours.[154] However, due to the strong van der Waals forces and electrostatic attractions between particles,[206] most of these starch NPs showed aggregation or cluster formation (Fig. 9B), which could limit their application in drug delivery. In order to decrease this aggregation, octenyl succinic anhydride (OSA) starch was used as the raw material because of its hydrophobicity (Fig. 9C). 1-(3-hydroxypropyl)-3-methylimidazolium acetate ([C_3OHMIM][Ac]) was tailor-made to serve as the polar phase, combining the surfactant (polyethylene glycol octylphenol ether), the cosurfactant (1-butanol), and the oil phase (cyclohexane), to prepare nonaqueous IL-microemulsion.[156] The mean diameter of the acquired particles was 86.69 nm and no clusters of starch NPs was observed.

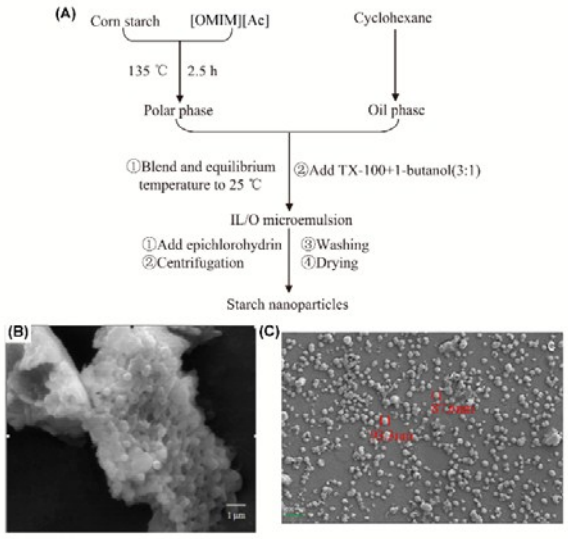

Fig. 9. Preparation and characterization of starch nanoparticles in ionic liquid-in-oil microemulsions system. (A) Scheme of the microemulsion-crosslinking reaction of starch using 1-octyl-3-methylimidazolium acetate ([OMIM][Ac]) as the polar phase (TritonX-100 (TX-100) as the surfactant, 1-butanol as the cosurfactant)). Adopted from Ref.205, Copyright (2014), with permission from Elsevier; (B) SEM images of starch nanoparticles prepared by corn starch using [OMIM][Ac]. Reprinted from Ref.205, Copyright (2014), with permission from Elsevier; (C) SEM images of octenyl succinic anhydride (OSA) maize starch using 1-(3-hydroxypropyl)-3-methylimidazolium acetate ([C_3OHMIM][Ac]). Reprinted with permission from Ref.156. Copyright (2017) American Chemical Society.

Due to the unique interfaces of microdroplets in ILs, simple and rational methods for preparing biopolymer-encapsulated protein microcapsules have been developed. When using microemulsions to prepare protein microcapsules, the O/W type has always been adopted,[207, 208] however the inner oil droplets are not suitable to dissolve water-soluble guest biopolymers. This issue can be addressed by taking advantage of ILs. Besides, microcapsules formed in the IL phase can be easily extracted to the aqueous phase after consecutive crosslinking and surface modification reactions; thus, the whole processes can be carried out in one pot.[209] It was found that the capsule-forming (host) proteins such as BSA and β-lactoglobulin (β-Lg) could rapidly form microcapsules at the W/ILs interface under mild conditions, while the guest biopolymers (*e.g.*, enzymes) remain quantitatively encapsulated in the inner aqueous pool (Fig. 10). As a result, BSA microcapsules with diameters of 7–15 μm were observed, whereas red-blood-cell-like flattened microcapsules (diameter, 2–7 μm) were shown for β-Lg. This difference was related to the number of charged residues on protein surfaces, that is, the proportion of lysine residues contained in these two proteins.[209] Besides, enzymes confined in the inner water phase of aqueous protein microcapsules showed innate activity, suggesting the success of this novel method to prepare protein microcapsules with an effective protection of bioactive substances.

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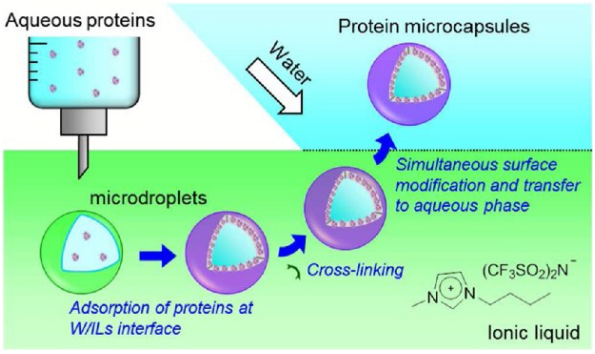

Fig. 10. Schematic illustration for the interfacial synthesis of protein microcapsules and their one-pot extraction into the aqueous phase. Reprinted with permission from Ref.209. Copyright (2012) American Chemical Society.

In recent years, surfactant ILs have emerged as substitutes for traditional surfactants to stabilize IL-microemulsions, particularly for those surface-active ionic liquids (SAILs) with long-chain alkyl groups in their cations.[81] For example, 1-hexadecyl-3-methylimidazolium bromide ([C_{16}MIM][Br]) was found to act as the surfactant in the microemulsions to prepare starch NPs.[155, 157] SAILs, especially imidazolium-based SAILs, possess superior surface activity over the conventional analogous surfactants in aqueous and nonaqueous media. This is because of the existence of imidazolium head groups, which display significantly superior properties such as a stronger tendency toward self-aggregation and stronger attraction to aromatic rings through π–π interactions.[210-212] Together, ILs can play versatile roles in the emulsion process. As an example, starch NPs can be prepared in a dual-ILs-based microemulsion system with [C_{16}MIM][Br] and [OMIM][Ac] simultaneously used as the surfactant and the polar phase, respectively.[157] Compared with the formerly obtained starch NPs in the IL-microemulsions,[154, 205] these starch NPs had smaller particle sizes with a mean diameter of 80.5 nm, which may be on account of the nonpolar part of the ILs, acting as a surfactant helping to stabilize the suspended phase. Besides, ILs may induce electrostatic charges on the surfaces of polymer particles to keep them from coalescence.[200]

3.4 Physical interactions of biopolymers with ILs

Because of its tremendous sources from animals, plants, and microorganisms, biopolymers with particular structure features (such as carboxyl groups of alginic acid[116] and amino groups of chitosan[36]) exhibit huge potential in the development of supramolecular polymers for drug/gene delivery purposes. These biopolymers can self-assemble into supramolecular complexes by blending with the counterpart molecules with sophisticated structures and functions. This could lead to, for example, pH-responsive drug delivery carriers based on chitosan polyelectrolyte complexes.[213] Another typical example is cyclodextrins (CDs). Due to the relatively hydrophobic cavity of CDs,[214] they have been extensively studied in supramolecular chemistry as host molecules. CDs are capable of containing guest molecules ranging from small organic/inorganic compounds to polymers through hydrophobic interactions to

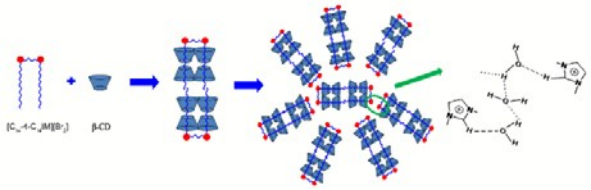

Fig. 11. Schematic diagram of the hydrogel formed by imidazolium Gemini surfactant ([C_{14}-4-C_{14}IM][Br_2]) and β-cyclodextrin (β-CD). Adopted from Ref.222, Copyright (2016), with permission from Elsevier.

form supramolecular complexes.[215-217] Such interactions can provide a delicate balance that is expected to yield interesting soft matter phases. On the other hand, results showed that ILs can also self-assemble into highly structural nanomaterials.[81] Therefore, for the application of pharmaceutical formulations, the use of biopolymer-IL combinations for colloidal supramolecular complexes can be of high interest.

It is well known that traditional surfactants are capable of interacting with biopolymers to form various self-assembled nanostructures.[218, 219] Motivated by this strategy to enrich biopolymer materials, surfactant ILs can be exploited in conjugation with biopolymers to maximize their use in colloidal formulations and to understand the fundamental nature of interactions existing in such systems. For example, inclusion complexes can be formed by the supramolecular assembly of β-CD as the host and SAIL as the guest,[220, 221] such as vesicles prepared in the concentrated aqueous solution of 1-dodecyl-3-methylimidazolium bromide ([C_{12}MIM][Br]) and β-CD.[221] Usually, surfactants ILs can outperform traditional surfactants in the formation of nanomaterials.[159] Besides, IL-type imidazolium Gemini surfactants can also be used to prepare supramolecular matrices with biopolymers. These imidazolium Gemini surfactants are usually made up of two hydrophobic chains and two hydrophilic imidazolium head groups covalently linked through a spacer group,[210] such as [C_{14}-4-C_{14}IM][Br_2].[222] Driven by the hydrogen bonds between β-CDs, between β-CD and the imidazolium head group of [C_{14}-4-C_{14}IM]$^{2+}$, and between β-CD and the solvent, and the hydrophobic interactions between the hydrophobic chains of [C_{14}-4-C_{14}IM][Br_2], two-component hydrogels were formed (Fig. 11). Interestingly, due to the temperature-sensitive formation of hydrogen bonds between β-CD and [C_{14}-4-C_{14}IM][Br_2], the properties of these hydrogels were responsive to external temperature and can be controlled by changing the host/guest ratio.[222] By increasing the temperature, the hydrogels changed into solutions and this process was reversible and reproducible, which made these hydrogels as potential injectable DDSs.[210, 222] Yet, compared with traditional surfactants, surfactants IL have received less attention in their interactions with biopolymers.

Intermolecular noncovalent interactions have been found to be the driving force for the formation of biopolymer-IL supramolecular complexes (Table 4). In a system of biopolymer-IL combination, these interactions often coexist and had a synergistic effect on the formation of colloidal IL-contained biopolymer materials. For instance, cooperative interactions of SAILs (1-butyl-3-methylimidazolium octylsulfate ([BMIM][C_8OSO_3]), and 1-octyl-3-methylimidazolium chloride

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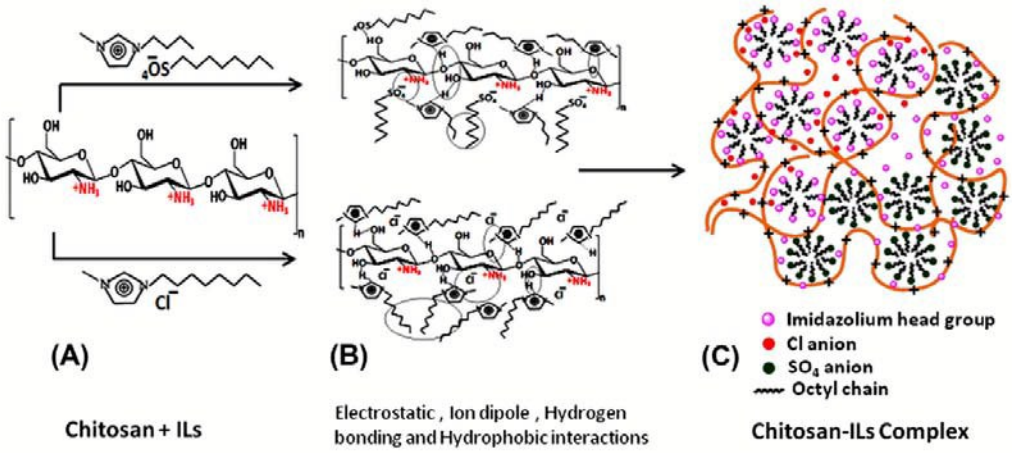

Fig. 12. Schematic diagram of ionic gelation of ionic liquids (ILs) ions with chitosan chains via different interactions, which finally forms chitosan-ILs complexes. Reprinted from Ref.158, Copyright (2013), with permission from Elsevier.

([OMIM][Cl])) with chitosan resulted in facile preparation of uniformly distributed chitosan NPs with excellent sphericity.[158] Specifically, at a low concentration, chitosan-IL aggregates were formed via ion dipole, electrostatic, and hydrophobic interactions. Nonetheless, above critical micelle concentration (CMC), chitosan-IL aggregates grew further and formed chitosan-directed micelles due to electrostatic and hydrophobic interactions. In this process, IL aggregates acted as a structure-directing template (Fig. 12). Moreover, in case of chitosan-[OMIM][Cl] system, the interaction behaviour was almost similar to that of classical nonionic polymer/anionic surfactant systems where the hydrophobic and ion-dipole forces played a major role rather than electrostatic interactions.[223, 224] Nevertheless, strong electrostatic interactions existed between the [C_8OSO_3] anion and positively charged chitosan chains, which made chitosan chain contraction significantly higher in the chitosan-[BMIM][C_8OSO_3] system.[158] This indicates the ease and flexibility of supramolecular particle preparations with controlled properties by changing the ion type and the alkyl chain length of ILs in biopolymer science.

As the replacement of biological viral vectors, nonviral gene carriers have entered the full, repaid period of development in the field of gene therapy. So far, DNA gels, which promise to be gene vectors, have attracted much attention. In aqueous dispersion solutions, DNA can interact with polymers to form DNA/polymer complexes by self-assembly, which are rich in soft matter phases and give rise to a wide range of morphologies.[225, 226] Inspired by these DNA gels, the interactions of ILs with nucleic acids have generated considerable interest in the recent past,[227, 228] which can be taken advantage of to form DNA gels to enlarge its application as gene delivery vehicles. Ionogels can occur automatically from the addition of ILs into DNA solutions, such as DNA ionogels from the IL solution ([EMIM][Cl]), which only cost 260 s of gelation time for 5% IL concentration. This is an easy and simple method with the use of ILs for the preparation of gene vectors. Results showed that the whole process was driven mostly by electrostatic interactions from the positively charged imidazolium head groups of IL molecules and the negatively charged phosphate groups of DNA.[32] Moreover, the radius of DNA gels usually increased due to the incorporation of IL molecules onto the surface of DNA.[32, 229] Yet, gene delivery is a complicated process, for which there are several systematic and cellular barriers to overcome, such as the slow diffusion of hydrophilic DNA across the hydrophobic lipid bilayer membrane, and the slight electrostatic repulsion due to anionic DNA and the anionic head groups of the bilayer membrane.[230] Thus, to improve the gene transformation efficiency, comparatively hydrophobic ILs was preferred to be crafted with DNA to efficiently transfer DNA across the bilayer membrane and prevent enzymatic damages. For example, hydrophobic IL ([BMIM][PF_6]) was chosen to form self-assembled nanostructures (69.5 nm) with plasmid DNA of various ratios.[229] It was found that the cationic groups ([BMIM]$^+$) not only bound parallel to the surface but also arranged on the surface of DNA (Fig. 13B), therefore changing the B-form conformation of DNA.[231] These nanostructures can enhance the rate of uptake of DNA molecules into the cell and protect DNA from physicochemical and biological destruction (Fig. 13A). In particular, DNA-IL nanostructures were found to enhance the efficiency of transformation by 3- to 4-folds as compared to that of pure plasmid DNA.[229] Moreover, SAILs can be applied to enhance the interactions between ILs and DNA to improve the transfection efficiency. In this case, the aggregation of SAIL on DNA chains was usually initiated not only by electrostatic attractions but also by hydrophobic interactions (Table 4). Furthermore, because of the steric hindrance of the long side chains of SAIL cations, the hydrophobic interactions were the main driving force to bind with DNA, enhance DNA condensation, and promote the transfection process of IL-DNA complexes.[160]. This can be verified by using imidazolium-based ILs with different alkyl side chain lengths (ethyl, butyl, and hexyl).[232] As expected, the increase in the length of hydrophobic

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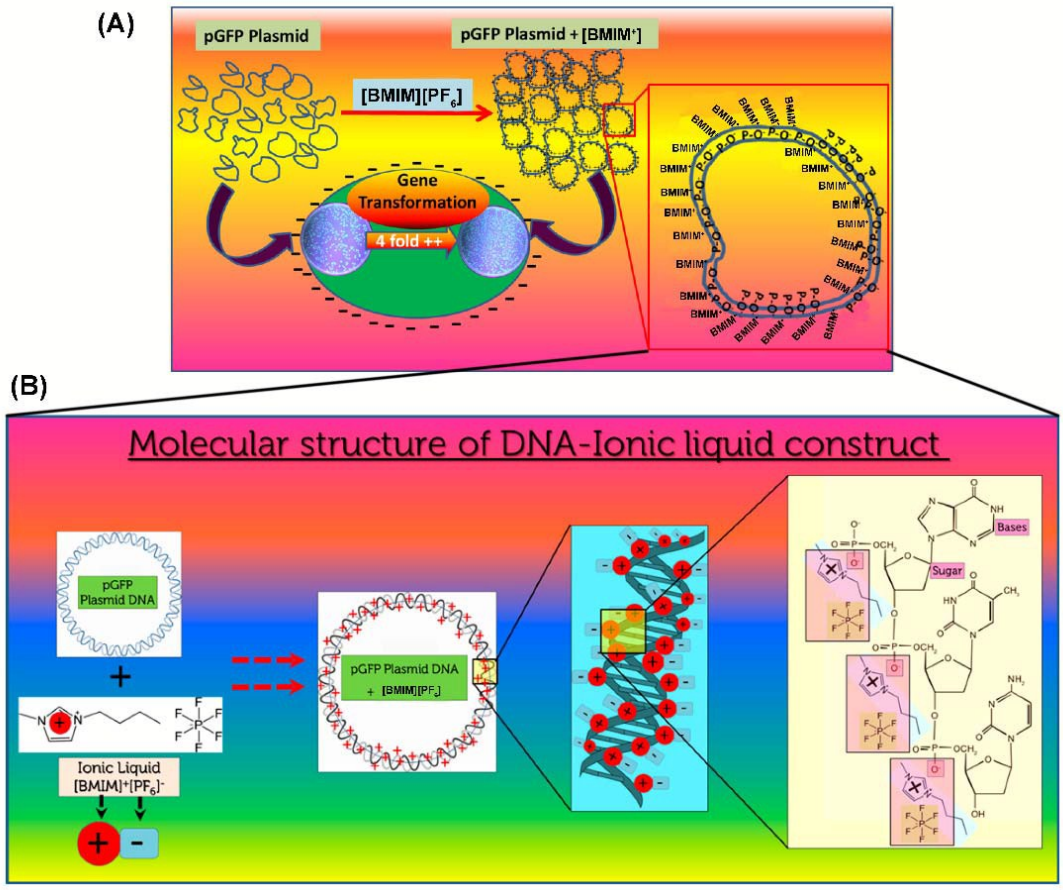

Fig. 13. Gene delivery of functional self-assembled nanostructure of plasmid DNA with ionic liquid (IL). (A) Enhanced efficiency in bacterial gene transformation of ionic gels composed of plasmid DNA (pGFP) with 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]). (B) Hierarchical assembly of purified pGFP plasmid DNA with [BMIM][PF_6] and the electrostatic interaction of the $[BMIM]^+$ ion and PO_4^- of the DNA strand, leading to the synthesis of a functional, stable DNA-IL construct. Adapted with permission from Ref.229. Copyright (2015) American Chemical Society.

alkyl chains in the cationic group was found to enhance the binding capacity with DNA, with the preference for long alkyl side chains (ethyl < butyl < hexyl).[232] Thus, the self-assembly process of SAILs with DNA was rather a result of their hydrophobicity. Interestingly, unlike small-molecule ILs,[32, 229] surfactants IL can reduce the charge repulsion by binding to DNA backbones, leading to the compaction of DNA and smaller sizes of DNA-SAIL complexes compared with native DNA.[119, 160] This compaction of DNA helped to cross cell membranes[160, 233] thus improving the efficacy of gene therapy.

Surfactant IL-DNA complexes can particularly favour transdermal drug delivery, since the surfactant ILs may act as a penetration enhancer to improve skin-permeating ability, which is the main limit of the efficiency of transdermal DDSs.[49] For instance, therapeutic RNA robed with IL moieties (benzyl dimethyl octyl ammonium (BDOA)) was exploited as a simple, scalable prodrug platform to treat skin disease.[234] The skin transport of this therapeutic RNA was significantly enhanced by robing with BDOA, with a higher applied dose delivered into the viable epidermis (9.85 ± 2.64%) compared to only 2.06 ± 0.15% for naked RNA. Besides, compared to naked siRNA, cell internalization was enhanced by robing with IL moieties. All the results verified its excellent transport into the deep viable skin layers (epidermis and dermis), its ability to improve cell internalization, and its superior biocompatibility.[234] In addition, if a new functional group is introduced into a surfactant IL, the new structure and property of the surfactant IL-DNA complexes may be produced. Efforts have been dedicated to developing the multifunctional surfactant IL-DNA complexes. For example, the photodynamic therapy and gene transportation were achieved simultaneously by introducing the photoactive isoquinolinium ring to the ILs to synthesize the photoactive IL surfactants (lauryl isoquinolinium bromide, [C_{12}iQuin][Br]).[160] At a low concentration, the photoactive isoquinolinium ring of [C_{12}iQuin][Br], which was an AT-specific minor groove binder, would be arranged to face the plane of the minor groove of DNA, and the hydrophobic tails of [C_{12}iQuin][Br] would be arranged parallel to the minor groove (Fig. 14). As a result, DNA molecules were strongly compacted at a low [C_{12}iQuin][Br] concentration. Subsequently, they underwent a complete coil-to-globule

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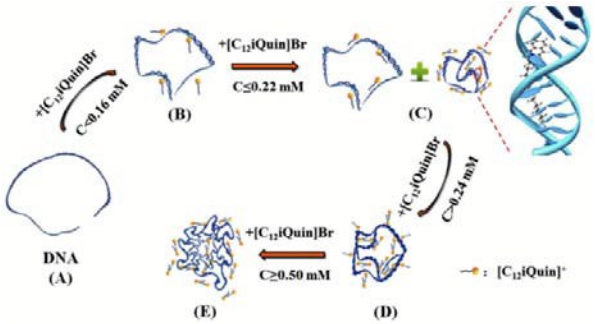

Fig. 14. Schematic illustration of the coil-to-globule structure transition and binding characteristics of DNA induced by photoactive ionic liquid surfactant (lauryl isoquinolinium bromide, [C_{12}iQuin][Br]). Reprinted from Ref.160, Copyright (2017), with permission from Elsevier.

structure transition upon further addition of [C_{12}iQuin][Br].[160] This unique binding mode of [C_{12}iQuin][Br] on DNA caused the formation of the new photoactive structures of complexes, which would promote the novel applications in the photodynamic therapy or the gene transportation.

3.5 Biopolymeric ILs

Due to its unique biological properties (Fig. 2), ILs themselves can be potential for DDSs in the form of IL-based drug formulations (*e.g.*, active pharmaceutical ingredients ILs) or anticancer and antimicrobial agents.[47] Given the wide variety of ions available, it is not difficult to prepare ILs to acquire specific functions. However, rare deliberation has been given to the development of these functional ILs. Thus, much attention is highly needed to prepare biopolymeric ILs, which can be considered as the promising candidate in the pharmaceutical industry. Moreover, the combination of biologically relevant compounds can improve the biocompatibility of the systems. Imidazolium or pyridinium-based ILs demonstrate significantly higher antimicrobial and antitumor activities than other ILs,[235, 236] which can be exploited as antimicrobial and antitumor substances in the pharmaceutic industry. As a result, early efforts have been dedicated to developing these antimicrobial and anticancer biopolymeric ILs. For example, a series of biopolymeric chitosan Schiff bases bearing salicylidene IL (IL-Sal) brushes and its metal complexes (Fig. 15) were developed as pharmacological candidates. The azomethine linkage (C=N) in these Schiff base composites showed stupendous biocidal efficacy (including antibacterial, antifungal, and antitumor activities),[237] which could contribute to its antimicrobial and anticancer properties.[238] The designed biopolymeric chitosan Schiff bases exhibited antitumor activities against human colon carcinoma (HCT-116) cell line and further metallization could enhance its antitumor activities significantly.[238] Moreover, this biopolymeric ILs and their metal complexes had moderate to excellent broad-spectrum antibacterial efficacy in comparison to the parent chitosan and standard antibiotic, with an ability to inhibit the growth of *Aspergillus flavus* < *Candida albicans* < *Escherichia coli* < *Staphylococcus aureus*.[238]

4 Toxicity and degradability of ILs for green carrier materials

The evaluation of the cytotoxicity and degradability of a biomaterial is the initial step when considering their practical and clinical applications. Normally, biopolymer-based DDSs could guarantee high biocompatibility and biodegradation.[239, 240] Thus, concerning the exploitation of ILs as highly promising solvents and/or materials for pharmaceutical applications, it is critical to assess the impact of ILs in terms of their cytotoxicity, biodegradability, bioaccumulation and environmental fate.

As for the impact of ILs on living organisms and the environment, toxicity studies have been carried out by performing a series of tests on enzyme activity (*e.g.*, acetylcholinesterase[241, 242]), bacteria and fungi (*e.g.*, *Escherichia coli*[243]), algae (*e.g.*, *Pseudokirchneriella subcapitata*[244]), cell viability (*e.g.*, HeLa cells,[245] CaCo-2 cells[246]), vascular plant (*e.g.*, wheat *Triticum aestivum*[247] and duckweed *Lemna minor*[248]), invertebrates (*e.g.*, *Daphnia magna*[244]), and vertebrates (*e.g.*, Zebrafish,[243] rats and mice[249]). In general, depending on the model system for acute toxicity testing, ILs showed moderate to high toxicity, in some cases, equal to or even two to four orders of magnitude higher than those of conventional organic solvents, such as benzene, methanol, DMF or propan-2-ol.[33, 34, 250] It has been found that the toxicity of ILs was mainly determined by the molecular structure (mostly due to the species and structural features of cations),[251] and special care should be taken in the design of ILs. When it came to the certain species of cations, the imidazolium cation showed the highest toxicity, whereas the ammonium cation demonstrated the lowest toxicity.[251] Besides, the hydrophobicity, which corresponds to the increasing alkyl chain length on the IL cation, was found to induce rising toxicity.[252, 253] The toxicity mechanism of ILs is not yet fully understood, but it has been proposed that the mode of toxic action takes place through membrane disruption. Specifically, the long alkyl chains increase the possibility of their interactions with cell membrane phospholipid bilayers and hydrophobic domains of membrane proteins, leading to disruption of membrane physiological functions and, consequently, to cell death.[254] Thus, increasing the hydrophilicity and polarity by introducing functional groups (*e.g.*, ether, hydroxyl or nitrile functions) to the IL cations can decrease its toxicity.[255] So far, the toxicity mechanism of the anionic part is less understood, although the toxicity of anions, such as PF_6, BF_4 has been proposed to be the reason. Due to their hydrolysis and formation of fluorides, they may act as potential inhibitors of Na^+, K^+ ATPase, which could be involved in the maintenance of static electric potential stations and transport and the regulation of cell volume.[256]

Nevertheless, when the biodegradability of ILs is concerned, it is notable that the goal of biodegradability inherently conflicts

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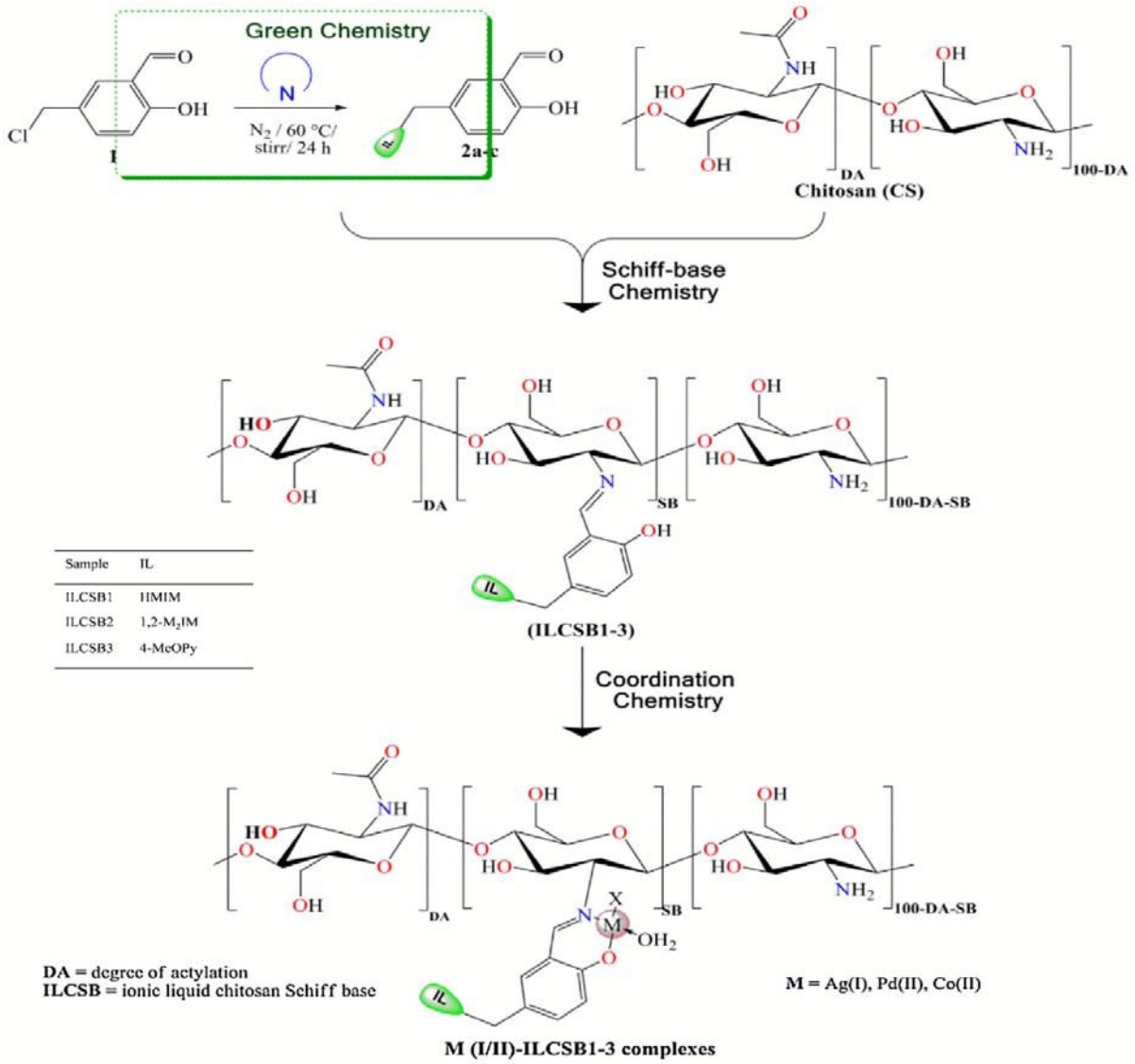

Fig. 15 Schematic diagram for the synthesis of ionic liquids-based salicylaldehydes (ILs-Sal, 2a-c), surface-functionalized chitosan and their complexes. Reprinted from Ref.238, Copyright (2016), with permission from Elsevier.

with the design of biocompatible ILs. For example, although IL cations with a short alkyl chain showed low toxicity, these ILs have been proven to resist biodegradation.[257] In fact, the biodegradability of ILs is highly dependent on the side chains. Good biodegradability was observed in ILs with longer alkyl side chains (>C_6) at the cationic core, whereas the same head cationic groups with shorter side chains were only poorly biodegradable.[258] On the other hand, unlike biocompatibility, the nature of the anions was proven to play a significant role in the biodegradability of ILs, that is, longer linear-chain anions, the higher was the biodegradability.[47] High biodegradability activity was also observed for ILs with pyridinium head group and the introduction of polar functional groups (*e.g.*, ether, hydroxyl or nitrile functions).[35, 259] Furthermore, different anions based on acetate, sulphate, and phosphate groups could also be readily biodegradable and considered nontoxic.

Despite the increasing understanding of the biological properties of ILs, the toxicity of ILs and their biodegradation routes in the human body have not been fully understood. Yet, regarding the clinical applications for the treatments of various diseases, it is critical to understand and guarantee the biocompatibility of biopolymer materials prepared by ILs. Thus, in most cases of biopolymer-based carrier materials where ILs were not involved in the matrices but only acted as solvents and reaction media, ILs were removed from the resulting matrices to eliminate their potential toxicity.[42, 142, 143, 147] The IL removal process can be achieved using solvent dilution and wash,[62, 175, 260] or Soxhlet extraction.[43, 45, 112, 153] For example, Soxhlet extraction or the combination of Soxhlet extraction and SCF have been applied to eliminate [BMIM][Ac] from chitosan-silk[48] and chitin gels.[100] The efficient removal of ILs could be detected by the colour change of the matrix from yellowish to

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transparent when coloured ILs were used,[100, 163] or the progressive decrease in the conductivity during the extraction process.[100] Yet, the methods commonly used for the removal of ILs are energy-intensive and time-consuming,[48, 112] and the disposal of ILs after removal from biopolymer matrices have not been discussed. Only a few studies considered the IL recycling and reuse,[42, 117] even though these aspects are vital for the economic, environmental and toxicity considerations about ILs. Therefore, it is important to develop techniques for the removal and recycling of ILs for the green chemistry of biopolymer materials. After the IL removal, the biocompatibility of the prepared matrices and copolymers were confirmed, which showed no or negligible *in vitro* cytotoxicity.[48, 103, 107, 112, 166, 188, 261, 262] For instance, no apparent inhibition effect of 3T3 fibroblast was observed when the concentration of cellulose-*g*-PLA copolymer was below 700mg/L.[147] ILs did not cause any deleterious effect on cell viability, which in turn suggests efficient IL removal from the chitin structures.[100, 263] Nonetheless, for those matrices in which ILs participate through physical interactions or chemical synthesis, ILs remained in the biopolymer materials. Thus, except for those biopolymeric ILs, of which the toxic nature is beneficial for the development of antimicrobials and pharmaceuticals, the biocompatibility of those biopolymer-IL composites should be highly concerned, especially with those SAILs with long alkyl side chains and fluoride ILs. No toxicity to *E. coli* DH5α cells was found for a self-assembled functional nanostructure of DNA with [BMIM][PF_6].[229] Moreover, when robed with BDOA, negligible cytotoxicity of RNA was observed (up to 300 nM compared with cells incubated with the medium alone).[234] Yet, up to now, the toxicity data of all biopolymer-based carrier materials processed in ILs are rare and only from *in-vitro* tests, especially those with ILs as a component. There remains a scope for further investigation of the overall toxicity of these IL-biopolymer composites and materials.

To increase the number of environmentally friendly IL candidates, there has been an effort to develop biodegradable and biocompatible ILs in particular for biomedical applications. To obtain "fully green" ILs, the starting materials must be at least nontoxic, whilst for a perfect solution, they should even be renewable to overcome the petroleum and toxic feedstock of traditional IL raw materials.[264] Biorenewable natural compounds are ideal materials from the viewpoints of both environmental and economic concerns, since these ILs can be synthesized via a simple neutralization reaction to reduce the energy input, with water as the only byproduct.[265] ILs can be prepared from sugars, amino acids, and biomolecules that exist in nature.[266, 267] These novel compounds have unique physicochemical properties quite close to those of common ILs, which make them applicable in various industrial processes. Among them, amino acid-based and choline-based ILs are considered to be the most promising and safe ILs to be used in the development of pharmaceutical and medical applications.[31] Despite the high potential of these biocompatible ILs, there are only a few studies on their application in biopolymer materials.[123, 191] For example, [Ch][Cl] and [Ch][DHP] were used to prepare electrical and pH-sensitive chitosan-based materials for improved drug delivery.[31] Furthermore, a new generation of liquid salts based on mixtures of a nontoxic quaternary ammonium salt (*e.g.*, choline chloride) and an uncharged hydrogen-bond donor (*e.g.*, amines, amides, alcohols and carboxylic acids),[268, 269] which are called deep eutectic solvents (DESs), have recently gained attention. The interaction of the hydrogen-bond donor with the salt reduces the anion–cation electrostatic force, and thus, the freezing point of the mixture decreases.[270] The syntheses of these compounds proceed simply by mixing two safe components, which are capable of forming a eutectic mixture, without the use of additional solvents and the formation of byproducts. This could result in easily biodegradable products with lower associated costs.[271] This new generation of liquid salts, DESs, have been used as solvents for the production of biopolymer matrices for DDSs such as choline chloride–thiourea.[167] Chitin nanofibres of diameter 20–30 nm could be obtained using the DESs (choline chloride/thiourea=1:2) with a yield of 84% (w/w). After addition of these chitin nanofibres, calcium alginate bionanocomposite gel beads were able to release about 70% of the drug after 24h at pH 7.4, showing the slow release ability of these composites.[167] Moreover, DESs can be formed by bioactive compounds or pharmaceutical ingredients. A controlled DDS was developed by impregnating a starch/PCL polymeric blend with a menthol:ibuprofen therapeutic DES after SCF sintering.[272] Drug release studies showed that the cumulative mass of drug released was higher with a high content (20 wt%) of the therapeutic DES incorporated. This demonstrates the feasibility to couple green technologies for the development of enhanced biomaterials for pharmaceutical applications.[272] Yet, the application of natural ILs and DESs in biopolymer materials is still a new field of research that has not been extensively explored. More efforts are highly demanded to make full use of multifunctional ILs for pharmaceutics applications.

5 Conclusion and future prospects

The application of ILs in the biopolymer-based carrier materials for pharmaceutics has undergone a veritable explosion of interest in recent years. ILs are claimed to be effective to construct biopolymer-based DDSs. There are three main roles of ILs in the construction of biopolymer materials for drug/gene delivery applications. Firstly, ILs have been demonstrated to be highly capable as excellent solvents and/or catalytic media for the dissolution, processability, and functionalization of biopolymers to generate a diversity of matrices based on green chemistry and engineering. In addition, ILs can participate in the microemulsions as the polar/nonpolar phase and/or surfactants to prepare uniform and small-sized biopolymer NPs. Furthermore, because of the unique physicochemical and biological properties of ILs, biopolymer-based DDSs and drug formulations can be achieved with ILs as material components by ways of physical interactions of ILs with biopolymers or chemical synthesis of ILs with active biocompounds. Overall, the application of green process principles, herein represented by the use of ILs, in the creation of high-value-added biopolymer

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materials has promoted a wide, sustainable use of biopolymers, which promises new application possibilities in drug/gene delivery.

Despite the promising results achieved for biopolymer-based DDSs,[273, 274] research on biopolymer-based carrier materials prepared with ILs for pharmaceutical applications has just been started. This field is still in its infancy and improvement of the currently developed systems is urgently needed. For example, despite the huge advances in carrier materials in DDSs,[1] there are limited data on the IL-assisted biopolymer-based carriers with stimulus-responsiveness, not to mention target-specificity, to protect drug/gene from destruction and control the drug release at the specific body parts or targeted cells. Secondly, compared with ILs as the dissolution and reaction media, the function of ILs to assist or participate in the formation of matrices needs to be further exploited. Thirdly, while ILs have been found to be effective in dissolving drug molecules that are sparingly soluble in water and most pharmaceutically accepted organic solvents,[275, 276] this huge advantage of ILs has not been exploited for the preparation of biopolymer materials. Future efforts should be dedicated to preparing biopolymer-based DDSs in ILs meanwhile overcoming the difficulties in delivery of poorly soluble drugs by the assistance of ILs.[277] Moreover, no research has been reported regarding the *in-vivo* biocompatibility and biodegradation of the biopolymer-based carrier materials prepared in ILs, which, however, is the prerequisite for the pharmaceutics and clinical applications of these next-generation materials.

Last but not the least, the completely green aspects related to the utilization of ILs in biopolymer materials need to be highly concerned and developed as follows. Firstly, new raw materials and methods for the synthesis as well as the recycling and reuse of ILs are highly needed for the environmental-friendly and cost-effective production of biopolymer materials. Secondly, the physics and chemistry involved in the processing of biopolymers should be understood at the mechanistic level so that the processes can be improved with higher versatility. Specifically, mild dissolution temperature, reduced dissolution time, higher solubility, and the ability to treat a wider range of raw biopolymers are desired. Thirdly, while only limited data have concerned about the total removal ILs from biopolymer materials, more emphasis should be put on the residual ILs based on the present removal methods, and their potential influence on the properties (especially biocompatibility) of biopolymers. The application of ILs will only be achieved if the advantages of ILs outweigh their drawbacks, most prominently the prices of ILs relative to the value of the material processed by these ILs.

Abbreviations

General

ATRP	Atom transfer radical polymerization
CMC	Critical micelle concentration
CNTs	Carbon nanotubes
DA	Degree of acetylation
DD	Degree of deacetylation
DDSs	Drug delivery systems
DESs	Deep eutectic solvents
DP	Degrees of polymerization
DS	Degree of substitution
GD	Grafting degree
LCST	Lower critical solution temperature
MPs	Microparticles
M	Molecular mass
M_n	Number-average molecular mass
M_w	Weight-average molecular mass
MS	Molar substitution
MNPs	Magnetite nanoparticles
MWNTs	Multiwall carbon nanotubes
NPs	Nanoparticles
RAFT polymerization	Reversible addition-fragmentation chain transfer
RES	Reticuloendothelial system
ROP	Ring-opening polymerization
SCF	Supercritical fluid drying
W/O	Water (W) / oil (O)

Chemicals

AOT	Sodium *bis*(2-ethylhexyl) sulfosuccinate
β-Lg	β-Lactogloblin
BSA	Bovine serum albumin
BDOA	Benzyl dimethyl octyl ammonium
CDs	Cyclodextrins
CEL	Cellulose
CEL-*g*-PLA	Cellulose-graft-poly(L-lactide)
CMC	Critical micelle concentration
CS	Chitosan
CS-*g*-PEI	Chitosan-graft-polyethylenimine
DMF	Dimethylformamide

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DMSO	Dimethylsulfoxide
DXA	Sodium phosphate dexamethasone
HAP	Hydroxyapatite
HEC	Hydroxyethyl cellulose
KER	Keratin
OSA	Octenyl succinic anhydride
PDEAEMA	Poly[2-(diethylamino)-ethyl methacrylate]
PNIPAM	Poly(*N*-isopropylacrylamide)
PCL	Polycaprolactone
PDMAEMA	Poly(*N*,*N*-dimethylamino-2-ethyl methacrylate)
PLA	Poly(L-lactide)
PNIPAM	Poly(*N*-isopropylacrylamide)

Ionic liquids

ILs	Ionic liquids
P(IL)	Poly(ionic liquid)
RTILs	Toom-temperature ionic liquids
SAILs	Surface-active ionic liquids
[AMIM][Br]	1-Allyl-3-methylimidazolium bromide
[AMIM][Cl]	1-Allyl-3-methylimidazolium chloride
[BMIM][Ac]	1-Butyl-3-methyl imidazolium acetate
[BMIM][Br]	1-Butyl-3-methylimidazolium bromide
[BMIM][C_8OSO_3]	1-Butyl-3-methylimida-zolium octylsulfate
[BMIM][Cl]	1-Butyl-3-methylimidazolium chloride
[BMIM][PF_6]	1-Butyl-3-methylimidazolium hexafluorophosphate
[BMIM][SCN]	1-Butyl-3-methylimidazolium thiocyanate
[C_{12}iQuin][Br]	Lauryl isoquinolinium bromide
[C_{12}MIM][Br]	1-Dodecyl-3-methylimidazolium bromide
[C_{16}MIM][Br]	1-Hexadecyl-3-methylimidazolium bromide
[C_{16}MIM][Cl]	1-Hexadecyl-3-methylimidazolium chloride
[C_2OHMIM][Cl]	1-(2-Hydroxyethyl)-3-methylimidazolium chloride
[C_3OHMIM][Ac]	1-(3-Hydroxypropyl)-3-methylimidazolium acetate
[Ch][Cit]	Choline citrate
[Ch][Cl]	Choline chloride
[Ch][DHP]	Choline dihydrogen phosphate
[Ch][Hex]	Choline hexanoate
[Ch][Lac]	Choline lactate
[DMBIM][Cl]	1-Butyl-2,3-dimethylimidazolium chloride
[EMIM][Ac]	1-Ethyl-3-methylimidazolium acetate
[EMIM][Ba]	1-Ethyl-3-methylimidazolium benzoate
[EMIM][Cl]	1-Ethyl-3-methylimidazolium chloride
[EMIM][DEP]	1-Ethyl-3-methylimidazolium diethyl phosphate
[EMIM][MP]	1-Ethyl-3-methylimidazolium methylphosphonate
[EtMIM][Cl]	3-Methyl-1-(ethylacetyl)imidazolium chloride
[$NH_3(CH_2)_2OH$][Ac]	2-Hydroxyethylammonium acetate
[NH_3OH][Ac]	Hydroxylammonium acetate
[OMIM][Ac]	1-Octyl-3-methylimidazolium acetate
[OMIM][Cl]	1-Octyl-3-methylimidazoliu chloride

Conflicts of interest

There are no conflicts to declare.

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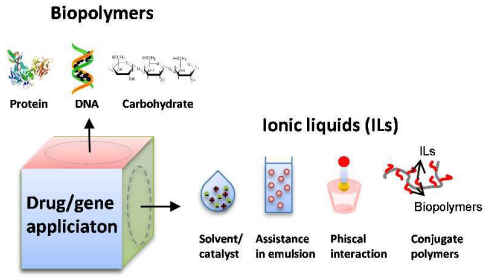

Ionic liquids present huge potential in fabrication of biopolymer-based pharmaceutical materials for accurately controlled drug/gene delivery.