RSC Applied Interfaces

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d5lf00393h

Ionic liquids as promising biomaterials: revolutionizing nano drug delivery systems

Tewodros Assefa Chaklie, [a] Mohammad Abu Jafar Mazumder, [bc] Anwarul Hasan [ad] and Shihab Uddin *[ad]

Received 17th December 2025,
Accepted 3rd March 2026

DOI: 10.1039/d5lf00393h

rsc.li/RSCApplInter

Ionic liquids (ILs) have become versatile biomaterials due to their ability to overcome significant drawbacks of traditional pharmaceutical materials, including limited solubility, stability, and bioavailability, as they can have their polarity tuned, with low volatility and high thermal stability. Having evolved to become bioresponsive and self-assembly solvents, ILs are currently used as catalysts, stabilizers, surfactants, and active carriers of pharmaceutical ingredients, which places them as sustainable competitors to overcome important drug delivery and biomedical engineering barriers. This review discusses their synthesis, classification, and incorporation into nanocarriers, hydrogels, and polymeric matrices, with multifunctional applications in improving permeability, controlled release, and biocatalytic activity in a wide range of therapeutic applications, including oncology, diabetes, infectious diseases, and neurological disorders. The major issues such as cytotoxicity, viscosity, low biodegradability, and scalability are discussed and newer strategies of designing biocompatible and task-specific ILs by green chemistry and computational methods are considered. Overall, ILs will transform biomedical innovation by providing personalized and environmentally friendly platforms to deliver precision therapeutics, but further translation will need to be enhanced with safety verification measures, life-cycle analysis, and nanotechnology and smart biosensing. As rational molecular design and regulatory alignment continue to advance, ILs have high potential to transform the following generation of drug delivery and sustainable biomedicine.

1 Introduction

Ionic liquids (ILs) represent a broad class of salts composed entirely of ions that remain liquid below 100 °C, typically under ambient or near ambient conditions. First discovered over a century ago with Walden's synthesis of ethyl-ammonium nitrate in 1914, ILs have undergone transformative development from early molten salt systems into highly tunable materials with vast structural diversity and functional potential (*e.g.*, imidazolium, phosphonium, ammonium, and amino acid derived ILs).[1,2] This history reflects a progression from simple first-generation ILs with limited stability, through more robust second-generation systems featuring weak-coordination anions, to modern task-specific and biologically oriented third and fourth-generation ILs designed for targeted applications across disciplines. The unique physicochemical properties of ILs such as negligible vapor pressure, high thermal and chemical stability, wide liquidus range, strong ionic interactions, and broad solvent polarity, originate from the inherent flexibility of ionic design. By varying cation and anion combinations, properties such as solvation ability, hydrogen-bonding capacity, viscosity, and polarity can be systematically tuned, enabling the creation of task-specific ILs tailored to defined functions in chemical processes and material applications.[3] This molecular design flexibility distinguishes ILs from conventional organic solvents and has been leveraged extensively in green chemistry, catalysis, electrochemistry, and separation technologies.

There has been an increasing recognition of the potential of ILs in biomedical and pharmaceutical contexts. Initially explored as alternative low-volatility solvents in synthesis and formulation, ILs have emerged as active agents in enhancing drug solubility, stabilizing labile biological molecules, modulating membrane permeability, and serving as functional excipients or active pharmaceutical ingredient ionic liquids (API-ILs).[4] Their innate tunability enables engineered interactions with hydrophobic drugs, proteins, and cell membranes, addressing long-standing formulation challenges such as poor aqueous solubility, instability, and limited bioavailability that constrain conventional drug delivery strategies.

[a] *Department of Bioengineering, King Fahd University of Petroleum & Minerals, 31261, Dhahran, Saudi Arabia. E-mail: shihab.uddin@kfupm.edu.sa*
[b] *Department of Chemistry, King Fahd University of Petroleum & Minerals, Dhahran 31261, Saudi Arabia*
[c] *Interdisciplinary Research Center for Refining and Advanced Chemicals, King Fahd University of Petroleum & Minerals, Dhahran 31261, Saudi Arabia*
[d] *Interdisciplinary Research Center for Bio Systems and Machines, King Fahd University of Petroleum & Minerals, 31261, Dhahran, Saudi Arabia*

More recently, the intersection of IL chemistry with nanotechnology has expanded their applications in drug delivery systems (DDS). ILs have been integrated into nanocarrier platforms including micelles, nanoemulsions, gels, and vesicles to enhance drug loading, control release kinetics, and enable responsive or targeted delivery, as highlighted in several recent analyses focusing on IL-based nanocarriers and stimuli-responsive systems.[5] These hybrid materials exploit ILs' ionic nature to facilitate self-assembly, improve colloidal stability, and tailor interaction with biological environments. Despite this progress, the translation of ILs into clinical and regulatory frameworks remains constrained by concerns over toxicity, synthesis complexity, and the influence of trace impurities on biological outcomes. Such limitations are particularly significant for imidazolium-based and long-alkyl-chain ILs, which can exhibit enhanced membrane activity and cytotoxicity if not carefully designed. Thus, ongoing research continues to emphasize the development of biocompatible ILs with favorable safety profiles and scalable synthetic routes.[6] While existing reviews have provided valuable surveys of ILs in specific biomedical domains such as solubility enhancement and membrane permeability for oral and transdermal delivery, there remains a need for an integrative and multidisciplinary perspective that treats ILs as adaptive biomaterials rather than solely as solvents or excipients. Most reviews focus on solubility and permeability enhancement in selected delivery contexts, but broader analyses incorporating IL-mediated stabilization of biologics, API-IL design, and nanocarrier formulation strategies are comparatively limited.[6]

In this review, we aim to address these gaps by presenting a comprehensive analysis of ILs across their historical development, core physicochemical principles, and evolving roles in advanced drug delivery and biopharmaceutical innovation. We discuss fundamental design strategies for biocompatible ILs, their emerging roles in nanocarrier engineering, and considerations for toxicity, pharmacokinetics, and clinical translation. By framing ILs as versatile biomaterials with multifunctional potential, this work highlights their transformative impact and future prospects in sustainable biomedical technologies.

2 Revolution of ILs as biomaterials

According to their traits and functions, ILs can be divided into four generations. MacFarlane and associates mentioned a new generation of ILs, *i.e.*, fourth generation.[7] The fundamental characteristics of ILs over generations are summarized in Fig. 1.

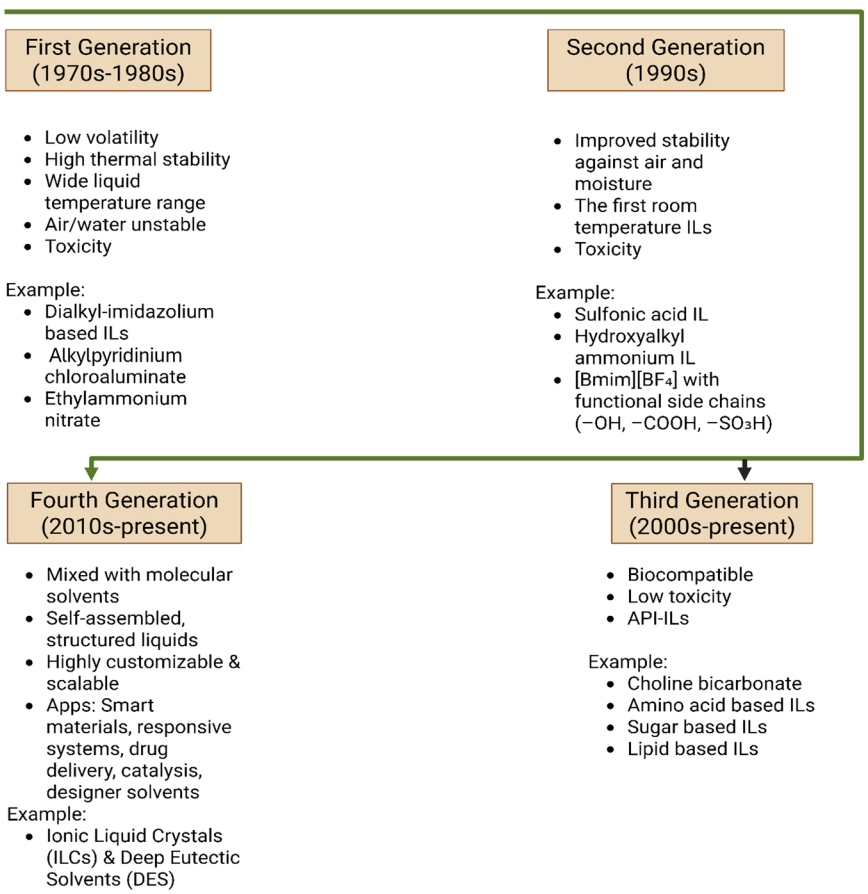

Fig. 1 The evolution of ILs across generations.

2.1 1st generation ILs

The discovery of chemicals with remarkable qualities, including minimal or extremely low volatility, thermal stability, and wide liquid temperature ranges, led to a significant expansion in the field of ILs in the 1970s and 1980s. These substances created the so-called first generation of ILs which is defined by easy-to-identify physical characteristics, such as excellent thermal stability and low vapor pressure. Anions like chloroaluminate and other metal halides, as well as cations such as alkyl pyridinium and dialkyl imidazolium derivatives, are the main constituents of these ILs.[8]

2.2 2nd generation ILs

The second generation of ILs was created in the 1990s to overcome the drawbacks of the first generation, mainly its susceptibility to moisture and air. Weakly coordinating anions like BF_4 and PF_6 were used in this new generation because they offered more stability when air and water were present. The second generation of ILs was developed to address molecules requiring specific and adjustable physical and chemical characteristics. The primary objective of this initial effort was to lessen the inert nature of ILs so that working with them under ambient circumstances was possible. The first IL of this generation was introduced in 1992.[9] These substances' cations are made with one or more functional groups that allow them to participate in specific chemical interactions and activities. They can behave like complex ligands or as efficient lubricants, for instance.

2.3 3rd generation ILs

Third-generation ILs incorporate biologically active pharmaceutical compounds with ionic structures, resulting in ILs that retain low toxicity and typical IL physical properties. These innovative ILs combine therapeutic functionality with biocompatibility.[10] The third generation comprises easily accessible and biodegradable ions, including naturally occurring carboxylic acids, amino acids, and natural bases like choline.[11] The third generation of ILs produces task-specific ILs (TSILs) with biological properties suited to targeted applications. Because of their distinct physicochemical characteristics, ILs can provide slow-release and innovative delivery methods that increase the bioactivity of APIs.[12,13] TSILs improved the usage of ILs in the pharmaceutical and biomedical industries by enabling researchers to create compounds with antifungal and antibacterial properties and employ ILs with physiologically active ions.[14]

2.4 4th generation ILs

A fourth generation of ILs has been postulated by MacFarlane and associates, who have concentrated on the new behaviors that arise when ILs are mixed with molecular liquids. These IL mixes, in contrast to conventional salt-in-solvent solutions, have characteristics that defy straightforward mixing laws because of intricate connections between ions and solvent particles. This equilibrium of interactions results in unique physicochemical characteristics that greatly expand the range and possible uses of ILs in domains such as materials research, biomedical engineering, and catalysis.[7] Fourth-generation ionic liquids are distinguished by their ability to self-assemble, blend with molecular solvents, and form highly customizable structured liquids, making them well-suited for advanced applications such as smart materials, targeted drug delivery, and designer solvents. Often represented by deep eutectic solvents (DESs), they are also valued for their simple synthesis, low toxicity, and biodegradability, offering a greener and safer alternative for pharmaceutical and biotechnological innovations.[15]

3 Fundamental properties of ILs as biomaterials

The melting point, viscosity, density, thermal stability, and polarity of ILs are all influenced by the ions' nature, which includes ion size, charge distribution, and steric hindrance. As a result, their characteristics are incredibly adjustable. The fundamental qualities of ILs are examined in this section, along with how their unique qualities add to their growing potential as biomaterials. The unique properties of ILs are shown in Fig. 2. Generally, ILs are stable and heat-resistant up to about 300 °C. They have high electrical conductivity and remain liquid over a broad temperature range, usually up to 200 °C. Nevertheless, they typically don't mix well with many common organic solvents.[16,17]

4 Synthesis, purifications, and characterization process of IL-biomaterials (IL-BMs)

To optimize IL-based biomaterials to biomedical applications, it is necessary that the synthesis process is precise, the purification process is effective, and the characterization process is detailed. Synthetic strategies such as the use of old-fashioned alkylation to the latest technology such as the use of microwaves and ultrasound enable the introduction of ILs into hydrogels, polymers and nanomaterials with desirable physicochemical and therapeutic characteristics. Purification is used to guarantee biocompatibility by eliminating impurities whereas characterization tools are used to determine the structure and performance, which are all used to help them support the application of advanced drug delivery systems.

4.1 Synthetic pathways

Traditional IL synthesis techniques are modified to produce IL-based biomaterials that improve stability, functionality, and biocompatibility for use in biomedicine. ILs can also be included in hydrogels, polymers, and other biomaterials to

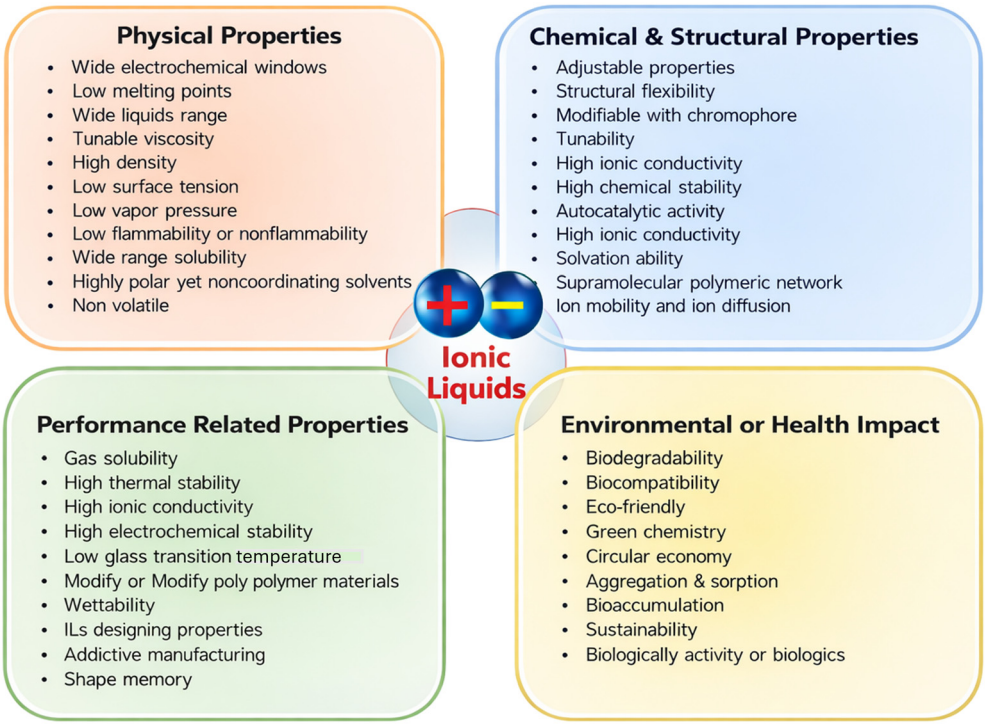

Fig. 2 The distinct characteristics of ILs.

improve their mechanical stability, ionic conductivity, and antibacterial qualities. Furthermore, by integrating ILs directly into polymer networks through procedures like *in situ* polymerization, flexible and conductive materials perfect for tissue engineering and wound healing can be produced. Table 1 lists common types of cations and anions used in the synthesis of biocompatible ILs.

In 1914, the first room-temperature ionic liquid, $[EtNH_3][NO_3]$, was found. Its melting point was 12 °C. However, it wasn't until the creation of binary ionic liquids—which are created by combining aluminum(III) chloride with 1,3-dialkylimidazolium chloride or *N*-alkylpyridinium—that there was noticeable interest in ionic liquids.[33] As shown in Fig. 3, various ways exist to create ILs. The precise technique selected will rely on the functional groups and cation–anion pairing that are sought, and these are discussed in the following sections.

4.1.1 Direct alkylation (quaternization). This process entails using an alkyl halide or other alkylating chemicals to directly alkylate a nitrogen or phosphorus base (such as imidazole, pyridine, or phosphine). The required anion can then be coupled with the cation that is created in this phase. The availability of an extensive range of reasonably priced haloalkanes and the fact that substitution reactions usually operate smoothly at low temperatures are two benefits of the alkylation process. Furthermore, it is simple to transform the halide salts created into salts with various anions. In theory, quaternization reactions are rather straightforward: the desired haloalkane is combined with the amine (or phosphine), stirred, and heated.[34] Many ionic liquids, such as those based on ammonium, imidazole, pyridinium, and phosphonium, contain alkyl cations that are usually created by combining an alkylating agent, like haloalkanes or dialkyl sulfates, with a suitable precursor, such as a nucleophile. For example, imidazole can be easily alkylated to produce alkyl imidazoles, which are essential ingredients in imidazole-based ionic liquids. Alkyl salts of pyridinium are produced by alkylating pyridine with haloalkanes. Phosphorus tetrachloride derivatives and other asymmetric halides are frequently created by making tertiary phosphines more nucleophilic, which makes it easier for them to react with haloalkanes.[35] For example, 1-butyl-3-methylimidazolium bromide ([BMIM]Br) can be synthesized by quaternization of 1-methylimidazole with 1-bromobutane under heating: 1-methylimidazole + 1-bromobutane → [BMIM]Br.

4.1.2 Anion exchange. Anion exchange is used to swap out the halide anion for other anions following quaternization. In the anion exchange reaction between metal halides and halides, Lewis acidic ILs are produced.[34] Anion exchange processes also create ILs based on Brønsted acidic and ion-exchange resin compounds.[36] Ionic liquid anion-exchange processes can be broadly classified into two types: direct treatment of halide salts with Lewis acids and anion metathesis.[34]

4.1.2.1 Lewis acid-based ionic liquids. Ionic liquids based on Lewis acids are created by mixing a Lewis acid, like boron trifluoride or aluminum chloride, with a halide salt or another source of counterions. This is a reaction that often requires stoichiometric care and the absence of moisture to form stable molten salts with unusual acidic properties. The

Table 1 List of different cations and anions for bio-IL synthesis

Cation	Anion	Properties	Applications	Ref.
Ammonium	Br^-, Tf_2N^-, NO_3^-	Biocompatibility, low toxicity	Pharmaceuticals, solvents	18
Imidazolium based cations (1-ethyl-3-methylimidazolium, 1-hexyl-3-methylimidazolium)	HSO_4^-, ethyl sulfate, bis(trifluoromethylsulfonyl) imide	High antimicrobial activity, low cytotoxicity, suitable for biomedical use	Antibacterial agent, polymeric antimicrobial coatings	19
Tetramethylguanidinium	Benzoate, salicylate, lactate, dihydrogen phosphate, nitrate, formate, acetate, propanoate, butanoate and valerate	Non-toxicity and biodegradability in studies with cell cultures and bacterial tests		20
Tetrabutylphosphonium	Biological buffers such as TAPS, MOPS, EPPS, CAPS, and BICINE	Excellent biocompatibility, maintaining optimum pH range and extraction	Enzymatic research	21
Pyrrolidinium	BF_4^-, Tf_2N^-, Cl^-, NO_3^-	Good surface activity and aggregation behavior, enhanced micelle stability	Antimicrobial agents, micellar catalysis, drug delivery	22
Thiazolium	BF_4^-, Tf_2N^-, NO_3^-, Cl^-	High polarity and thermal stability, potential for strong hydrogen bonding and π–π interactions	Biocatalysis, electrolytes, drug solubilization and delivery systems	23
Cholinium	Cl^-, acetate, bicarbonate	Low toxicity, biocompatibility	Biochemistry, drug delivery	24
Choline	Citrate	Skin permeation enhancer	Dermal delivery of hyaluronic acid without irritation	25
Cholinium	Caffeate	Antioxidant, anti-inflammatory, water soluble, biocompatible	Drug delivery for osteoarthritis, inhibition of TNF-α and IL-6 cytokines, promotes chondrocyte growth and ECM formation	26
Choline	Geranic acid (CAGE IL)	Penetrates biological membranes, facilitates drug solubility and transport	Oral and transdermal delivery of insulin, siRNA, and macromolecules	25
Choline	*Trans*-2-hexenoic acid	Biocompatible, electrostatically coats nanoparticles, reduces cytotoxicity	Drug delivery, RBC-hitchhiking, enhanced stability of linear-dendritic block copolymer nanoparticles	27
Choline	Carboxylic acids (general)	Forms stable IL-nanoassemblies, alters surface charge, enhances shelf-life, biocompatible, biodegradable, surface-active	Nanoformulation of linear and dendritic polymers	25, 27
Choline	Methotrexate, sulfasalazine, ketoprofen	Strong ionic interactions, improved solubility	API-ILs for oral and transdermal drug delivery, reduced systemic toxicity	25
Amino acid (glycine, alanine, lysine)	NO_3^-, Br^- or Cl^-	Biodegradable, tunable hydrophilicity	Biomaterials, enzymatic reactions, drug delivery	28
Amino acid ethyl esters (*e.g.*, proline ethyl ester)	Fatty acids (*e.g.*, laurate and oleate)	Amphiphilic, form micelles, biocompatible	Skin permeation enhancers, solubilization of luteolin and ibuprofen	25
Proline ethyl ester	Salicylate, ibuprofen, favipiravir	Enhanced water solubility, reduced polymorphism	API-ILs for oral delivery, increased bioavailability of crystalline drugs	25
Glycine betaine ester	Natural carboxylic acids (*e.g.*, citric and tartaric acids)	Green, biodegradable solvents	Used in formulation of API-ILs for enhanced solubility and permeability	25
Cholinium	Amino acids (alanine, proline, and methionine)	Biocompatibility, low toxicity, high solubilizing ability	Catalysis, biomedical applications, solubilization of acyclovir, paclitaxel, and other poorly soluble drugs	25
Ethanolamine	Acetate	Low toxicity, biocompatible, moderate lignin dissolution	One-pot bioethanol production, sugar yield enhancement	29
N-Methyl-2-pyrrolidone	Methotrexate (API)	Good tissue penetration, enhanced drug accumulation	Topical drug delivery of anti-cancer drugs	25
Lipid	Fatty acid anions (*e.g.*, oleate and palmitate)	Amphiphilic, compatible with membranes	Drug carriers, antimicrobial agents	30
Sugar	Glucose, fructose (*e.g.*, with acetate or Cl^-)	Renewable, hydrophilic, biocompatible	Green solvents, pharmaceutical formulations	31
$GMIM^+$ (glucosyl-methylimidazolium)	I^-	Biocompatible, moderate antimicrobial effect	Antimicrobial agents, bio-material research	32
$GOIM^+$ (glucosyl-octylimidazolium)	I^-	Strong antimicrobial activity but higher cytotoxicity	Potential antifungal applications	32
$GMIM^+$ (glucosyl-methylimidazolium)	Tf_2N^-	Strong antimicrobial effect against *Candida auris*, higher lipophilicity	Antifungal treatment research	32

Table 1 *(continued)*

Cation	Anion	Properties	Applications	Ref.
$GMIM^+$ (glucosyl-methylimidazolium)	OMs^- (methanesulfonate)	Improved biocompatibility compared to the iodide counterpart	Safer IL formulation	32

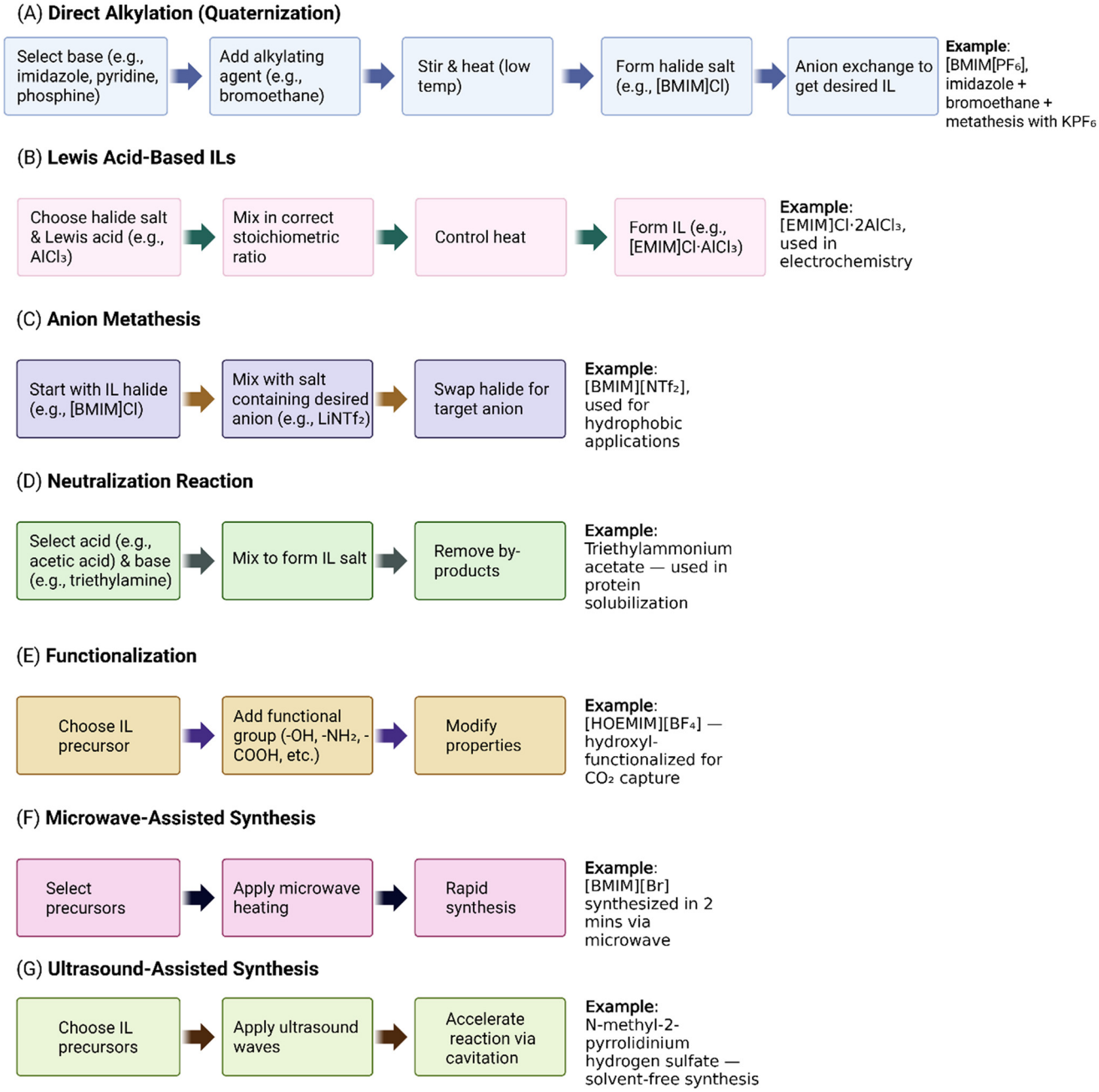

Fig. 3 Common ways for the synthesis of ILs.

flexibility, thermal stability, and catalytic properties of these ILs are of high value in terms of their use in material production, electrochemistry, and catalysis. The simplest method of making such liquids is by pure mixing of the Lewis acid and the halide salt; this forms the ionic liquid instantly upon contact. One must take care when adding one reagent to another as this reaction is usually very exothermic. Even though the salts are usually stable at high temperatures,

Table 2 Modification of functional groups of ILs to improve their properties

Modification	Functional group added/altered	Purpose/improved properties	Ref.
Alkyl chain shortening	Reduced alkyl chain length	Improves biocompatibility by reducing cytotoxicity	40
Introduction of hydroxyl groups	Addition of an –OH group to the cation/anion	Enhances solubility and hydrogen bonding with drugs	41
Carboxylic acid functionalization	Addition of –COOH to the cation structure	Increases drug-loading capacity and biocompatibility	42
Amino group incorporation	Addition of $-NH_2$ groups	Improves biocompatibility and facilitates drug conjugation	24
Aromatic substitution	Substitution with benzyl or phenyl groups	Enhances stability and drug interactions	43
Phosphate functionalization	Integration of phosphate groups	Boosts biocompatibility and compatibility with nucleic acids	44
Sulfonic acid groups	Addition of $-SO_3H$ to the cation	Enhances ionic conductivity and compatibility	45
Introduction of hydrophobic alkyl chains	Attachment of long alkyl chains to the IL's cation or anion	Increases viscosity and melting point due to stronger interaction forces	46

the ionic liquid may break down and change color if there is too much-localized heat. Chilling the mixing container (which can be difficult in a dry box) or adding one component at a time while letting the heat spread will prevent this.[36] For example, a typical Lewis acidic ionic liquid is formed by mixing 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl) with $AlCl_3$, producing $[EMIM][Al_2Cl_7]$ depending on stoichiometry: $[EMIM]Cl + AlCl_3 \rightarrow [EMIM][Al_2Cl_7]$.

4.1.2.2 Anion metathesis. Anion metathesis is a popular technique for creating ILs that involves a straightforward ion exchange process to swap the anion of a precursor ionic liquid with a desired anion. A halide or alkyl sulfate-based ionic liquid frequently reacts with a salt containing the target anion in this procedure. The reaction produces high-purity ionic liquids usually carried out in an appropriate solvent or directly in the liquid phase. A variety of anions can be added without changing the cation structure thanks to anion metathesis, which is very useful for customizing ionic liquids with unique characteristics. Several commercially available alkylammonium halides are suitable for direct use in metathesis processes.[37] For example, anion metathesis is commonly illustrated by the conversion of [BMIM]Cl to $[BMIM][PF_6]$ using potassium hexafluorophosphate: $[BMIM]Cl + KPF_6 \rightarrow [BMIM][PF_6] + KCl$.

4.1.3 Neutralization reaction. ILs can be created easily and efficiently using neutralization processes. The required cation and anion are produced when an acid and a base, such as an amine or imidazole derivative, react to form a salt. The contamination issue is avoided by using the acid–base neutralization procedure. This approach works incredibly well when using tertiary amines with halide acids or certain organic acids. The only issue is that the acids are weaker than hydrohalic acids. In this instance, hydroxide quaternary cations must be used for neutralization.[38] An example of ionic liquid formation *via* neutralization is the reaction of 1-ethyl-3-methylimidazolium hydroxide ([EMIM]OH) with acetic acid, yielding [EMIM][OAc]: $[EMIM]OH + CH_3COOH \rightarrow [EMIM][OAc] + H_2O$.

4.1.4 Functionalization. Cation or anion functional groups can be added to ILs to improve their physicochemical characteristics, such as conductivity, hydrophobicity, or catalytic activity. For instance, hydroxyl, alkoxy, or amino groups can be added to imidazolium-based ILs for different uses, such as CO_2 capture. Table 2 summarizes various functional group modifications in ILs. This method makes TSILs possible, broadening the variety of ILs and frequently accomplishing this by straightforward synthetic pathways. However, variables like anion/cation pairing, alkyl chain length, and the functional group type affect these alterations' effectiveness. Even though functionalized ILs appear promising, further study is required to fully understand their potential, especially when combined with molecular solvents like water.[39] Functionalized ionic liquids can be synthesized by introducing hydroxyl groups into the cation structure, such as the preparation of 1-(2-hydroxyethyl)-3-methylimidazolium chloride *via* alkylation of 1-methylimidazole with 2-chloroethanol: 1-methylimidazole + 2-chloroethanol → [HO-EMIM]Cl.

4.1.5 Microwave assisted synthesis. The process of microwave-assisted synthesis uses microwave radiation to quickly and evenly heat processes, which frequently speeds up chemical reactions and increases yields. By delivering energy directly to the molecules, microwaves speed up the reaction rate in comparison with traditional heating. Compared to conventional synthesis techniques, microwave irradiation procedures have several benefits, such as quicker reaction times, more selectivity, and environmentally favorable features.[36] This method has been used to synthesize different ILs over the years. Microwave irradiation was used to create solvent-free 1-alkyl-3-methylimidazolium halide (chloride and bromide) and dialkyl-3-methylimidazolium dihalide ILs with yields exceeding 70% in less than two minutes.[47] Similarly, a variety of ILs based on imidazolium and pyridinium cations were made using solvent-free microwave irradiation.[48] Additionally, ILs based on chiral and amino acids were produced in a microwave and used for a variety of purposes.[49] For example, under microwave irradiation, 1-butyl-3-methylimidazolium bromide ([BMIM]Br) can be synthesized solvent-free by reacting 1-methylimidazole with 1-bromobutane, achieving yields above 70% within minutes as follows: 1-methylimidazole + 1-bromobutane → [BMIM]Br.

4.1.6 Ultrasound assisted synthesis. ILs are synthesized *via* ultrasound-assisted synthesis, which uses high-frequency sound waves to speed up chemical reactions. The ultrasonic vibrations increase reaction rates by producing localized high temperatures and pressures by acoustic cavitation, which produces and collapses bubbles. This method is an environmentally friendly synthesis technique that produces large quantities of products without the need for solvents. Some ionic liquids synthesized using this method include 1-alkyl-3-methylimidazolium-based cations paired with various anions such as halides (Cl, Br, and I), BF_4, PF_6, CF_3SO_3, and BPh_4.[50] Additionally, an *N*-methyl-2-pyrrolidinium hydrogen sulfate-based ionic liquid was produced with favorable yields using the ultrasound-assisted technique without the use of a solvent.[51] An ultrasound-assisted approach has been used to synthesize 1-alkyl-3-methylimidazolium tetrafluoroborate ([AMIM][BF_4]) by reacting the corresponding halide IL with $NaBF_4$ under ultrasonic irradiation: [AMIM]Cl + $NaBF_4$ → [AMIM][BF_4] + NaCl. Table 3 lists several IL synthesis techniques and how each affects the improvement of important properties.

4.2 Purification of IL-BMs

ILs must be purified to guarantee their high purity and appropriateness for a range of uses, particularly in areas like electrochemistry and catalysis. Impurities like water, leftover solvents, or synthesis by-products are frequently present in ILs and substantially impact their characteristics and functionality. Various ways can be used to purify ILs as illustrated in Fig. 4. These methods usually include molecular sieves, vacuum drying, solvent washing, distillation, recrystallization, nitrogen gas sweeping, and ion exchange. Water and volatile contaminants are eliminated by vacuum drying, whereas molecular sieves efficiently adsorb moisture and tiny organic pollutants. Soluble impurities can be removed by solvent washing, and undesired anions or cations can be replaced by ion-exchange methods to improve purity. Distillation and recrystallization are used to separate or purify the IL by eliminating undesirable substances or leftover solvents. Frequently used with modest heating, nitrogen gas sweeping quickly eliminates volatile contaminants such as solvents and water. The types of impurities and the purity standards for the IL's intended use are considered when selecting these methods. Ionic liquids cannot be purified by distillation because of their low vapor pressure. This is countered by the fact that distillation can theoretically remove any volatile contaminant from an ionic liquid.[55]

4.3 Characterization techniques

Understanding the versatile qualities of ILs, such as their ionic conductivity, viscosity, and thermal stability, which make them appropriate for use in energy storage, green chemistry, and drug administration, requires characterization. A range of analytical techniques are employed to measure their molecular interactions, structure, and purity (*e.g.* spectroscopic (*e.g.* NMR, IR, and Raman), thermal (*e.g.* DSC and TGA), electrochemical, and microscopic (*e.g.* SEM, TEM, and AFM)). Even though NMR spectroscopy and X-ray crystallography can confirm the IL structure, they do not ensure purity since most impurities are non-measurable. The features of ILs are further investigated by mass spectrometry (MS), FTIR to identify functional groups, and XRD and XPS to study the surface and structure of ILs. With these methods, scientists can adjust ILs to suit certain purposes, which makes them more effective in the fields of science and industry.

A representative example of how FTIR and NMR are used to confirm ionic liquid formation is provided by Mobin *et al.*,[56] who reported the synthesis and characterization of cholinium

Table 3 The synthesis of ILs for improved properties

Synthesis method	Description	Impact on IL properties	Ref.
Neutralization of amines	Mixing tertiary amines with organic acids or acid esters	Easy synthesis, allows for control over ion pairing and low melting point	49
Quaternization of amines	Reacting tertiary amines with alkyl halides followed by anion exchange	Enables preparation of hydrophobic or hydrophilic ILs	49
Functional group modification	Adding functional groups to IL structures, such as carboxyl or hydroxyl	Changes the melting temperature, viscosity, and polarity	52
Solvent-free synthesis	Direct alkylation without solvents to minimize impurities like halides and enhance product purity	Produces high-purity ILs with less adverse effect on the environment and enhanced catalytic activity	10
Chiral ionic liquid synthesis	Employs chiral precursors (*e.g.*, amino acids and sugars) for creating enantiomerically enriched ILs	Facilitates asymmetric catalysis and green chemistry applications	10
Magnetic ionic liquid–nanoparticle integration	Disperses magnetic nanoparticles (*e.g.*, Fe_3O_4) in non-magnetic RTILs	Stabilizes nanoparticles for enhanced magnetic fluid and catalytic applications	53
Microwave irradiation	A quick synthesis technique that frequently doesn't use solvents and uses microwave energy	Produces high atom efficiency, improved selectivity, and maximum yields within short reaction times	47
Ultrasound-assisted	Increases reaction rates by using high-frequency sound waves, especially at the interface between immiscible liquid layers	Increases the efficiency of material transformation, improves reaction rates, and shortens response times	54

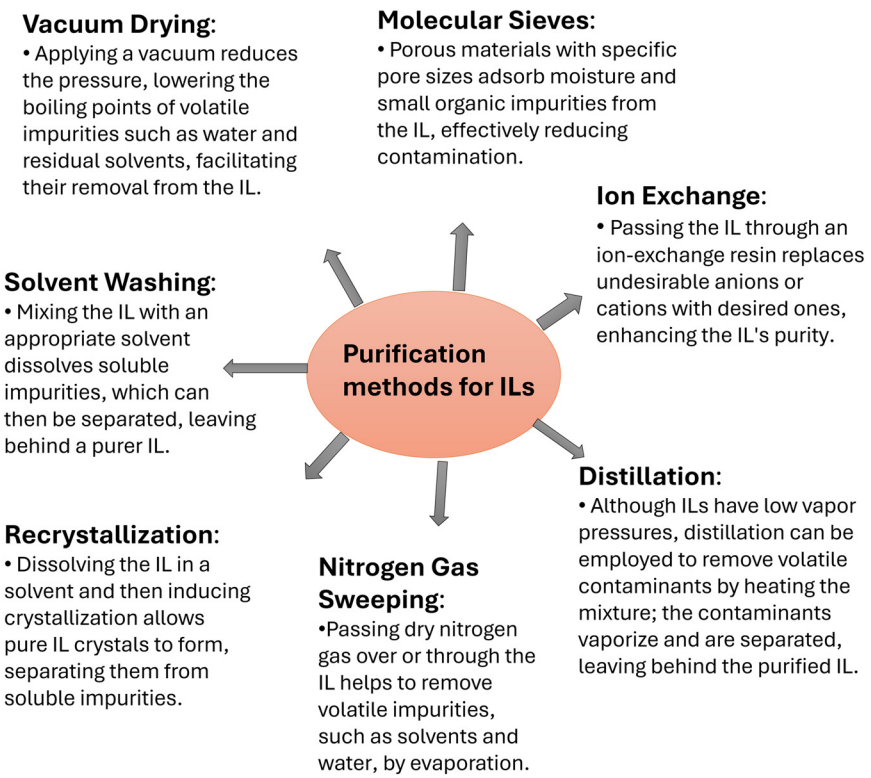

Fig. 4 General ways used in the purification of ILs.

acetate (ChA) and cholinium formate (ChF). In their FTIR (KBr) spectra, both ILs showed bands consistent with ionic pairing between the cholinium cation and the carboxylate anion. For cholinium acetate, characteristic absorption bands were observed at 3436 cm^{-1} (assigned to the N–H/O–H region), 1086 cm^{-1} (C–O/C═O-related vibration as reported by the authors), and a prominent carboxylate band at 1558 cm^{-1} (COO^-). Similarly, cholinium formate exhibited FTIR bands at 3416 cm^{-1}, 1096 cm^{-1}, and 1597 cm^{-1} (COO^-), supporting formation of a carboxylate-containing ionic liquid rather than a simple physical mixture.

The same work illustrates how NMR provides complementary structural confirmation. In ^{13}C NMR (400 MHz, DMSO-d_6), both ILs displayed a carbonyl resonance at δ 176.5 ppm, consistent with a carboxylate/carbonyl environment, alongside signals attributable to the cholinium framework. For cholinium acetate, resonances were reported at δ 72.6, 65.3, 55.7 (3× CH_3), and 24.4 ppm (CH_3). For cholinium formate, peaks were reported at δ 67.7, 65.3, and 55.7 ppm (3× CH_3) in addition to the carbonyl signal. In ^1H NMR (400 MHz, DMSO-d_6), cholinium acetate showed signals at δ 4.18 (OH), 3.81, 3.40, 3.09 (9H, CH_3) and 2.48 ppm, while cholinium formate showed signals at δ 8.43, 4.06 (OH), 3.82, 3.40, and 3.09 ppm (9H, CH_3). Taken together, the presence of the COO^- FTIR bands and the expected $^1H/^{13}C$ NMR chemical shifts provides a clear example of how FTIR confirms functional group conversion/ionic pairing and NMR verifies structural integrity and composition, which are essential for validating IL synthesis in both materials and biomedical applications.[56]

5 Role of ILs in drug delivery systems (DDS)

Due to the enormous number of possible cation–anion interactions, ILs provide numerous opportunities towards effective drug formulations. Since ILs have different physicochemical properties, *e.g.* low level of volatility, biocompatibility, and adjustable solubility, they are nowadays very promising and versatile products in drug delivery processes. The solubility, stability, and bioavailability of various medicinal compounds that can be useful in drug delivery can be enhanced by IL engineering, unlike traditional solvents. Biocompatible ILs have also shown potential in solving the issues of poor water-solubility of medications and controlled drug delivery. These ILs are also designed to reduce toxicity and maximize the therapeutic performance. Also, ILs may be adapted to make contact with biological membranes, which would help reduce adverse effects and allow the delivery of medication in a targeted manner. Fig. 5 illustrates the numerous functions ILs perform in DDS that overcome such challenges as solubility, targeted delivery, and sustainability.

5.1 Mechanistic role of ionic liquids in nano drug delivery systems

Beyond their conventional role as alternative solvents or formulation stabilizers, ionic liquids (ILs) exert fundamental mechanistic control over the formation, stability, and

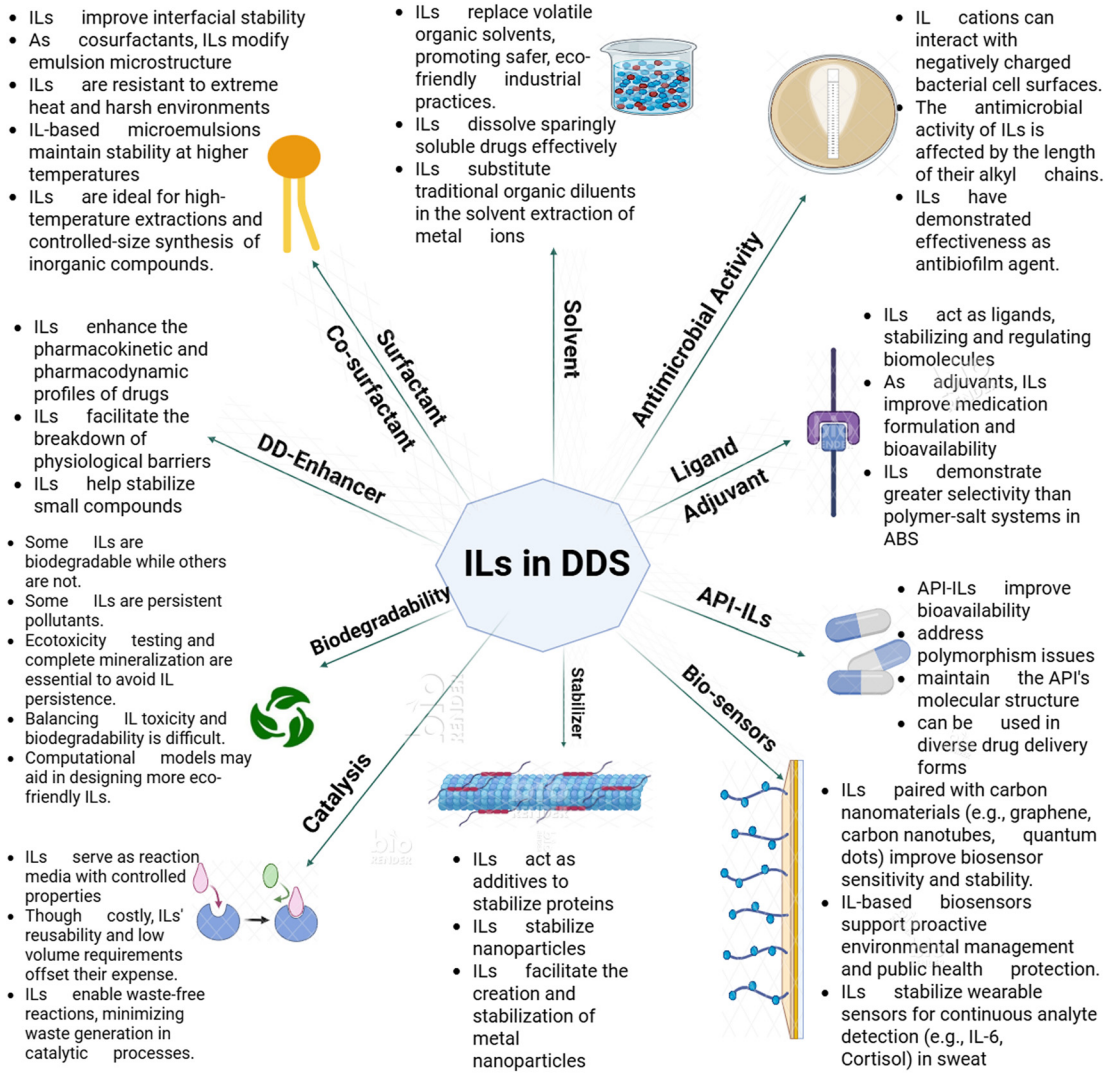

Fig. 5 The role of ILs in drug delivery systems.

biological fate of nano drug delivery systems (nano-DDS). These effects arise from a unique combination of ionic interactions, nanostructuring behavior, and interfacial activity, which distinguish ILs from traditional molecular excipients.

Ionic interactions and nanostructure formation. At the molecular level, ILs engage in strong and tunable electrostatic interactions, hydrogen bonding, and π–π stacking, enabling them to organize into nanoscale domains even in the absence of conventional surfactants. Many ILs exhibit intrinsic nanosegregation, forming polar and nonpolar domains whose size and dynamics depend on the cation–anion structure, alkyl chain length, and functionalization. This intrinsic nanostructuring directly influences drug encapsulation by stabilizing hydrophobic drugs within nonpolar domains while maintaining overall colloidal stability in aqueous environments.[15] In nanocarrier systems, ILs can therefore act as structural directors, governing particle size, internal organization, and drug distribution. For example, surface-active ionic liquids (SAILs) self-assemble into micelles or vesicle-like architectures that encapsulate therapeutics through cooperative electrostatic and hydrophobic forces, often reducing critical micelle concentration and enhancing loading efficiency compared to classical surfactants.[4,53]

Interfacial stabilization and colloidal integrity. ILs also exert strong control at interfaces, a critical determinant of nano-DDS stability. When incorporated into nanoparticles, emulsions, or lipid-based carriers, ILs modulate interfacial tension, surface charge, and hydration layers, leading to enhanced resistance against aggregation, Ostwald ripening, and premature drug leakage. Unlike neutral stabilizers, ILs generate persistent electrostatic repulsion and structured solvation shells that remain effective even under physiological ionic strength and temperature variations.[39,57,58] Furthermore, ILs can replace or complement traditional surfactants, enabling lower excipient loadings and reduced toxicity while preserving nano-DDS

integrity. This mechanism is particularly relevant in long-circulating systems, where IL-mediated surface stabilization prolongs systemic residence time and improves biodistribution.

Membrane interactions and biological fate. A defining mechanistic feature of ILs in nano-DDS is their ability to modulate biological interfaces, especially cellular membranes. Amphiphilic and hydrogen-bond-rich ILs transiently interact with lipid bilayers, altering membrane fluidity, tight-junction permeability, and endocytic pathways without permanent membrane disruption when rationally designed. This property underlies the enhanced cellular uptake and transmucosal transport observed in IL-functionalized nanocarriers, including improved penetration across skin, mucosa, and the blood–brain barrier.[59,60] Importantly, the IL structure dictates biological fate: short-chain, cholinium- or amino-acid-based ILs favor reversible interactions and rapid clearance, whereas long-chain imidazolium ILs may induce membrane stress and cytotoxicity. Thus, structure–activity relationships (SARs) at the ionic and interfacial levels are central to determining circulation time, intracellular trafficking, and biocompatibility of IL-enabled nano-DDS.[61]

Beyond solvents: ILs as functional nano-engineering elements. Collectively, these mechanisms position ILs as active nano-engineering elements rather than passive formulation components. By simultaneously controlling nanostructure formation, interfacial stability, and biological interactions, ILs enable the rational design of multifunctional nano-DDS with enhanced drug loading, controlled release, and programmable biological responses. This mechanistic versatility explains why IL-based systems outperform traditional solvent- or polymer-based nanocarriers in complex biomedical environments and highlights their emerging role as foundational materials in next-generation drug delivery platforms.[62,63] Fig. 6 illustrates the mechanistic contributions of ionic liquids to nano drug delivery systems, including nanostructuring, interfacial stabilization, and membrane-mediated uptake.

5.2 ILs as APIs/bioactivity

Active pharmaceutical ingredient ionic liquids (API-ILs) have become a flexible platform through which the long-standing drug development challenges could be overcome. This approach could be useful in addressing polymorphism, enhancing solubility, increasing permeability, and controlling thermal stability, which are especially important with poorly soluble drugs, and has been demonstrated to enable synergistic effects, allowing multi-functional pharmacological responses to be achieved with API-ILs. Such changes are especially beneficial in poorly soluble drugs, in which API-IL conversion has been demonstrated to change solubility by several thousand-fold and

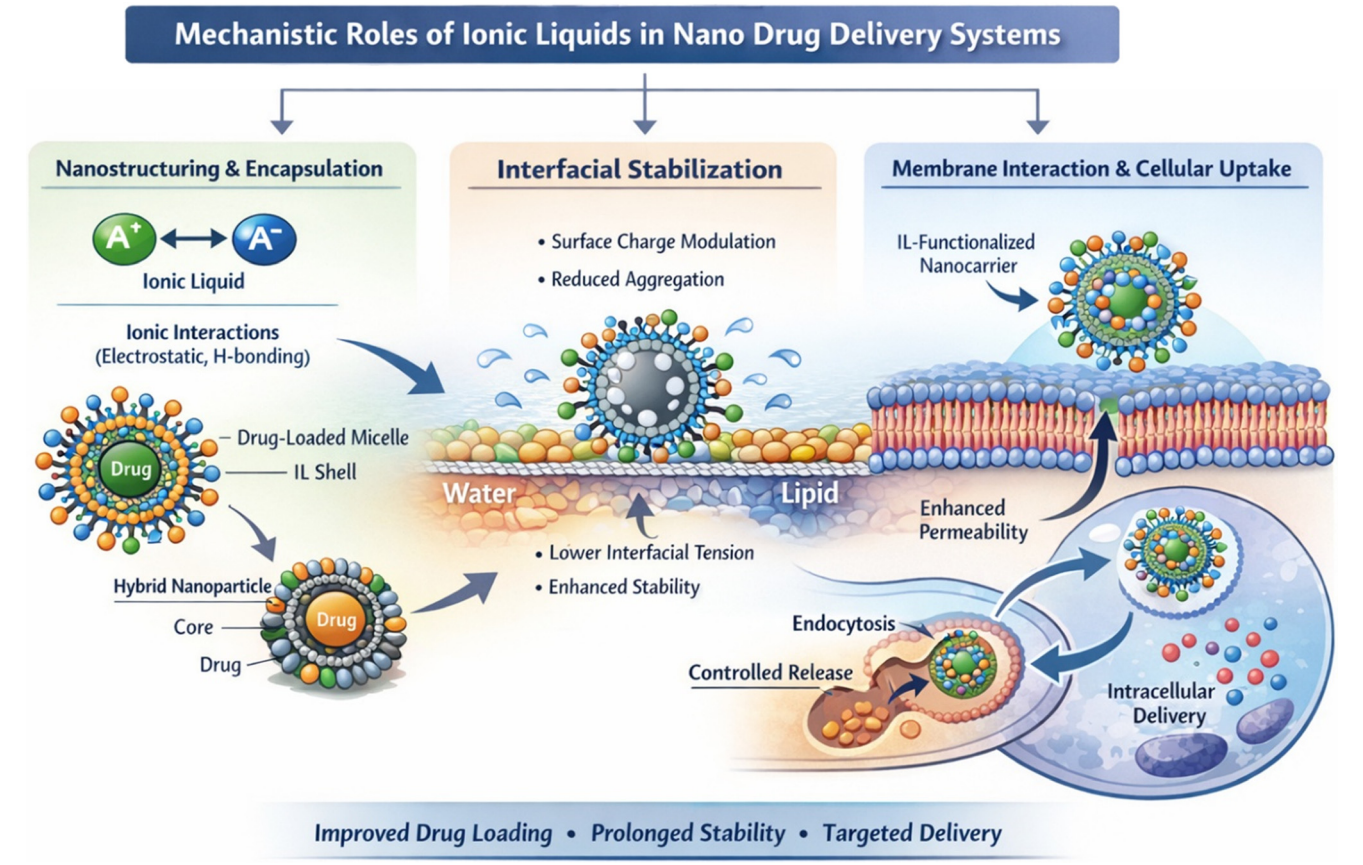

Fig. 6 Mechanistic roles of ionic liquids in nanocarrier design, interfacial stabilization, and membrane interactions for drug delivery.

enhance bioavailability and reduce systemic toxicity. Moreover, API-ILs offer opportunities for controlled release, targeted delivery, and improved tissue penetration, making them valuable for personalized and precision medicine applications.[64] Innovative designs such as dual API-ILs, where both the cation and anion exhibit therapeutic activity, allow for synergistic effects, enabling multi-functional pharmacological responses. Oligomeric API-ILs have also been utilized to remove crystalline phases to enable stable, liquid-state formulations suitable as a topical or transdermal drug delivery system with minimal irritation and increased patient adherence. Recent developments have shown the use of API-ILs in a wide variety of formulations: emulsions, patches, nanoparticles, and gels. These systems not only increase drug performance but also support other administration routes, such as non-invasive transdermal or buccal delivery, with less irritation and better patient compliance.[65]

This technology has entered clinical development translations by pharmaceutical companies. One example is the MEDRx system which has produced API-IL-based transdermal patches to treat pain and spasticity that demonstrate better bioavailability than conventional mixtures. The IL based on lidocaine had superior skin absorption and sustained release and better pharmacokinetic properties in comparison with the standard form. However, there are still obstacles in the form of complexity of synthesis, toxicity, and stringent purification procedures. Even minute impurities can be of great consequence to bioactivity, and it is the soundness of analytical control along with biocompatibility studies that will make API-ILs a key pillar in future drug formulation.[66] With continued refinement, API-ILs stand poised to become a cornerstone in next-generation drug formulation.

5.3 ILs in nanocarrier developments

Among the most important benefits of ILs in the formation of nanocarriers is the fact that they enhance the bioavailability and solubility of the drug. Many insoluble drugs can be dissolved in IL-based systems, thus improving their therapeutic efficacy. An example is the successful adoption of ILs into polymeric and lipid-based nanoparticles to enable the entrapment and targeted release of hydrophobic drugs. This is especially useful in anticancer and antiviral drugs which are typically poorly soluble and have poor absorption into the systemic circulation. Also, ILs are important in stabilizing nanocarriers to avoid aggregation and degradation. The high electrostatic forces contribute to the structural integrity of nanocarriers, which results in longer circulation and enhanced drug retention of the therapeutic payload to the desired site of action with minimal off-target effects.[67] The targeted drug delivery systems require this stability so that the therapeutic payload can be delivered to the desired site of action with little off-target effects.

The other possible application of ILs in development of nanocarriers is that they enhance cell uptake. ILs can enhance the drug movement across biological barriers, such as the blood–brain barrier (BBB), since they can adjust the membrane permeability. They are applicable to neuropharmaceutical delivery and IL-based nanocarriers have been demonstrated to be more penetrative and be retained in brain tissues.[5] In addition, ILs have also been used to design responsive nanocarriers, which can release their cargo in response to a certain stimulus, *e.g.*, pH, temperature or enzymatic activity. Such intelligent drug delivery systems enable accurate regulation of the drug release kinetics, which decreases systemic toxicity and improves therapeutic outcomes.[68]

Moreover, ILs, especially surface-active and magnetic ILs, have also become promising nanocarrier systems in drug delivery because of their peculiar physicochemical characteristics and high design flexibility. SAILs are surface-active ionic liquids which have long hydrophobic alkyl chains and are amphiphilic, meaning that they are capable of self-assembly to form nanoscale structures, including micelles, vesicles, and microemulsions. These assemblies enable easy encapsulation and release of a large variety of therapeutic agents such as hydrophilic, hydrophobic, and amphipathic drugs. As an example, magnetic SAILs based on valine, such as $[ValC_{16}][FeCl_4]$, embedded in gelatin hydrogels showed high drug loading efficiencies to 5-fluorouracil and ornidazole, and allowed the magnetic control of release and the stable interaction with biomolecules such as DNA.[69] Rational design of SAILs to meet the individual drug characteristics is also supported by computational methods such as molecular dynamics simulation and COSMO-RS, which makes IL-based nanocarriers a powerful and efficient system to be used as a drug delivery system in practice.[52] The biocompatibility of building blocks, including choline, amino acids, and fatty acids, also eliminates the issue of toxicity, which makes IL-based nanocarriers a universal and efficient technology to be used as a drug delivery system. To graphically sum up the incorporation of ILs in various nanocarrier systems, Fig. 7 shows a conceptual map which highlights the major uses and the benefits they will have in drug delivery.

With these benefits, there are still difficulties in the extensive use of ILs in the development of nanocarriers. The problem of cytotoxicity, biodegradability, and regulatory approval should be resolved to make them safe and efficient in terms of their use in medicine. Further studies are to be performed on the rational design of biocompatible ILs and their interactions with biological systems to utilize them to the maximum in drug delivery technologies.[70]

5.4 ILs in bio-sensing

ILs have become revolutionary elements in biosensor technology because of their extraordinary electrochemical stability, adjustability and biocompatibility. Their ability to

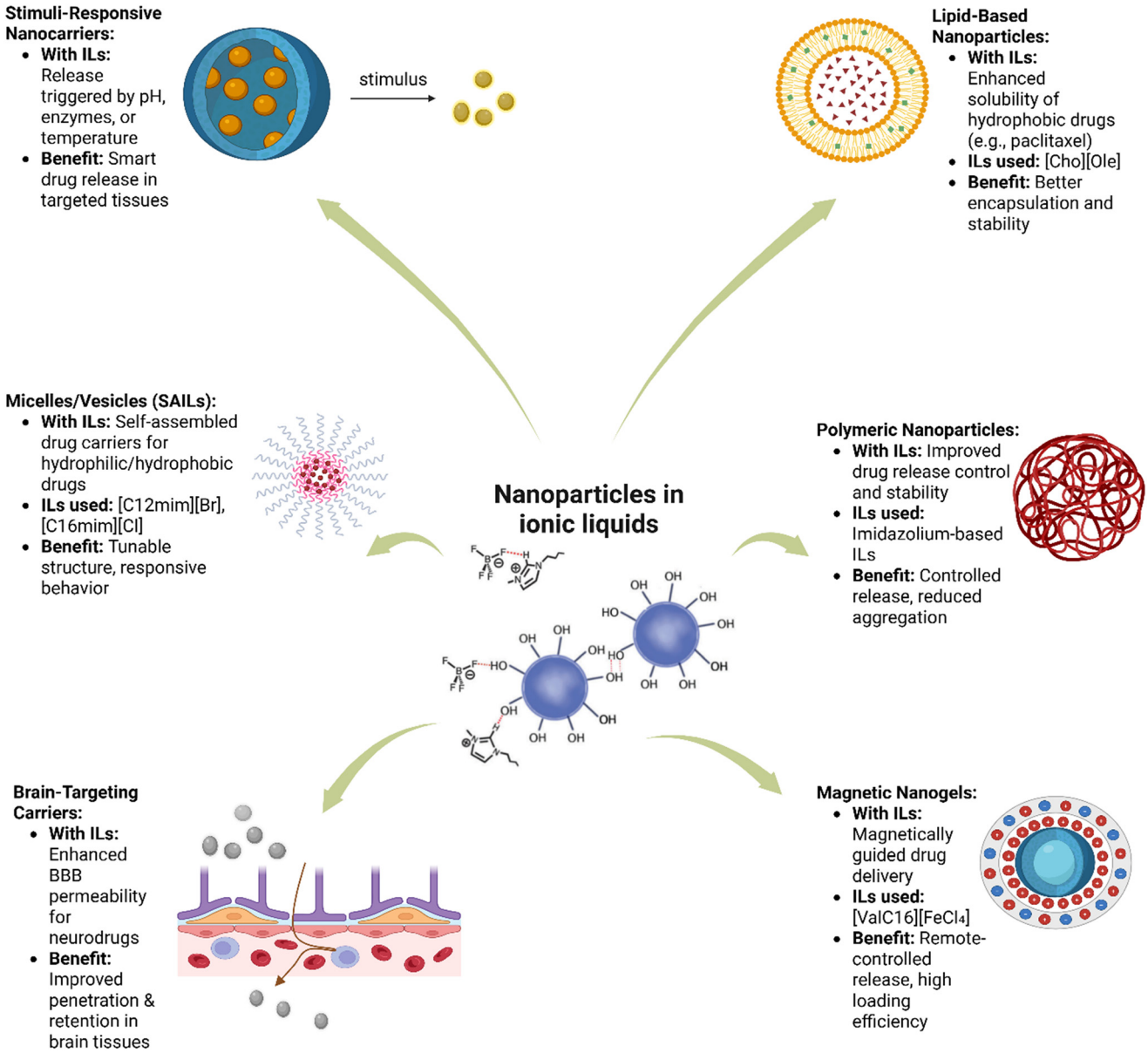

Fig. 7 Schematic representation of various nanocarrier systems enhanced by ionic liquids.

act as solvent media, immobilization matrices and structure enhancers allow them to be used as high-performance detection platforms with a broad repertoire of biological targets. ILs also enable the direct electron transfer of redox-active biomolecules including hemoglobin and horseradish peroxidase, which make third-generation biosensors have higher sensitivity, selectivity and stability of operation. As an illustration, enzymes have been immobilized on composites such as ILpolypyrrole-gold (ILPpyAu) to detect hydrogen peroxide and cholesterol electrochemically with low detection limits and improved electrocatalytic performance.[71]

In addition to enzymatic detection, ILs have made it possible to develop molecularly imprinted sensors and aptamer-based devices, leading to the use of ILs in nonenzymatic detection of proteins, neurotransmitters, and environmental toxins. ILs have also been incorporated in carbon nanotubes and graphene electrodes to create sensors with high sensitivity to dopamine, glucose, and trichloroacetic acid by providing a superior microenvironment in which the biomolecules can interact with the electrodes and transfer electrons. The application of ILs in flexible and wearable biosensors has further enhanced their use as they enable continuous, non-invasive health monitoring on sweat-based sensors. As an example, wearable CRP biosensors with IL-enhanced graphene and gold nanoparticle composites have demonstrated real-time monitoring of inflammation in the context of chronic disease.[72] IL-based electrochemical impedance spectroscopy (EIS) biosensors represent an effective format of point-of-care diagnostics. These platforms take advantage of the capability of ILs to create stable, conductive layers on electrodes, which allow the immobilization of

biomolecules and amplification of signals. These configurations have particularly been useful in cytokine detection where trace sensitivity is required. IL-enabled biosensors are being developed to be integrated with microfluidic systems, optical transducers, and smartphone interfaces, which is why they are selected as important in early disease diagnosis, environmental monitoring, and food safety evaluation.[72]

5.5 ILs as catalysts

Unlike conventional solvents, ILs can facilitate waste-free reactions with minimal by-product formation, aligning with green chemistry principles. They are also perfect catalysts to stabilize transition states and modify reaction environments, which is why they are the best to catalyze sensitive reactions during the production of pharmaceutical compounds. An example is the use of ILs in the production of bioactive heterocycles, such as quinazolines and quinazolinones, by multicomponent and tandem reactions. These molecules are important scaffolds in a range of anticancer and antibacterial drugs.[73,74] In addition, IL-based catalysts have facilitated high-purity bioactive product formation under mild conditions through a range of Mannich-type and aza-Friedel Crafts reactions, which are critical in therapeutic development.[75,76]

ILs also play a crucial role in improving drug formulation through their use in synthesizing functional polymeric drug carriers. For example, amphiphilic ILs were used to catalyze the green synthesis of isosorbide-based optical polymers with enhanced biocompatibility, mechanical flexibility, and transparency, properties essential for biomedical devices like intraocular lenses.[77] Additionally, tetrabutyl methyl carbonate ILs have shown superior catalytic efficiency compared to traditional catalysts in synthesizing non-isocyanate polyurethanes *via* ring-opening polymerization, with potential biomedical coating applications due to their safety and reusability.[78] Other than in the synthesis of polymers, ILs have been shown to catalyze the conversion of bio-derived feedstocks into useful pharmaceutical intermediates. Recently, Brønsted acidic ILs have been used as catalysts in esterification and transesterification reactions in the production of lipid-based drugs and prodrugs.[79] Moreover, dual-functional ILs combining acidic and nucleophilic sites have enabled regioselective glycosylation and sulfonation reactions, which are pivotal for the construction of antiviral and anti-inflammatory drug candidates. These advances highlight ILs not only as green alternatives to conventional catalysts but also as essential tools for precision synthesis in modern pharmaceutical innovation.

5.6 ILs as drug delivery (DD)-enhancers

ILs are increasingly recognized for their role in enhancing drug delivery by improving drug permeability, stability, and bioavailability. It is possible to design ILs rationally to be tunable with respect to their physicochemical properties due to which they can be used as effective chemical permeation enhancers across biological barriers like skin and mucosa. Choline-based ILs, especially choline geranate (CAGE), have been shown to have an impressive capacity to increase the solubility and permeation of various therapeutics into cells as well as the extracellular space, with transcellular and paracellular transport being greatly enhanced.[80] These are small molecules, such as diltiazem and cefadroxil, and macromolecules, such as insulin and ovalbumin, whose delivery was significantly enhanced through IL-mediated skin and mucosal delivery.[80,81] The amphiphilic properties and high potential hydrogen bonding of ILs enable them to be partitioned in lipid layers and to regulate drug–membrane interactions, which leads to high drug absorption and release. Also, ILs prepared using biocompatible compounds like amino acids and fatty acids can be utilized to both improve drug retention and mechanical properties of delivery systems.[81] Their synergistic interaction with other chemical penetration enhancers has been demonstrated to increase dermal transport of insoluble drugs such as acyclovir and celecoxib by up to five-fold.[82] These results justify the growing application of ILs as multipurpose drug enhancers that can allow effective and non-invasive methods of delivering drugs such as small molecule drugs and biologics. Fig. 8 shows how ILs have been incorporated at different points of drug delivery using nanocarriers with a particular focus on the use of ILs to enhance drug solubility, biological permeability, targeting of cells, and controlled release into the cell.

5.7 ILs as solvents

ILs have emerged as transformative solvents for enhancing the solubility and delivery of poorly water-soluble drugs, particularly those in BCS class II. Among the ILs, dicationic ionic liquids (DcILs) have shown superior performance over their monocationic counterparts (McILs), achieving 30–35-fold improvements in the solubility of drugs like ibuprofen and ketoprofen. DcILs, especially those with ammonium cations and carboxylic or *N*-acetyl amino acid-derived anions, exhibit high biocompatibility and low cytotoxicity toward L929 fibroblast cells, particularly when short or ether-based linkers are used between the cationic heads. These enhancements are driven by strong hydrogen bonding and electrostatic interactions between ILs and drugs, as confirmed by 2D NOESY NMR studies.[83] Mechanistic information is further given by computational methods, such as molecular dynamics simulations and density functional theory (DFT). These studies indicate that the ability of drugs to be solubilized in ILs is a combination of the acidity and basicity of the elements of ILs. In the case of aspirin, which has strong hydrogen-bond donating groups, ILs with basic anions such as acetate ($[OAc]^-$) provide covalent-like hydrogen bonding to cause solubilization. Conversely, such drugs as etomidate that do not contain any hydrogen-bond donors depend more on electrostatic interactions with cations and are better supported by ILs with weakly interacting anions such as Tf_2N^-. π–π stacking between aromatic cations and etomidate contributes to its solubility, albeit to a lesser extent.[84]

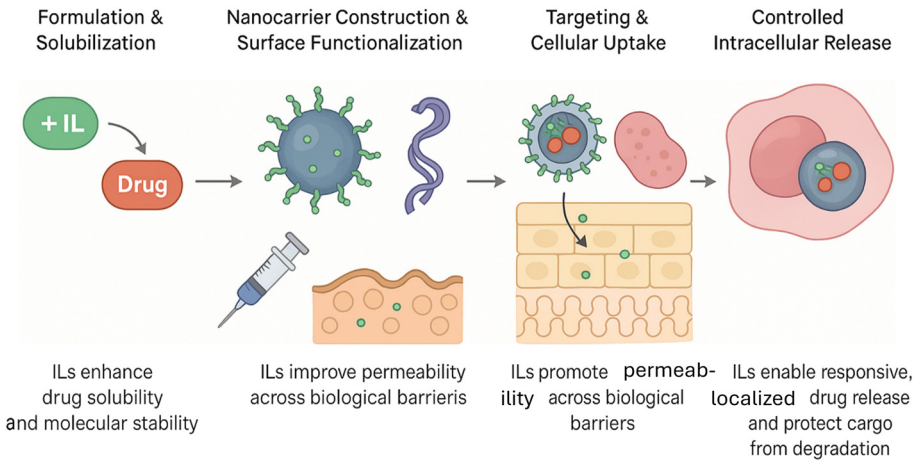

Fig. 8 Role of ILs in enhancing nanocarrier-based drug delivery.

Beyond classical drugs, ILs have gained traction for their ability to fine-tune drug partitioning behavior and optimize formulation design. Their tunable ionic architecture and polarity allow modulation of drug lipophilicity (log *P*), enhancing oral bioavailability and improving compatibility with hydrophilic carriers. ILs such as [C_4mim][OAc] and CAGE have already been successfully applied in marketed formulations and biologic delivery platforms, where they increase permeability, stabilize therapeutics, and eliminate cold-chain requirements.[85] Additionally, ILs offer control over polymorphism and crystallization, and serve as green solvents with low volatility and favorable biodegradability, supporting their use as safe, sustainable alternatives in pharmaceutical processing.[86,87]

5.8 ILs as stabilizers, ligands and adjuvants

ILs have shown exceptional promise as multifunctional agents in pharmaceutical formulations by acting as stabilizers and performance enhancers. As stabilizing media, ILs, particularly those based on imidazolium and amino acids, significantly improve the stability of metal nanoparticles (MNPs) like gold nanoparticles (AuNPs), which are widely used in drug delivery and diagnostics. These ILs penetrate the solvation layer and increase electrostatic repulsion, preventing aggregation and extending shelf life without requiring additional surfactants or capping agents. The structural attributes of the ILs, especially the imidazolium ring and specific anions like leucinate, play a dominant role in maintaining nanoparticle dispersion and functionality under physiological conditions.[88] In addition to nanoparticle stabilization, ILs are increasingly recognized for their ability to maintain the structural fidelity of therapeutic proteins. Choline-based ILs have shown remarkable potential in stabilizing proteins like insulin and monoclonal antibodies (mAbs) by enhancing thermal stability and inhibiting aggregation. For instance, choline valinate elevated insulin's melting temperature by 13 °C, while choline dihydrogen phosphate increased trastuzumab's thermal stability by over 21 °C (100). However, these effects are concentration-dependent, and while colloidal stability often improves with higher IL concentrations, conformational integrity can be compromised, underscoring the importance of optimal IL selection and dosage. ILs also enhance stability in protein-based formulations through hydration-mediated non-covalent interactions. Choline-based ILs, particularly [Cho][OAc], demonstrate superior capability in stabilizing insulin dimers *via* strong hydrogen bonding and electrostatic interactions.[89]

ILs also function as molecular regulators that modulate interactions with metal centers and biological macromolecules. Their tunable ionic structure enables selective binding and stabilization of biomolecules, optimizing enzymatic activity and preserving drug potency during formulation and delivery.[86] Recent studies have demonstrated that triazolium-based ILs, such as 1-pentyl and 1-hexyl-1,2,4-triazolium trifluoroacetates, can effectively stabilize bovine serum albumin (BSA) by forming strong hydrophobic interactions and inclusion complexes with β-cyclodextrin. These ILs protect proteins from denaturation, even in the presence of strong chemical denaturants like urea, making them ideal candidates for bioformulations that demand structural integrity of therapeutic proteins.[90]

IL-based nanocarriers functionalized with therapeutic or targeting moieties offer improved drug release profiles, biocompatibility, and intracellular uptake when compared to conventional delivery systems.[5] Additionally, their ability to adapt physicochemical properties makes them ideal for designing stimuli-responsive drug platforms and biosensors.[86] Additionally, ILs serve as separation enhancers in bioprocessing, particularly in aqueous biphasic systems (ABS), where they influence protein partitioning through specific hydrophobic and electrostatic interactions. Chloride-based ILs are useful in polymer–polymer ABS to regulate phase behavior to selectively isolate proteins including BSA, IgG and Cyt C based on the IL type and concentration. Their selectivity against traditional salts results in increased purity and productivity in the subsequent bioseparation methods,

which are critical to the development of pharmaceuticals.[91] ILs are collectively an effective toolkit to improve the physical, chemical, and biological properties of drug formulations.

5.9 ILs as surfactants and cosurfactants

The special physicochemical characteristics of ILs such as low volatility, thermal stability, and structural tunability have made these compounds promising alternatives to traditional surfactants and cosurfactants in pharmaceutical preparations. These characteristics enable them to be particularly effective in stabilizing emulsions and nano systems in the delivery of drugs. ILs are surfactants that increase interfacial stability and decrease the critical micelle concentration (CMC), improving the solubilization and bioavailability of poorly soluble drugs. An example is the IL-based surfactant [TDMB]Br (1-tetradecyl-3-methylimidazolium bromide), which, when added in combination with other surfactants, has been shown to stabilize nimodipine-loaded polymeric nanoparticles, enhancing greatly its dissolution rate and stability.[92] It has also been demonstrated that IL-stabilized microemulsions can be used at temperatures up to 100 °C, which extends their use into higher temperature extractions and injectable formulations.[93] ILs like [C_{12}mim][Br] and cholinium-derived ILs have also been shown to improve the formation and stability of o/w and w/o microemulsions, increasing their utility in high-temperature extractions and inorganic nanoparticles.[94]

Another potentially effective use would be surface-active ILs (SAILs) to enhance the delivery of rifampicin. SAIL-based micellar systems increased the aqueous solubility of the drug and provided improved drug loading and release control and maintained structural integrity under physiological conditions, including in the formulation of insulin-loaded nanocarriers where ILs led to decreased surfactant concentrations and decreased toxicity without compromising formulation activity.[95,96] Importantly, ILs also exhibit synergistic behavior when combined with traditional surfactants, allowing for lower surfactant concentrations and reduced toxicity while maintaining formulation performance. Their customizable cation–anion combinations allow targeted manipulation of interfacial tension and emulsion viscosity, optimizing encapsulation efficiency and drug release profiles across diverse therapeutic agents.[97,98] IL-based microemulsions have successfully been employed to encapsulate rifampicin, a poorly water-soluble antitubercular drug. The use of ILs together with non-ionic surfactants, such as Tween-20, led to microemulsions that are thermostable and able to sustain continuous structures and enhance drug dispersion. The multifunctional nature of ILs as surfactants and cosurfactants provides a sustainable and flexible versatile system for use in drug delivery in the 21st century, allowing high-performance formulations with a high degree of drug solubilization, stability and controlled release.[99]

5.10 ILs across different types of drug formulations and delivery

The peculiarities of physicochemical characteristics of ILs have attracted the interest of pharmaceutical scientists as a means of creating new drug delivery modes. Their integration in micro and nano scale systems, *e.g.* emulsions, liposomes, and nanoparticles, has made it possible to design highly customizable carriers that are advantageous towards specific therapeutic applications. In addition to the delivery of small molecules, ILs can be used as advanced excipients by stabilizing proteins, peptides, and nucleic acids, thus facilitating the formulation and production of biopharmaceuticals. Fig. 9 demonstrates how ionic liquids can be used as multifaceted agents to improve drug delivery and biopharmaceutical applications including transdermal and mucosal transport enhancement and structural stabilization of biologics, in a wide variety of carrier systems.

5.10.1 ILs in micro/nano drug delivery systems for biomedical applications. Introduction of ILs into microemulsions, nanoemulsions, liposomes, niosomes, ethosomes, nanoparticles, and lipid nanoparticles (LNPs) is reshaping the field of drug formulation in the biomedical field. Microemulsions based on ILs provide thermodynamic stability and better solubility of drugs. Choline and geranic acid (CAGE) formulations, for instance, have been shown to enhance the transdermal delivery of methotrexate (MTX), a poorly soluble drug. In one study, a thermo-responsive IL microemulsion hydrogel (MTX/ME@Gel) improved MTX solubility nine-fold and enhanced skin permeation by over 27%, also exhibiting anti-inflammatory and antibacterial effects, an encouraging platform for psoriasis therapy.[100] Similarly, IL-stabilized microemulsions have been employed for site-specific delivery of anti-inflammatory and antiretroviral drugs, ensuring better permeability and sustained release.[101,102]

Nanoemulsions incorporating ILs have demonstrated high efficacy in vaccine delivery. A choline–niacin ([Cho][Nic])-based oil-in-IL (o/IL) nanoemulsion enhanced antigen stability and the immune response to intranasal influenza vaccine, improving IgA titers and $CD4^+$ T-cell activation.[103] A similar nanoemulsion preserved the structural integrity of inactivated foot-and-mouth disease virus, outperforming traditional adjuvants in immune activation.[104] IL-based nanoemulsions have also enhanced the solubility and stability of lipophilic drugs such as curcumin, protecting against photodegradation and boosting bioavailability.[105] ILs are also highly effective in liposomal and ethosomal formulations. Their amphiphilic nature improves encapsulation efficiency, membrane fluidity, and drug permeability. In ethosomes, ILs act as stabilizers and penetration enhancers, enabling efficient transdermal delivery of peptides and proteins.[106] Likewise, ILs enhance the loading and release control of liposomes and LNPs, which is particularly beneficial in vaccine and cancer drug delivery.[93] In niosomal systems, ILs optimize vesicle size,

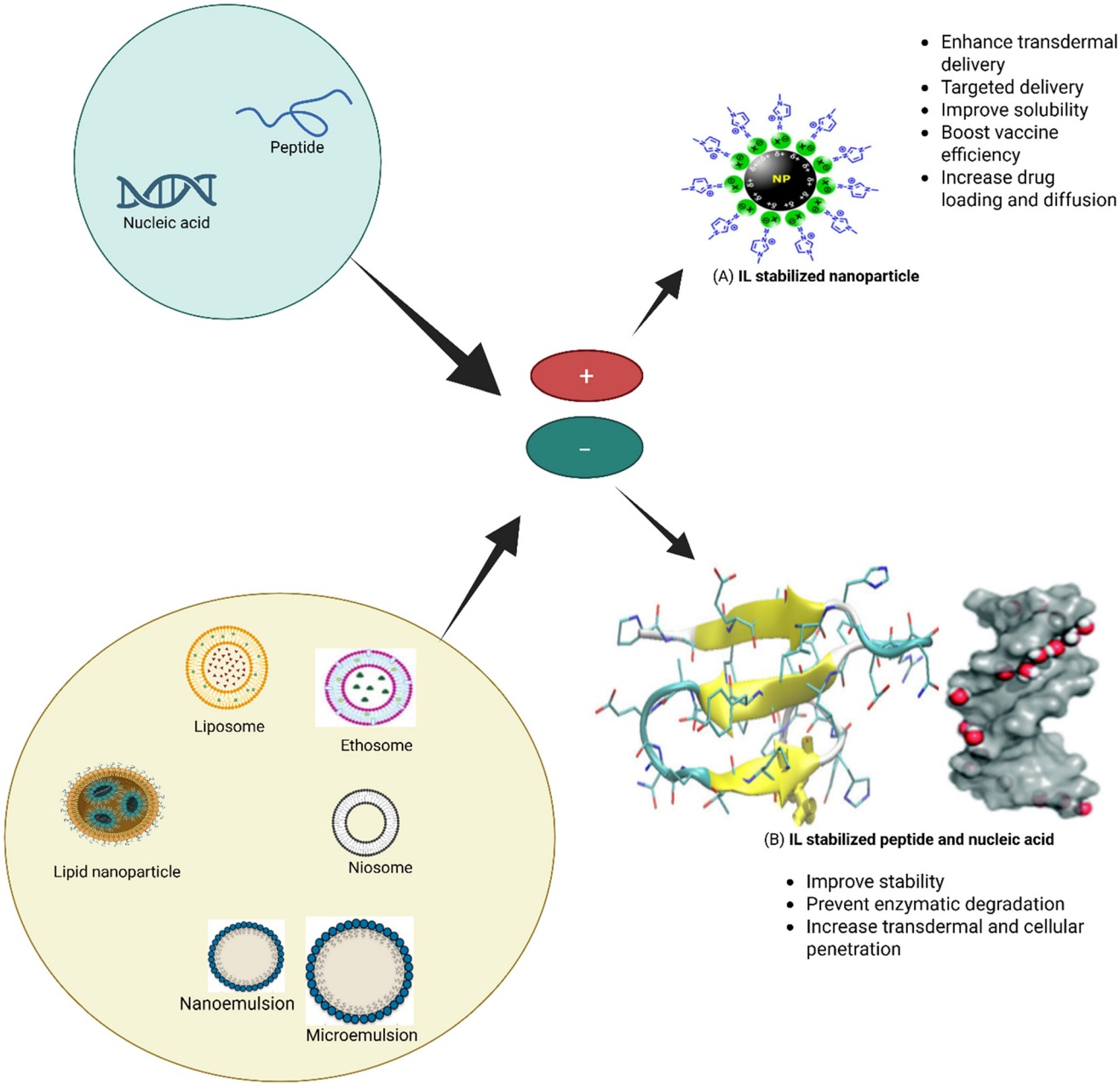

Fig. 9 ILs as functional drivers in advanced drug delivery platforms.

stability, and entrapment efficiency. Catanionic niosomes made from CTAB and SDS surfactants, combined with ILs, showed improved drug loading and diffusion for anticancer delivery using cabozantinib.[107] Other studies confirmed that IL-modified niosomes enhance oral and topical delivery of various hydrophobic drugs.[106,108]

ILs are also important in the surface engineering of nanoparticles. As an illustration, the coating of PLGA nanoparticles with ILs made of choline carboxylic acid significantly prolonged the circulation time of the nanoparticles and improved the targeted delivery after administration of the nanoparticles to a murine model *via* intravenous injection.[5] Other than drug carriers, ILs have also been relevant in biosensor design and diagnostics. The use of IL-modified carbon paste electrodes has also been demonstrated to be very sensitive in the detection of glutathione, which is an important marker in oxidative stress and neuroinflammatory states, with much better electrochemical performance and selectivity.[109] ILs have also been shown to be very useful in transmucosal delivery to enhance drug permeability at nasal, oral and gastrointestinal membranes. Mucoadhesivity increases bioavailability and targeted release and extends residence time and decreases enzyme degradation.

5.10.2 ILs as advanced excipients for protein, peptide, and nucleic acid therapeutics. ILs enhance the formulation and

downstream processing and transform the biopharmaceutical industry. They maintain the stability and purity of proteins, peptides and nucleic acids and improve their recovery and purity. As excipients, ILs ensure the therapeutic activity of such biomacromolecules, stabilize them and protect them against degradation. This dual role has rendered ILs innovative tools of development of biopharmaceuticals that will be prepared reliably and produced economically. ILs improve stability, prevent enzymatic degradation, and increase transdermal and cellular penetration, all of which improve the delivery of peptides, proteins, and nucleic acids. They work well in gene delivery and non-invasive treatments because they break down skin lipids to facilitate macromolecule transport and preserve structural integrity.[97] Furthermore, one study confirmed that ILs in protein-containing nanocarriers (PCNCs) improve transdermal administration by increasing protein transport and disrupting skin lipids. PCNCs increased ovalbumin (OVA) delivery 25–28 times compared to aqueous formulations. They also demonstrated excellent anticancer effects by boosting CD8+ T cells and promoting immunological responses, making them promising for tumor immunotherapy.[110] ILs present a possible substitute for water as nucleic acid solvents with their special electrolyte and stabilizing qualities maintaining their usefulness. By promoting nucleic acid stability and regulated nanostructure creation, ILs open new avenues for nanotechnology and drug delivery applications beyond aqueous settings. ILs are also essential for nucleic acid diagnostics. One study showed that ILs in a platform modified by graphene oxide improve hybridization sensitivity and efficiency, enhancing BRCA1 gene detection. As evidence of ILs' contribution to developing nucleic acid diagnostic tools, the IL-based biosensor successfully separated complementary sequences from mismatched or non-complementary ones with a low detection limit of 1.48 μg mL^{-1} and remarkable selectivity.[111]

5.11 Therapeutic and diagnostic applications of ILs across a spectrum of diseases

Recent research has highlighted the potential of ionic liquids (ILs) to address several long-standing challenges in drug delivery, including poor solubility, limited bioavailability, and inadequate targeting of therapeutic agents. Due to their versatile nature regarding physicochemical properties, it is possible to design systems that can be used to improve the performance of drugs in a broad spectrum of pathological conditions. The potential of ILs to enhance the delivery of a wide range of therapeutics, including enhancing the solubility of hydrophobic anticancer drugs and promoting the delivery of drugs across complicated biological barriers including the blood–brain barrier, is actively being explored. This increasing concern highlights their new application as multi-purpose instruments in the development of disease-specific drug delivery models.

5.11.1 Implications of ILs for infectious disease diagnosis and therapy. ILs are now finding their way into infectious disease research because they possess distinctive physicochemical characteristics, adjustable structures, and bioactivity. They can be utilized in diagnostics, drug delivery, and antimicrobial therapy, and they can be promising in the fight against bacterial and viral infections. ILs are useful as functional additives in biosensors to enhance sensitivity and specificity in the detection of infectious biomarkers. An example is the IL-modified carbon electrode that has been used to increase the electrochemical detection of a single oxidative stress biomarker, glutathione, which is associated with viral and bacterial infections, by improving the transfer of electrons and surface conductivity.[112]

Also, ILs exhibit good antimicrobial effects as they can disrupt the membranes of microbes, inhibit formation of biofilms, and stop crucial enzyme activities. Natural antimicrobial moieties, including salicylate, menthol or amino acids, have been found to be effective as ILs against resistant pathogens. As an example, ILs containing proline ethyl ester and salicylate have been shown to be highly active as antibacterial agents with low cytotoxicity, allowing their application in topical preparations to treat skin infections.[105] ILs functionalized with metal complexes, including silver or zinc, can also be used to treat Gram-positive and Gram-negative bacteria with reduced cytotoxicity.[113] Certain ILs are promising antiviral carriers or agents against viral infections. ILs based on cholinium have been found to increase the transdermal delivery of macromolecules such as siRNA and interferons, which may provide a mechanism-based approach to direct viral inhibition with reduced systemic side effects.[114] ILs based on cholinium can also disrupt the integrity of the viral envelope, providing a mechanism-based strategy of direct viral inhibition with reduced systemic side effects.[115]

Although these advances have been made, problems still exist. IL-based antibiotic resistance among bacteria is a developing problem. Adaptation to ILs by bacteria can occur due to a change in membrane fluidity, the expression of efflux pumps, or degradation by enzymes. In particular, Gram-negative bacteria have been shown to be more resistant, altering membrane lipid structures decreasing the permeability and efficacy of ILs.[116] These adaptive mechanisms have shown the necessity of designing ILs judiciously to prevent microbial resistance and guarantee the sustainability of antimicrobials.

5.11.2 ILs in anticancer drug delivery. By enhancing drug carrier performance, stability, and production, ILs play a major role in the delivery of anticancer drugs. This enables more effective cancer treatments through improved loading, targeted distribution, and controlled release. A study revealed that the chemotherapy medication imatinib mesylate can be encapsulated in a temperature-responsive gel made of cetylpyridinium salicylate (CetPySal), a surface-active ionic liquid. The prolonged drug release of this ionogel suggests that it could be used as a low-cost, thermo-responsive

material to enhance the administration of anticancer medications.[117] In addition, the insoluble anticancer pigment violacein (Viol) was successfully dissolved by surface-active ionic liquids (SAILs) based on 1-alkylimidazolium cations. Because of its low cytotoxicity and capacity to keep violacein in solution, the [C_{16}Him]-S SAIL was chosen. To improve anticancer medication delivery, this combination was utilized to create a folate-targeted solid lipid nanoparticle (SLN) carrier that showed a five-fold increase in the incorporation of Viol nanoparticles in folate receptor-positive cancer cells.[118] ILs based on noscapine have also been created to increase the solubility of the drug, which, along with its derivatives, has the potential to be used as an anti-cancerous agent.[119]

ILs are also found to increase the efficacy of anticancer drugs. The anticancer effects of sorafenib (SRF) are improved by ionic liquid CAGE (choline and geranic acid), which enhances intracellular retention and penetration without increasing cellular absorption. Low doses of CAGE increase the anticancer efficacy of SRF by up to five times by blocking cell-cycle progression, promoting apoptosis, inhibiting exocytosis, and increasing SRF penetration across multicellular structures. This combination shows promise as a novel approach to successfully stop the growth of tumors.[120] To improve methotrexate's oral bioavailability, a recent study looks into turning it into ILs. Proline ethyl ester MTX (IL[ProEt][MTX]) demonstrated a 4.6-fold increase in bioavailability and a reduction in systemic toxicity across the various ILs examined when compared to MTX sodium. IL[ProEt][MTX], which also showed improved absorption, better pharmacokinetics, and enhanced antitumor activity, demonstrated the potential of MTX-based ILs as a successful strategy for improving the oral distribution of poorly soluble drugs like MTX.[121]

In addition to serving as delivery systems for anticancer drugs, ionic liquids have intrinsic anticancer properties. A recent study found that ILs are appealing anti-cancer agents due to their special qualities, which include chemical stability, selectivity for cancer cells, and tunability. Among the various ILs that demonstrate significant efficacy against cancer cell lines through oxidative stress induction, DNA interaction, and cellular membrane disruption are imidazolium and phosphonium-based compounds. ILs are positioned as innovative candidates for cancer treatments in the future due to their structural adaptability, which allows optimization for enhanced therapeutic potential with fewer side effects.[122] Table 4 highlights recent research studies showing the various functions of ILs in anticancer drug delivery, such as their capacity to improve drug solubility, offer inherent anticancer qualities, and enable targeted delivery methods.

5.11.3 ILs in the management of diabetes and diabetic ulcer. The potential of ILs to improve insulin administration, especially through non-invasive delivery methods, is one of their most promising contributions. By using ILs as skin pretreatment and then applying insulin, choline-based ILs have demonstrated the ability to increase transdermal insulin permeability. When compared to traditional insulin delivery, this method produced noticeably stronger glucose-lowering effects and prolonged hypoglycemia in diabetic rat models while maintaining skin integrity. Insulin's structure can be stabilized by ILs like [Ch][Ge] and [Ch][Ci], which also improve insulin's solubility and skin permeability and raise its relative bioavailability.[123] Oral insulin delivery has also benefited from IL technology, further expanding this use. One of the long-standing problems with oral insulin therapy has been resolved by encasing insulin in IL-functionalized silica nanoparticles, which protect it against enzymatic degradation and pH changes within the gastrointestinal tract. This allows for sustained release and improved absorption.

ILs have demonstrated inherent antidiabetic qualities in addition to improving delivery systems. When tested in α-amylase inhibition assays, imidazolium-based ILs showed significant enzyme inhibition, frequently outperforming well-known medications like acarbose.[124] Similarly, compounds with strong antioxidant qualities and α-amylase inhibitory activity were produced by DABCO-based ILs used as catalysts in the synthesis of indeno-benzofuran derivatives, indicating a dual therapeutic mechanism against oxidative stress and postprandial hyperglycemia.[125] These results suggest that ILs

Table 4 Role of ILs in anticancer drug delivery

Role of ILs	Key findings	ILs used	Cancer types/drugs targeted	Ref.
ILs enhance the solubility of poorly soluble drugs like methotrexate (MTX) and violacein	ILs improve the bioavailability and pharmacokinetics of drugs, offering enhanced drug delivery and reduced systemic toxicity	[ProEt][MTX], [C_{16}Him]-S	MTX (oral bioavailability), violacein (nano-carrier)	121
ILs with intrinsic anticancer properties	ILs exhibit efficacy against various cancer cell lines, induce oxidative stress, disrupt cell membranes, and interact with DNA	Imidazolium, thiazolium, ammonium, phosphonium-based ILs	Breast, lung, colon, and ovarian cancers	122
ILs designed to enhance the solubility of noscapine	Noscapine-based ILs show increased solubility, stability, and potential for improved anticancer efficacy	Noscapinium-based ILs	Noscapine-related anticancer activity	119
ILs used to dissolve violacein and develop targeted delivery systems	ILs improve solubility of violacein and enhance its delivery *via* nanoparticles targeting folate receptors, five-fold higher uptake in cancer cells	[C_{16}Him]-S	Folate receptor-positive cancers	118

have the capacity to act as both carriers and bioactive agents that can directly affect glucose metabolism. By reducing issues related to protein aggregation, ILs are also helping to improve protein therapeutics. One of the main obstacles to insulin stability during storage and delivery, insulin fibrillation, has been successfully prevented by choline–amino acid-based ILs. Insulin's native conformation was preserved under heat and chemical stress by ILs such as choline glycinate, providing a workable way to extend the shelf life and therapeutic consistency of insulin.[126]

Another crucial area where ILs have proven useful is diagnostics. A sensitive, colorimetric detection technique for acetone, a crucial indicator of diabetic ketoacidosis in urine, has been made possible by IL-functionalized silver nanoparticles. This IL-enhanced sensor demonstrated promise for point-of-care diagnostics in low-resource settings by enabling quick, visual detection with excellent sensitivity and inexpensive hardware.[127] Furthermore, by enhancing signal responsiveness and stability in glucose-sensitive electrodes, the electrochemical and conductive characteristics of ILs have improved biosensor performance for continuous glucose monitoring.[128]

ILs have become essential instruments in the management of diabetes-related comorbidities, including chronic and infected wounds, in addition to systemic glucose regulation. Advanced wound dressings with multifunctional therapeutic characteristics have been developed as a result of the incorporation of ILs into hydrogels. For example, 1-vinyl-3-butylimidazolium bromide-infused hydrogel showed conductive, antibacterial, and anti-inflammatory properties, especially when combined with electrical stimulation. In diabetic wound models, this combination increased angiogenesis, collagen deposition, and tissue healing without requiring the release of antibiotics.[129] The inclusion of a near-infrared fluorescent probe incorporated into a PIL-based hydrogel was another breakthrough that promoted wound healing while enabling real-time visualization of hypochlorous acid, a reactive oxygen species linked to inflammation.[130] Researchers created a sericin-based hydrogel functionalized with phenylboronic acid and imidazole groups to combat drug-resistant bacterial infections. This hydrogel was able to capture and eradicate methicillin-resistant *Staphylococcus aureus* (MRSA). The outcome was a significant decrease in inflammation and quicker healing, confirming ILs' therapeutic potential in the treatment of complicated diabetic ulcers.[131] These clever wound dressings demonstrate how ILs can be tailored to address the microbiological and metabolic issues that arise in chronic wounds.

All things considered, ILs' distinct physicochemical and biological characteristics—such as their capacity to improve solubility, stabilize proteins, promote membrane permeability, conduct electricity, and display intrinsic bioactivity—make them extremely useful instruments in the battle against diabetes. ILs offer a multifaceted approach to managing diabetes, whether they are used to improve insulin administration, function as antidiabetic agents, stabilize therapeutic proteins, support diagnostics, or promote wound healing. Unlocking their full potential in clinical settings will require more investigation of their toxicity profiles, long-term biocompatibility, and structure–activity connections. ILs have the potential to have a big impact on diabetes treatment and personalized medicine in the future, as the existing body of research shows.

5.11.4 ILs in cardiovascular disease: emerging applications and cautions. Their catalytic role in drug production is among the most obvious instances of IL usefulness. Phytosterol ferulate (PF), a bioactive molecule that combines the antioxidant advantages of ferulic acid with the lipid-lowering characteristics of phytosterols, has been produced using acidic ILs. PF was produced in large quantities through IL-mediated esterification and showed notable decreases in plasma cholesterol, triglycerides, and hepatic lipid accumulation in hyperlipidemic mice. These benefits outweighed those of either product alone, indicating that ILs can aid in the synthesis of therapeutically superior compounds with compounded cardioprotective properties.[132] In order to improve cardiovascular monitoring, ILs have been included into diagnostic systems concurrently with therapeutic production. Notably, a choline-based IL was used to create a wearable organo–ionic gel-based electrode (OIGE), resulting in an extremely conductive and durable ECG sensor. This device is a great option for long-term, real-time cardiac monitoring because it maintained accurate signal capture in harsh environments like humid, cold, and even underwater conditions. Both biocompatibility and electrochemical stability, which are necessary for patient-specific applications under unpredictable conditions, were made possible by the IL component.[133]

Additionally, ILs are essential to biosensing. To detect vitamin B6 with remarkable sensitivity, a room-temperature IL (1-hexyl-3-methylimidazolium hexafluorophosphate) was added to a platinum/graphene nanocomposite sensor. The capacity to effectively monitor vitamin B6 trace levels promotes more comprehensive cardiovascular risk assessment methodologies because vitamin B6 has been associated with lower risks of atherosclerosis and myocardial infarction. This IL-enhanced sensor showed the potential of ILs in point-of-care diagnostics with a detection limit in the nanomolar range and robust performance in real-world food and environmental samples.[134] ILs have also been tested as embolic agents in more sophisticated interventional techniques. A first-in-human clinical trial evaluated a novel water-based IL embolic agent designed for vascular blockage. In patients receiving treatment for renal tumors, portal vein embolization, and associated disorders, the material—which solidifies in response to physiological ionic strength—achieved total vascular closure. Compared to conventional agents, particularly those needing polymerization or hazardous solvents, this IL-based embolic agent showed a safer and more controllable profile with no unexpected side events and excellent procedural success.[135] ILs have been

utilized to enable the transdermal administration of thrombin-sensitive nano sensors, hence increasing the potential for diagnosis. A choline–geranic acid IL (CAGE) allowed sensors to passively penetrate the skin in a mouse model, doing away with the requirement for injections. For up to three days after application, these sensors were able to identify thrombosis using urine biomarkers. This non-invasive method has a lot of potential for tracking clotting episodes in cardiovascular patients who are at risk, particularly those who are receiving anticoagulant medication or surgery.[136]

ILs are not without cautionary remarks, despite these encouraging developments. A risk of cardiotoxicity was found in studies on methylimidazolium-based ILs (MILs), particularly those with longer alkyl chains. Research conducted *in vitro* on rat cardiomyocytes revealed that ILs affected cell survival and electrical activity in a chain-length-dependent way. Following exposure, *in vivo* results verified structural changes in the heart and increased cardiac injury indicators. Furthermore, interspecies variations in transporter expression make safety evaluations even more difficult, highlighting the necessity of a comprehensive toxicological investigation prior to systemic administration of ILs in humans.[137]

5.11.5 ILs in neurologic disorders: emerging applications, diagnostic innovations, and neurotoxicity considerations. A major advance in neurotherapeutics involves the transformation of existing CNS drugs into ionic liquid formulations to improve their solubility and bioavailability. Tetrabutylphosphonium cations were employed to reorganize edaravone, an antioxidant medication used for ALS and ischemic stroke, as an IL, greatly improving its pharmacokinetics and water solubility. Edaravone-IL is a better option for managing acute stroke since it not only increased circulation time but also produced strong neuroprotective benefits with a lower renal load in mouse models of cerebral ischaemia.[138] Similarly, surface-active ILs (SAILs) based on ethanolamine and lauric acid were investigated in conjunction with gabapentin, an antiepileptic medication with limited gastrointestinal absorption. By promoting the creation of stable micelles, these SAILs enhanced the solubility and membrane permeability of gabapentin. Favorable drug–SAIL interactions were validated by thermodynamic and COSMO-based modelling, suggesting promise for clinical translation in optimized CNS medication delivery.[139] In non-invasive nose-to-brain administration, ILs have also demonstrated promise. An IL that combined proline ethyl ester and etodolac improved nasal retention and roughly 200-fold increased drug solubility. Intranasal delivery resulted in decreased systemic exposure and a seven-fold increase in brain delivery. It demonstrated effective central anti-inflammatory efficacy and highlighted ILs' potential as brain-targeted carriers *via* the olfactory pathway by lowering brain prostaglandin E_2 by around 40% in a neuroinflammation paradigm.[140]

In the field of neural healing, ILs have helped create biocompatible and conductive scaffolds for the treatment of spinal cord injuries. High neuronal survival and synaptic gene expression were shown by a chitosan-based hydrogel containing the ionic liquid $VPImBF_4$ (pCM@IL), promoting neuro-regeneration. The scaffold's *in vivo* stability, biodegradability, and pro-angiogenic qualities were confirmed by animal experiments, indicating its potential as a neuro-regenerative platform.[141] IL-based research also heavily emphasizes advances in diagnosis. IL-enhanced electrochemical sensors have been created to track neurotransmitter and neurological medication levels in real time. For example, a sensor integrating graphitic carbon nitride and tetrabutylammonium chloride ILs enabled precise detection of carbamazepine in both pharmaceutical and biological samples, offering a cost-effective and sensitive alternative to conventional analytical tools.[142] IL-based biosensors have also enabled multi-analyte neurotransmitter profiling in both animal and human fluids. Monoamines and amino acid neurotransmitters have been successfully measured in rat spinal cords, human plasma, and CSF using methods such ultrasound-assisted magnetic IL dispersive liquid–liquid microextraction (UA-MIL-DLLME) in conjunction with high-resolution mass spectrometry. These techniques, which employ ILs such as $[P6,6,6,14]_2[CoCl_4]$ and $[BMIM]BF_4$, have expedited neurochemical diagnoses for conditions like multiple sclerosis, schizophrenia, and Parkinson's.[143,144] Concurrently, wearable IL-based biosensors are being developed to facilitate monitoring of mental health. Heart rate variability (HRV) and pulse signals, which are important markers of emotional and autonomic states, were tracked using a flexible sensor modified with [EMIM][TFSI]. The system's ability to classify user emotional states with over 95% accuracy when combined with machine learning analysis suggests that it may be used in the future for individualized neuropsychiatric care.[145]

Notwithstanding these advantageous uses, ILs' neurotoxic potential needs to be carefully considered. In zebrafish, prolonged exposure to ILs such 1-octyl-3-methylimidazolium bromide ($[C_8mim][Br]$) has been linked to notable behavioral and neurochemical alterations, such as anxiety-like symptoms, cognitive impairment, neurotransmitter imbalance, and neuronal death. The downregulation of important neurotransmitter-related genes was verified by gene expression analysis.[146] Furthermore, there were complex interactions between IL exposure and heavy metals like lead (Pb). In a co-exposure paradigm with common carp, IL 1-methyl-3-octylimidazolium chloride reduced neuroinflammation and preserved the integrity of the blood–brain barrier while mitigating some Pb-induced damage. Although more thorough research is required, these results imply that certain ILs may have neuroprotective properties under particular toxicological circumstances.[147]

5.11.6 ILs in inflammatory and autoimmune diseases. One significant development is the reformulation of traditional medications, especially non-steroidal anti-

inflammatory medicines (NSAIDs), into ionic liquid formulations to improve pharmacokinetics and solubility. When imidazolium and cholinium cations are added to ibuprofen, ILs are created that show markedly enhanced water solubility, increased biological fluid compatibility, and either maintained or enhanced anti-inflammatory effectiveness. Selective COX-2 inhibition, which is advantageous for lowering inflammation with fewer gastrointestinal adverse effects, was demonstrated by these ILs. Crucially, even at doses higher than the maximum plasma levels of conventional ibuprofen, toxicity evaluations in HepG2 and Caco-2 cell lines showed appropriate safety margins and hemocompatibility.[148] In addition, ILs have made effective transdermal administration possible, which is especially beneficial for autoimmune skin disorders and chronic inflammatory diseases. Improved skin permeability, better drug absorption, and concurrent antibacterial activities were found in studies employing isopropyl amino acid ester-based ILs coupled with NSAIDs like ibuprofen. Particularly for diseases like psoriasis and atopic dermatitis, these characteristics provide a two-fold benefit in localized treatment with reduced systemic exposure.[149] Transdermal distribution of big, poorly soluble biologics like cyclosporine A (CsA) is an additional application of this approach. In an imiquimod-induced psoriasis model, researchers found that adding choline and geranic acid-based ILs (CAGE) to a Pluronic F127-based organogel increased CsA skin penetration by more than 100 times and decreased systemic drug levels while preserving therapeutic efficacy. Erythema, scaling, and skin thickness improvements highlight this delivery platform's therapeutic promise.[150]

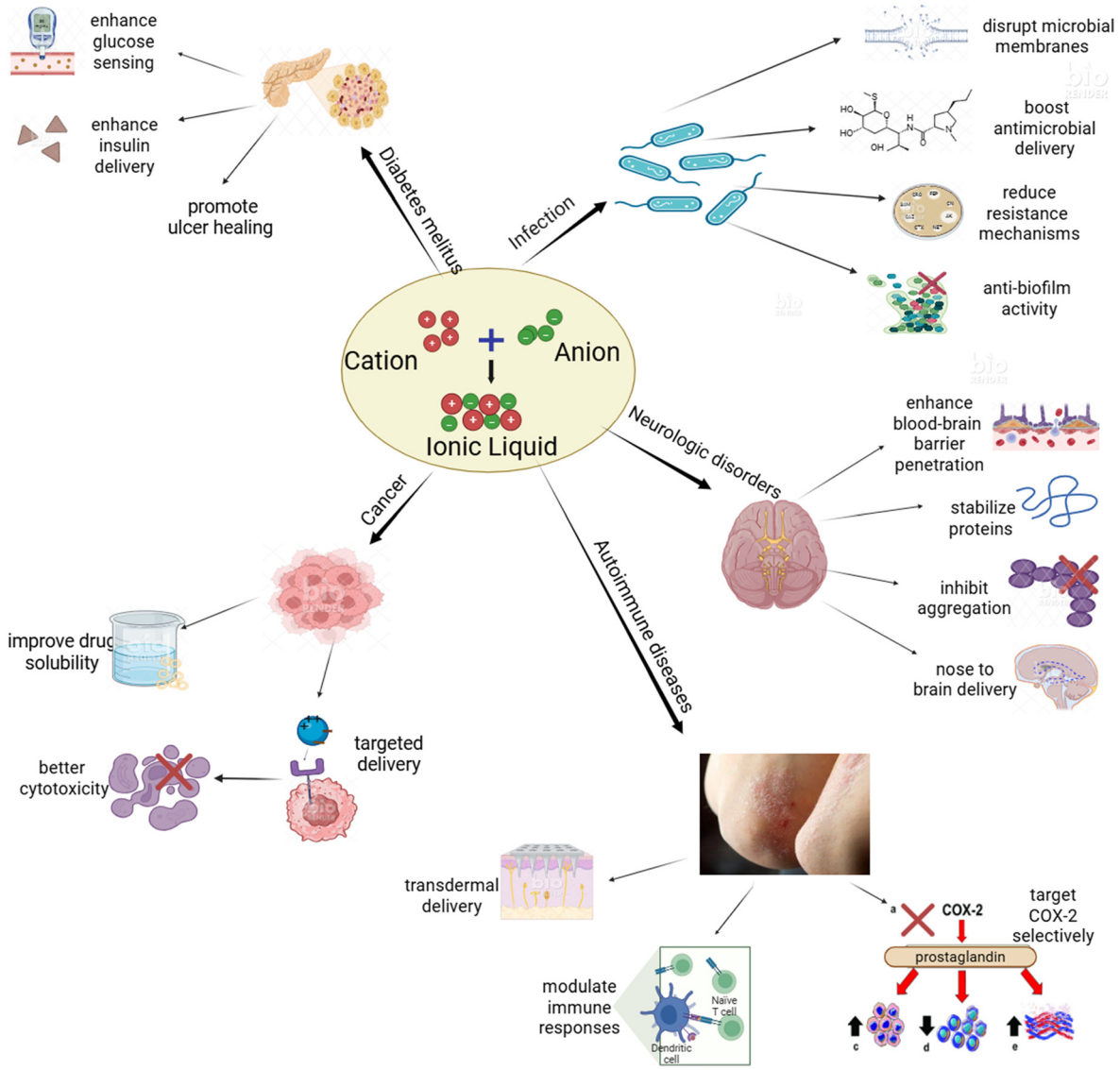

Fig. 10 Mechanisms underpinning the biomedical utility of ILs across disease states.

ILs are contributing creatively to the design of vaccination adjuvants in addition to medication delivery. It has been demonstrated that a new IL adjuvant made of sorbic acid and choline (ChoSorb) improves humoral and cellular immune responses. ChoSorb promoted Th1-biased isotype switching and strong T-cell activation when combined with FluBlok vaccination, which is important for regulating immune responses to intracellular infections and may be helpful in autoimmune control. The adjuvant's stability at room temperature and ease of production make it ideal for the development of vaccines worldwide.[151] ILs have transformed extraction techniques that preserve and even increase bioactivity in the field of natural product therapies. After carotenoids were extracted from peach palm waste using ILs, a formulation rich in lycopene and β-carotene with proven anti-inflammatory and antioxidant properties was produced. Supplementing with an IL-extracted product decreased renal inflammation, enhanced oxidative stress indicators, and decreased histopathological damage in rat models caused by a high-fat diet, indicating its use in metabolic-inflammatory illnesses.[152] Similarly, the yield and potency of Angelica sinensis's primary anti-inflammatory component, (*Z*)-ligustilide, were greatly enhanced by the application of IL-microwave-assisted hydrodistillation (IL-MAHD). The resultant essential oil showed significant bioactivity at low doses, indicating that it may be used therapeutically to treat conditions including chronic inflammatory syndromes and rheumatoid arthritis.[153] The various molecular functions of ionic liquids in disease-specific therapies are depicted in Fig. 10. It emphasizes how ILs assist regenerative approaches, improve therapeutic efficacy, facilitate targeted

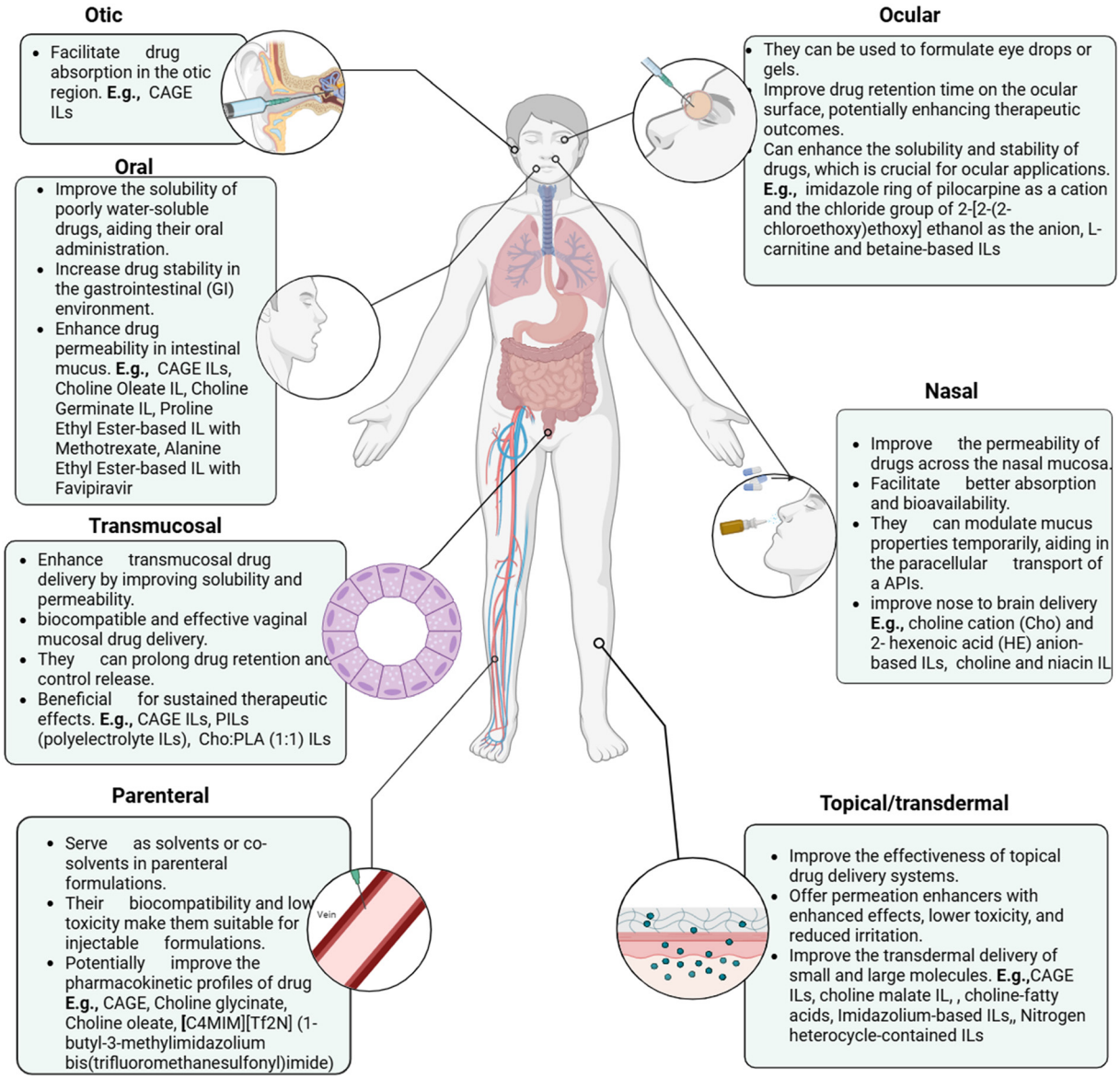

Fig. 11 Application of ILs across various drug delivery routes.

drug administration, and advance diagnostic advancements in the fields of oncology, diabetes, cardiovascular, neurological, inflammatory, and autoimmune disorders.

5.12 ILs in different drug administrative routes

ILs have shown promise across various drug delivery routes. Key routes, including oral delivery, transdermal and dermal delivery, pulmonary and nasal delivery, and transmucosal, rectal, and vaginal delivery, are summarized in Fig. 11.

5.13 Designing biodegradable drug systems with ILs

ILs are increasingly being engineered to improve the biodegradability of pharmaceutical formulations by replacing persistent organic solvents with environmentally benign alternatives. Current attempts concentrate on creating ILs with biocompatible ingredients that break down more easily in natural settings, like choline, amino acids, and carboxylic acids. For example, in conventional biodegradability tests, cholinium-based ILs mixed with organic acid anions such as acetate or glycolate showed over 60% mineralization, making them "readily biodegradable" according to OECD 301 criteria.[18] Similar to this, the dual functionality of cholinium alkanoates and cholinium amino acid ILs, improving solubility while providing safer environmental profiles, has demonstrated potential in medication administration. These ILs lower the dangers of long-term accumulation while also improving the environmental fate of medications. Because these groups are more vulnerable to enzymatic hydrolysis, ILs with ester, hydroxyl, or carboxylic acid functional groups on the side chains are especially potent. For instance, ILs such as cholinium glycolate and cholinium lactate minimize ecotoxicity under wastewater treatment conditions while supporting medicinal uses.[154]

Despite increasing interest in ionic liquids (ILs) as functional components of nanocarrier systems, their pharmacokinetics and long-term biological fate remain insufficiently understood, limiting translational confidence. Unlike conventional excipients, ILs possess highly tunable physicochemical properties, including polarity, lipophilicity, and ion pairing, which can substantially influence their absorption, distribution, metabolism, and excretion (ADME) once administered *in vivo*. When incorporated into nanocarriers, the biodistribution of ILs is primarily governed by carrier characteristics such as particle size, surface charge, and surface chemistry; however, IL–carrier interactions may alter release behavior and tissue exposure relative to free ILs. Available *in vivo* evidence suggests that ILs with higher lipophilicity, particularly those containing long alkyl chains, may preferentially accumulate in clearance organs such as the liver and spleen, consistent with uptake by the mononuclear phagocyte system.[155] Regarding metabolism, many commonly employed IL cations, including imidazolium- and pyridinium-based structures, appear to undergo limited biotransformation through classical enzymatic pathways, with reported metabolic events largely restricted to side-chain oxidation or dealkylation. Encapsulation within nanocarriers may further reduce metabolic accessibility, potentially prolonging systemic residence time. However, systematic studies examining intracellular metabolism following nanocarrier-mediated delivery remain scarce, and the identity and biological activity of potential IL metabolites are poorly characterized.[18,156–158]

Excretion pathways are similarly dependent on the IL structure. Hydrophilic ILs and low-molecular-weight degradation products are thought to undergo renal clearance, whereas more hydrophobic ILs may be eliminated more slowly *via* hepatobiliary routes. In nanocarrier formulations, overall clearance is additionally influenced by carrier degradation kinetics, raising the possibility of delayed elimination and prolonged tissue exposure. Importantly, repeated dosing studies have reported organ-specific accumulation for certain IL classes, particularly in the liver, kidneys, and lungs, highlighting potential long-term safety concerns.[159,160]

There are still issues despite these developments. IL design is complicated by the trade-off between structural characteristics that support biodegradability and those that improve drug solubilization. Longer alkyl chains frequently increase cytotoxicity and decrease biodegradation, despite being advantageous for drug penetration. Additionally, typical anions like Tf_2N^- and $[PF_4]^-$ are not ideal for sustainable uses since they are resistant to microbial attack. Industrial recovery and recycling of ILs are nevertheless inefficient, even with the addition of biodegradable components; typically, only 83% of ILs are recovered per cycle, resulting in cumulative waste over time. In order to overcome these constraints, the logical design of greener ILs is being guided by computational methods like life cycle evaluations and quantitative structure–activity relationship (QSAR) models. These methods facilitate the development of safer, biodegradable formulations by enabling researchers to forecast toxicity and environmental impact without requiring substantial empirical testing. Furthermore, a possible option in the creation of green pharmaceuticals is the discovery of natural deep eutectic solvents (NADESs), which replicate IL behavior but are made completely of natural, biodegradable components.[161]

6 Demands and aspirations for ILs

The primary topics of impurity impact, task-specific IL design, and toxicity concerns are examined in this section. Because contaminants might affect ILs' functionality and biocompatibility, they must be thoroughly cleansed. ILs can be tailored for well-defined biological roles through task-specific design, which boosts their efficacy. Lastly, toxicity remains a major problem that requires extensive testing and modifications to ensure safety for *in vivo* applications. The evolution of ILs in medical science is guided by these reasons. The primary challenges in developing biocompatible ILs are listed in Table 5.

Table 5 Key challenges and strategies in developing biocompatible ionic liquids

Aspect	Challenges	Strategies	Tools/methods	Ref.
Impurity impact	Viscosity, electrochemical stability, and biocompatibility are all impacted by impurities (such as water, halides, and metals)	– To reduce impurities, use non-halide precursors – Optimize the synthesis process to minimize and eliminate contaminants	Karl Fischer titration, HPLC, ICP-MS, ^{1}H NMR, Volhard titration	162, 163
Task-specific design	Modifying ILs while preserving functionality for applications, such as drug delivery	– To add desired qualities (such as reactivity or solubility), alter cations or anions – Use COSMO-RS and CAMD for logical design	Computer-aided molecular design (CAMD), COSMO-RS, 2D NMR	164
Toxicity concerns	Numerous ILs are harmful to living things, which limits their potential for use in medicine	– Create less harmful "green" and biocompatible ILs – Adjust the length of the alkyl chain or other molecular structures to lessen negative effects	Toxicological assays, ROS generation studies, protein interaction studies (*e.g.*, acetylcholinesterase models)	20, 165
Biocompatibility testing	Confirming the safety of ILs for use *in vivo*	– Extensive experiments on mammalian cells, bacteria, and other species – Examine protein stability and IL–membrane interactions	Dynamic light scattering, antimicrobial testing, mechanistic studies	166, 167
Environmental concerns	Preserving performance while making sure that ILs are eco-friendly	– Substitute environmentally friendly materials for potentially dangerous ones – Maximize the environmental impact of recovery and degradation processes	Green chemistry principles, lifecycle analysis	168, 169
Performance optimization	Achieving advanced applications by striking a balance between electrochemical, viscous, and thermal stability	– Minimize the effects of water (*e.g.*, restricted electrochemical window, changed viscosity) – Assess double-layer structures for specific uses, such as catalysis	Electrochemical studies, computational modeling	170

6.1 Impact of impurity in ILs

Metals, halides, organics, and water are the four primary categories of common impurities identified in ILs. To accurately identify and measure each kind of impurity, certain techniques are required. Impurities have a significant influence on ILs, changing their viscosity and possibly their biocompatibility. By employing non-halide precursors to refine synthesis techniques, impurity levels can be decreased, resulting in biocompatible ILs with fewer and easier-to-remove impurities like carbon dioxide or water. One of the common impurities in the synthesis of ILs is water. Water is a typical contaminant in ionic liquids that can alter their physical–chemical characteristics and potential uses. According to one study, viscosity can drop by 30% with a 10% rise in molar water concentration. Although the samples can be dried, water cannot be completely removed, especially in the case of hydrophilic ionic liquids. In carefully dried hydrophobic ILs, the presence of water up to a particular amount (50 ppm) has no discernible effect on density or viscosity; nevertheless, hydrophilic ILs are more challenging to control in terms of water content.[171]

6.2 Task-specific ILs

The term "task-specific ionic liquid" (TSIL) refers to an ionic liquid with a reactive functionality that is covalently bonded. This function bestows additional qualities (chemical, optical, magnetic, physical, or biological) upon the assembly, which can then be utilized to accomplish a particular purpose.[14] Ionic liquids can undergo significant physicochemical property changes and acquire a specific reactivity pattern when functional groups are added to their cations and/or anions. TSILs typically exhibit very little vapor pressure, a physical characteristic similar to that of non-functionalized ILs. The type of functional group also has a significant impact on other physicochemical characteristics, like solubility in molecular solvents or thermal stability, as well as chemical characteristics, including reactivity and complexation ability.[172]

ILs can be task-specifically designed by modifying their chemical makeup to suit certain uses, such as drug delivery or catalysis. This is achieved by selecting appropriate cations and anions that support the necessary characteristics, including perfect solubility, thermal stability, or viscosity. Design models like computer-aided molecular design (CAMD) are crucial for anticipating properties based on the chemical structure in order to ensure that the ILs meet industry criteria and application-specific constraints. This technique helps create durable, efficient ILs for specific activities. The adaptability of TSILs is demonstrated in Fig. 12, highlighting their customized features and wide range of uses in scientific and industrial fields.

In recent years, TSILs have drawn much interest since they may be made to have precise IL composition based on the

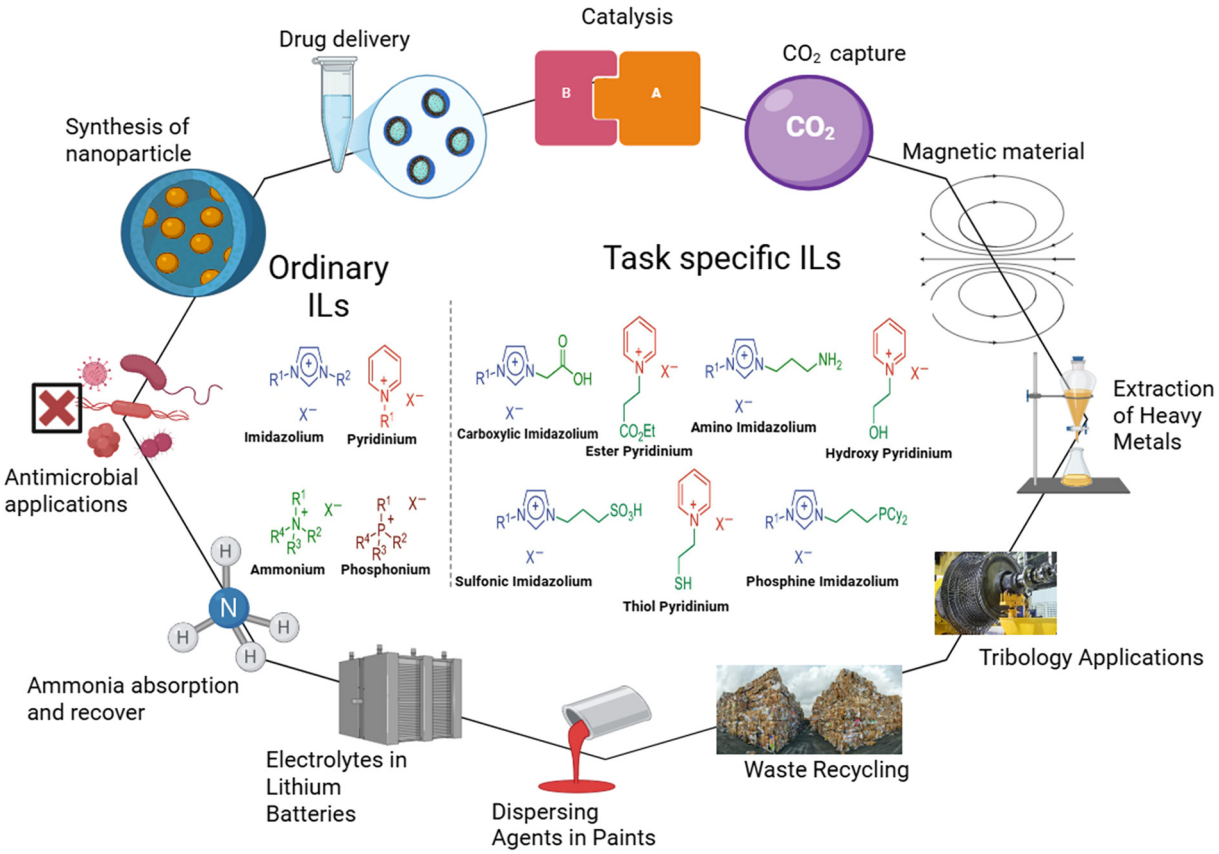

Fig. 12 Application of task-specific ILs.

user's requirements for the required physical, chemical, and biological qualities. These intriguing substances have demonstrated encouraging outcomes in several fields, including organic synthesis, catalysis, and, most recently, the use of functionalized ILs for chiral and nanoparticle synthesis.[173] Comprehending how ILs interact microscopically with solvents and biological materials is essential since brute-force screening is insufficient to understand their wider consequences. According to limited studies, the behavior of drugs or other solvents after delivery can be influenced by the specific structures that ILs might form with them. To comprehend how ILs work in antimicrobial applications and protein stability, a microscopic-level study employing methods like 2D NMR and dynamic light scattering is crucial. Research has demonstrated that ILs can affect cell migration by changing the flexibility of membranes, underscoring the need for additional mechanistic studies to develop biomedical technology.[174]

6.3 Toxicity and safety concerns

ILs have attracted considerable interest in drug delivery, yet their toxicity and long-term safety remain critical concerns. The biocompatibility and cytotoxicity of ILs are closely tied to their structural features, particularly the nature of the cation, anion, alkyl chain length, and functional groups. ILs with longer alkyl chains typically exhibit greater cytotoxicity due to enhanced membrane penetration, disrupting cellular integrity and inducing oxidative stress, especially in imidazolium and pyridinium-based ILs that impair mitochondrial and lysosomal function.[80,161] However, structural modifications can enhance safety without sacrificing functionality. ILs based on amino acids and cholinium, such as proline ethyl ester–salicylate and cholinium–salicylate, have shown little toxicity in HepG2 and Caco-2 cell lines, indicating their potential in oral and transdermal formulations.[80] In a similar vein, short or ether-linked dicationic ILs aid in lowering cytotoxicity while preserving a high capacity for drug loading. Despite being lethal, ferrocene-functionalized ILs exhibit selective activity against cancer cells such as MCF-7 by inhibiting cathepsin B, suggesting their potential as therapeutic agents.[161]

The environmental permanence and toxicity of ILs to terrestrial and aquatic ecosystems are significant, notwithstanding their potential. Because of their stability and solvation capacity, many ILs can concentrate in biological tissues and withstand decomposition, polluting soil and groundwater.[175] Despite being more biodegradable and less ecotoxic, even "green" ILs based on betaine, choline, or amino acids may still have unanticipated dangers and need careful confirmation.[176] Predictive computational models like QSAR and life cycle analysis can create safer ILs with less of an impact on the environment in order to overcome these

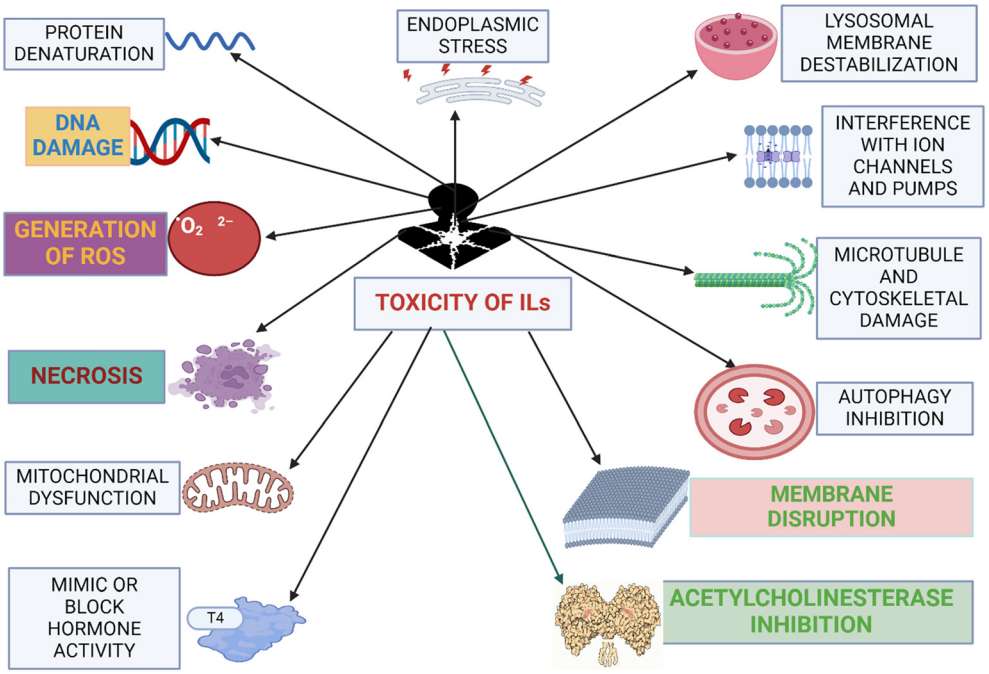

Fig. 13 Toxicological effects of ILs.

difficulties. However, before ILs are widely used in clinical and industrial pharmaceutical contexts, thorough toxicological profiling—including cytotoxicity, genotoxicity, and immunogenicity—as well as long-term exposure studies is still necessary. To ensure the safe and efficient use of ILs in medication administration, rational IL design and sustainable lifetime management must be integrated.[176] Toxicity mechanisms of ILs are depicted in Fig. 13.

7 Limitation of ILs in DDS

ILs in DDS have numerous drawbacks despite their positive traits. One major concern is their potential toxicity. Many common ILs are known to damage DNA, change cellular membranes, and produce reactive oxygen species (ROS) when taken *in vivo*.[177] Table 6 lists the different difficulties. Our limited understanding of how ILs function in complex biological environments makes it more challenging to predict how they would interact in DDS. ILs may interact with biological systems in diverse ways depending on the kind of tissue, injection techniques, and local physiological parameters. Further substantial study into the structure–function relationships of ILs is required, especially regarding toxicity, in order to overcome these challenges and enable safer, more effective drug delivery applications.

Table 6 Challenges and mitigation strategies for the use of ionic liquids in drug delivery systems (DDS)

Limitation	Description	Mitigation strategy/approach	Ref.
Toxicity concerns	Biological systems may be at risk from certain ILs, particularly ones that include harmful cations or anions	Before using the formulation, biocompatible ILs are chosen, and their cytotoxicity is assessed	70
High viscosity	The high viscosity of many ILs can make it difficult for them to mix and flow with other materials in DDS	For the necessary consistency, use low-viscosity ILs or dilute with solvents	178
Limited biodegradability	Concerns over long-term safety and environmental effects are raised by the restricted or sluggish biodegradability of certain ILs	Creating biodegradable ILs or adding chemicals to improve biodegradation	179
Chemical stability	The efficacy of several ILs as a DDS medium can be diminished by their degradation in the presence of light, heat, or moisture	Techniques that improve stability, including cautious storage conditions or encapsulation in protective carriers	180
Cost and scalability	It can be expensive to produce high-purity ILs, and it might be difficult to scale up their application for commercial DDS	Scaling up technology and optimizing synthetic processes to cut expenses	181, 182
Potential for immunogenic responses	When used in DDS, certain ILs may cause immunological reactions, which could result in inflammatory reactions or other negative effects	Preclinical testing to evaluate immune responses and the creation of immunologically suitable ILs	110, 183
Limited compatibility with other excipients	Some ILs may limit formulation flexibility by negatively interacting with common DDS excipients or medicinal components	IL–excipient interactions are systematically screened, and customized DDS are created for compatibility	184

8 Future directions of ILs in DDS

The development of ILs in drug delivery systems depends on logical design approaches that put safety, effectiveness, and environmental sustainability first. Future studies should concentrate on creating task-specific ILs that are suited to certain therapeutic requirements, especially those that have improved biocompatibility and decreased toxicity without sacrificing functional qualities.[161] Drug loading, release profiles, and overall therapeutic efficacy can be greatly enhanced by investigating the molecular-level interactions between ILs and biological molecules such as nucleic acids, peptides, and hydrophobic medications.[80] IL-functionalized liposomes, nanoparticles, and hydrogels are examples of emerging IL-based nanohybrid systems that show tremendous potential for overcoming biological barriers such as the blood–brain barrier or tumor microenvironment, allowing for more accurate and efficient medication targeting. Simultaneously, combining ILs with intelligent technologies like wearable biosensors, stimuli-responsive platforms, and 3D bioprinting may open up new avenues for real-time health monitoring and personalized therapy. Lastly, the development of green synthesis techniques that use affordable, renewable, and biodegradable feedstocks to satisfy environmental and regulatory requirements will be essential to the future scalability and adoption of ILs. Life cycle assessments and computational tools, such as QSAR models, should be used to guide the development of eco-safe ILs while maintaining their potent biomedical potential.

Conclusion

In the realm of drug delivery, ILs have become revolutionary materials because they provide a versatile platform that overcomes important shortcomings of traditional approaches. Their special physicochemical characteristics, including low volatility, variable solubility, and structural adaptability, make it possible to create sophisticated formulations that enhance medication stability, bioavailability, and targeted delivery. In addition to acting as solvents and excipients, ILs also act as active pharmaceutical ingredient transporters and functional nano structuring agents, improving the solubility of weakly water-soluble pharmaceuticals, stabilizing biomacromolecules, and providing controlled-release profiles. Their versatility in addressing a broad range of therapeutic difficulties is highlighted by their incorporation into many delivery modalities, including nanoparticles, emulsions, gels, and micelles. Despite their great potential, careful toxicological evaluations and logical molecular design are necessary for the safe and long-term use of ILs in pharmaceutical formulations. Safety issues have been greatly reduced by ongoing developments in green IL synthesis, computational modelling for toxicity prediction, and the creation of biodegradable and biocompatible ILs. Clinical translation, however, requires thorough *in vivo* research, lifecycle evaluations, and regulatory harmonization. Overall, by enabling precision treatments, reducing systemic toxicity, and pushing the boundaries of personalized medicine, the strategic use of ILs in drug delivery continues to transform pharmaceutical innovation.

Statement of human and animal rights

This article does not contain any studies on human and animal subjects performed by any of the authors.

Author contributions

Tewodros Assefa Chaklie, MD, is involved in original draft writing, data curation, software, figure drawing, table input, and conceptualization. Dr. Mohammad Abu Jafar Mazumder and Dr. Anwarul Hasan are involved in manuscript review and editing. Dr. Shihab Uddin is involved in conceptualization, figure input, reviewing and editing the original draft writing manuscript, supervision, project administration, and resource management.

Conflicts of interest

The authors assert that they don't have any identifiable conflicts.

Data availability

No data were used for the research described in the article.

Acknowledgements

This study was funded by the Interdisciplinary Research Center for Bio Systems and Machines, King Fahd University of Petroleum & Minerals, 31261, Dhahran, Saudi Arabia, and the funded project or fund number INBS2504. The authors acknowledge the Department of Bioengineering and the Interdisciplinary Research Center for Bio Systems and Machines, King Fahd University of Petroleum & Minerals, 31261, Dhahran, Saudi Arabia.

References

1 R. Ghosh, Discovery of Room Temperature Ionic Liquid: P C Rây versus P Walden, *Resonance*, 2021, **26**, 241–244.
2 T. Welton, Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis, *Chem. Rev.*, 1999, **99**, 2071–2083.
3 E. Kianfar and S. Mafi, Ionic Liquids: Properties, Application, and Synthesis, *Fine Chem. Eng.*, 2021, **2**, 21–29.
4 M. Goto and M. Moniruzzaman, *Application of Ionic Liquids in Drug Delivery*, Springer Nature, 2021, DOI: 10.1007/978-981-16-4365-1.
5 T. S. De Almeida, A. Júlio, J. P. Mota, P. Rijo and C. P. Reis, An Emerging Integration Between Ionic Liquids and

nanotechnology: General Uses and Future Prospects in Drug Delivery, *Ther. Delivery*, 2017, **8**, 461–473.
6 S. Gowda, *et al.*, Emerging applicative areas of ionic liquids in biomedical sciences: Unveiling new biological insights, *J. Mol. Liq.*, 2025, **427**, 127454.
7 D. R. MacFarlane, *et al.*, New dimensions in salt-solvent mixtures: A 4th evolution of ionic liquids, *Faraday Discuss.*, 2018, **206**, 9–28.
8 E. T. Adams Jr and J. M. Beckerdite, TABLE I; Self-Association Equilibrium Constants, *J. Phys. Chem.*, 1984, **88**, 73–80, https://pubs.acs.org/sharingguidelines.
9 G. Cravotto, *et al.*, Preparation of Second Generation Ionic Liquids by Efficient Solvent-Free Alkylation of N-Heterocycles with Chloroalkanes, *Molecules*, 2008, **13**, 149–156.
10 E. Kianfar and S. Mafi, Ionic Liquids: Properties, Application, and Synthesis, *Fine Chem. Eng.*, 2020, 22–31, DOI: 10.37256/fce.212021693.
11 I. B. Qader and K. Prasad, Recent Developments on Ionic Liquids and Deep Eutectic Solvents for Drug Delivery Applications, *Pharm. Res.*, 2022, **39**, 2367–2377.
12 M. Llaver, *et al.*, Task-specific ionic liquids: Applications in sample preparation and the chemistry behind their selectivity, *Adv. Sample Prep.*, 2022, **1**, 100004.
13 Y. Qu, Y. Zhao, D. Li and J. Sun, Task-specific ionic liquids for carbon dioxide absorption and conversion into value-added products, *Curr. Opin. Green Sustainable Chem.*, 2022, **34**, 100599.
14 B. A. D. Neto, A. A. M. Lapis and R. Y. Souza, Task-Specific Ionic Liquids: Design, Properties, and Applications, in *Encyclopedia of Ionic Liquids*, 2022, pp. 1273–1283, DOI: 10.1007/978-981-33-4221-7_33.
15 D. R. MacFarlane, *et al.*, New dimensions in salt–solvent mixtures: a 4th evolution of ionic liquids, *Faraday Discuss.*, 2017, **206**, 9–28.
16 A. Singh, N. Kaur, A. Parmar and H. K. Chopra, Structure and properties of Ionic liquids: Green aspects, *Ionic Liquids in Analytical Chemistry: New Insights and Recent Developments*, 2022, pp. 1–32, DOI: 10.1016/B978-0-12-823334-4.00004-7.
17 T. Mondal and P. Samanta, Study of Physicochemical Properties of Ionic Liquids, *Handbook of Ionic Liquids: Fundamentals, Applications and Sustainability*, 2023, pp. 51–67, DOI: 10.1002/9783527839520.CH3.
18 Y. Deng, *et al.*, When can ionic liquids be considered readily biodegradable? Biodegradation pathways of pyridinium, pyrrolidinium and ammonium-based ionic liquids, *Green Chem.*, 2015, **17**, 1479–1491.
19 M. M. Fernandes, *et al.*, Ionic Liquids as Biocompatible Antibacterial Agents: A Case Study on Structure-Related Bioactivity on Escherichia coli, *ACS Appl. Bio Mater.*, 2022, **5**, 5181–5189.
20 A. Pratap Singh, *et al.*, Environmentally benign tetramethylguanidinium cation based ionic liquids, *New J. Chem.*, 2017, **41**, 12268–12277.
21 B. S. Gupta, M. Taha and M. J. Lee, Self-buffering and biocompatible ionic liquid based biological media for enzymatic research, *RSC Adv.*, 2015, **5**, 106764–106773.
22 H. Kumar and G. Kaur, Scrutinizing Self-Assembly, Surface Activity and Aggregation Behavior of Mixtures of Imidazolium Based Ionic Liquids and Surfactants: A Comprehensive Review, *Front. Chem.*, 2021, **9**, 667941.
23 J. H. Davis and K. J. Forrester, Thiazolium-ion based organic ionic liquids (OILs).1,2 Novel OILs which promote the benzoin condensation, *Tetrahedron Lett.*, 1999, **40**, 1621–1622.
24 H. S. Dhattarwal and H. K. Kashyap, Unique and generic structural features of cholinium amino acid-based biocompatible ionic liquids, *Phys. Chem. Chem. Phys.*, 2021, **23**, 10662–10669.
25 R. Md Moshikur and M. Goto, Pharmaceutical Applications of Ionic Liquids: A Personal Account, *Chem. Rec.*, 2023, **23**, e202300026.
26 J. M. Gomes, S. S. Silva, L. C. Rodrigues and R. L. Reis, Alginate/acemannan-based beads loaded with a biocompatible ionic liquid as a bioactive delivery system, *Int. J. Biol. Macromol.*, 2023, **242**, 125026.
27 C. M. Hamadani, *et al.*, Improved nanoformulation and bio-functionalization of linear-dendritic block copolymers with biocompatible ionic liquids, *Nanoscale*, 2022, **14**, 6021–6036.
28 J. J. Andreu, E. Falomir, E. García-Verdugo and B. Altava, Tailored amino acid-derived ionic Liquids: Precision chemotherapy for tumors, *J. Mol. Liq.*, 2024, **411**, 125698.
29 Q. Zhu, *et al.*, Highly efficient one-pot bioethanol production from corn stalk with biocompatible ionic liquids, *Bioresour. Technol. Rep.*, 2023, **22**, 101461.
30 S. Uddin, *et al.*, Lipid-Based Ionic-Liquid-Mediated Nanodispersions as Biocompatible Carriers for the Enhanced Transdermal Delivery of a Peptide Drug, *ACS Appl. Bio Mater.*, 2021, **4**, 6256–6267.
31 M. Ghirardello, *et al.*, Synthesis of Chiral Ionic Liquids from Natural Monosaccharides, *Eur. J. Org. Chem.*, 2022, **2022**, e202200100.
32 S. Jopp, T. Fleischhammer, A. Lavrentieva, S. Kara and J. Meyer, Synthesis, biocompatibility, and antimicrobial properties of glucose-based ionic liquids, *RSC Sustainability*, 2023, **1**, 1751–1764.
33 K. Mikami, *Green Reaction Media in Organic Synthesis*, 2007, pp. 1–187, DOI: 10.1002/9780470988770.
34 P. Wasserscheid and W. Keim, Ionic liquids – New 'solutions' for transition metal catalysis, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772–3789, DOI: 10.1002/1521-3773(20001103)39:21<3772::aid-anie3772>3.0.co;2-5, Preprint.
35 M. J. Earle, *et al.*, The distillation and volatility of ionic liquids, *Nature*, 2006, **439**, 831–834.
36 S. K. Singh and A. W. Savoy, Ionic liquids synthesis and applications: An overview, *J. Mol. Liq.*, 2020, **297**, 112038.
37 T. Welton, Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis, *Chem. Rev.*, 1999, **99**, 2071–2083.

38 Y. Fukaya, Y. Iizuka, K. Sekikawa and H. Ohno, Bio ionic liquids: Room temperature ionic liquids composed wholly of biomaterials, *Green Chem.*, 2007, **9**, 1155–1157.
39 C. M. Hamadani, *et al.*, Improved nanoformulation and bio-functionalization of linear-dendritic block copolymers with biocompatible ionic liquids, *Nanoscale*, 2022, **14**, 6021–6036.
40 M. Villanueva, *et al.*, Effect of alkyl chain length on the thermal properties and toxicity of n-alkyl-ammonium nitrate ionic liquids (n = 2, 3, 4, 5, 6, 8) for energy applications, *J. Therm. Anal. Calorim.*, 2024, **150**, 6851–6861.
41 Y. Yang, *et al.*, Agile Construction of Porous Organic Frameworks Pending Carboxylic Acids and Imidazolium-Based Ionic Liquids for the Efficient Fixation of CO2to Cyclic Carbonates, *ACS Sustainable Chem. Eng.*, 2022, **10**, 7990–8001.
42 W. Xue, *et al.*, Selective extraction of Nd(III) by novel carboxylic acid based ionic liquids without diluent from waste NdFeB magnets, *J. Mol. Liq.*, 2022, **364**, 119919.
43 M. Ahmed, S. Bhowmick, A. Filippov, P. Johansson and F. U. Shah, Ionic Liquids and Electrolytes with Flexible Aromatic Anions, *Chem. – Eur. J.*, 2023, **29**, e202301000.
44 R. Adavodi and G. Dini, Benzotriazoium Bis(2-Ethylhexyl) Phosphate Ionic Liquid as a Catalyst and Multifunctional Lubricant Additive: Synthesis, Optimization, Characterization, and Tribological Evaluation, *Arabian J. Sci. Eng.*, 2024, **49**, 7995–8010.
45 Y. Xiao, *et al.*, Enhanced proton conductivity and stability of polybenzimidazole membranes at low phosphoric acid doping levels via constructing efficient proton transport pathways with ionic liquids and carbon nanotubes, *J. Power Sources*, 2022, **543**, 231802.
46 N. Lisiecka, *et al.*, Effect of cation hydrophobicity in dicamba-based ionic liquids on herbicide accumulation and bioavailability in soil, *J. Environ. Chem. Eng.*, 2023, **11**, 111008.
47 R. S. Varma and V. V. Namboodiri, An expeditious solvent-free route to ionic liquids using microwaves, *Chem. Commun.*, 2001, 643–644, DOI: 10.1039/b101375k.
48 B. M. Khadilkar and G. L. Rebeiro, Microwave-assisted synthesis of room-temperature ionic liquid precursor in closed vessel, *Org. Process Res. Dev.*, 2002, **6**, 826–828.
49 H. Ohno and K. Fukumoto, Amino acid ionic liquids, *Acc. Chem. Res.*, 2007, **40**, 1122–1129.
50 V. V. Namboodiri and R. S. Varma, Solvent-Free Sonochemical Preparation of Ionic Liquids, *Org. Lett.*, 2002, **4**, 3161–3163.
51 H. Naeimi and Z. S. Nazifi, A facile one-pot ultrasound assisted synthesis of 1,8-dioxo-octahydroxanthene derivatives catalyzed by Brønsted acidic ionic liquid (BAIL) under green conditions, *J. Ind. Eng. Chem.*, 2014, **20**, 1043–1049.
52 D. Kulkarni, *et al.*, Surface Functionalization of Nanofibers: The Multifaceted Approach for Advanced Biomedical Applications, *Nanomaterials*, 2022, **12**, 3899.
53 A. Kulshrestha, P. S. Gehlot and A. Kumar, Magnetic proline-based ionic liquid surfactant as a nano-carrier for hydrophobic drug delivery, *J. Mater. Chem. B*, 2020, **8**, 3050–3057.
54 M. Messali, *et al.*, New pyridazinium-based ionic liquids: An eco-friendly ultrasound-assisted synthesis, characterization and biological activity, *S. Afr. J. Chem.*, 2015, **68**, 219–225.
55 M. Mohan, J. D. Keasling, B. A. Simmons and S. Singh, In silico COSMO-RS predictive screening of ionic liquids for the dissolution of plastic, *Green Chem.*, 2022, **24**, 4140–4152.
56 M. Mobin, R. Aslam, R. Salim and S. Kaya, An investigation on the synthesis, characterization and anti-corrosion properties of choline based ionic liquids as novel and environmentally friendly inhibitors for mild steel corrosion in 5% HCl, *J. Colloid Interface Sci.*, 2022, **620**, 293–312.
57 Y. Pei, *et al.*, Recent progress in ionic liquids-based microemulsions, *Zhongguo Kexue: Huaxue*, 2020, **50**, 211–222.
58 C. M. Hamadani, *et al.*, Development of ionic liquid-coated PLGA nanoparticles for applications in intravenous drug delivery, *Nat. Protoc.*, 2023, **18**, 2509–2557.
59 P. Khare, *et al.*, Ionic liquid-coated lipid nanoparticles demonstrate prolonged circulation and brain uptake via red blood cell hitchhiking, *J. Controlled Release*, 2026, **389**, 114487.
60 M. K. Ali, R. M. Moshikur, R. Wakabayashi, M. Moniruzzaman and M. Goto, Biocompatible Ionic Liquid-Mediated Micelles for Enhanced Transdermal Delivery of Paclitaxel, *ACS Appl. Mater. Interfaces*, 2021, **13**, 19745–19755.
61 S. S. de Jesus and R. Maciel Filho, Are ionic liquids eco-friendly?, *Renewable Sustainable Energy Rev.*, 2022, **157**, 112039.
62 J. L. Shamshina and R. D. Rogers, Ionic Liquids: New Forms of Active Pharmaceutical Ingredients with Unique, Tunable Properties, *Chem. Rev.*, 2023, **123**, 11894–11953.
63 Y. Zhuo, H. L. Cheng, Y. G. Zhao and H. R. Cui, Ionic Liquids in Pharmaceutical and Biomedical Applications: A Review, *Pharmaceutics*, 2024, **16**, 151.
64 M. Handa, *et al.*, Active pharmaceutical ingredients (APIs) in ionic liquids: An effective approach for API physiochemical parameter optimization, *Drug Discovery Today*, 2022, **27**, 2415–2424, DOI: 10.1016/j.drudis.2022.06.003, Preprint.
65 R. Ferraz, L. C. Branco, C. Prudêncio, J. P. Noronha and Ž. Petrovski, Ionic liquids as active pharmaceutical ingredients, *ChemMedChem*, 2011, **6**, 975–985.
66 E. E. Tanner, A. M. Curreri, J. P. Balkaran, N. C. Selig-Wober, A. B. Yang, C. Kendig and S. Mitragotri, Design Principles of Ionic Liquids for Transdermal Drug Delivery, *Adv. Mater.*, 2019, **31**, 1901103.
67 C. Janiak, Ionic liquids for the synthesis and stabilization of metal nanoparticles, *Z. Naturforsch., B: J. Chem. Sci.*, 2013, **68**, 1059–1089.

68 M. Matczuk, A. R. Timerbaev, B. K. Keppler and L. Ruzik, Ionic liquid-mediated drug delivery: A review on progress and challenges focused on poly(ionic liquid) nanoplatforms, *J. Mol. Liq.*, 2024, **399**, 124403.
69 A. Kulshrestha, S. Sharma, K. Singh and A. Kumar, Magnetoresponsive biocomposite hydrogels comprising gelatin and valine based magnetic ionic liquid surfactant as controlled release nanocarrier for drug delivery, *Mater. Adv.*, 2022, **3**, 484–492.
70 K. Kuroda, A simple overview of toxicity of ionic liquids and designs of biocompatible ionic liquids, *New J. Chem.*, 2022, **46**, 20047–20052.
71 M. Ploner, M. Petrelli, B. Shkodra, A. Tagliaferri, P. Lugli, D. Resnati, L. Petti and M. A. Costa Angeli, A comprehensive review on electrochemical cytokine detection in sweat, *Cell Rep. Phys. Sci.*, 2024, **5**(8), DOI: 10.1016/j.xcrp.2024.101985.
72 M. Subawickrama and N. R. Widanaarachchige, *et al.*, Advancements in Breathomics: Special Focus on Electrochemical Sensing and AI for Chronic Disease Diagnosis and Monitoring, *ACS Omega*, 2025, **10**, 4187–4196.
73 P. Migowski, P. Lozano and J. Dupont, Imidazolium based ionic liquid-phase green catalytic reactions, *Green Chem.*, 2023, **25**, 1237–1260.
74 K. Sood, Y. Saini and K. K. Thakur, Ionic liquids in catalysis: A review, *Mater. Today: Proc.*, 2021, **81**, 739–744.
75 A. Bohre, *et al.*, Recent advances in supported ionic liquid catalysts for sustainable biomass valorisation to high-value chemicals and fuels, *Chem. Eng. J.*, 2022, **450**, 138032.
76 K. Singh, S. Mehra and A. Kumar, Metal-based ionic liquids: effective catalysts in aqueous media for the selective production of vanillin from alkali lignin at room temperature, *Green Chem.*, 2022, **24**, 9629–9642.
77 H. Wang, *et al.*, Amphiphilic ionic liquids as catalysts for efficient synthesis of novel isosorbide-based optical polymers with good biocompatibility and tunable properties, *Chem. Eng. J.*, 2024, **485**, 149715.
78 P. L. Yang, *et al.*, Ionic Liquid as a Catalyst toward NIPU via a Microwave Radiation Process, *Ind. Eng. Chem. Res.*, 2024, **63**, 17430–17440.
79 T. Wang, C. Shen, G. Yu and X. Chen, The upcycling of polyethylene terephthalate using protic ionic liquids as catalyst, *Polym. Degrad. Stab.*, 2022, **203**, 110050.
80 M. Kumar Shukla, *et al.*, Role and Recent Advancements of Ionic Liquids in Drug Delivery Systems, *Pharmaceutics*, 2023, **15**, 702.
81 T. Furuishi, S. Taguchi, S. Wang, K. Fukuzawa and E. Yonemochi, The Development and Characterization of Novel Ionic Liquids Based on Mono- and Dicarboxylates with Meglumine for Drug Solubilizers and Skin Permeation Enhancers, *Pharmaceutics*, 2024, **16**, 322.
82 T. Oshizaka, *et al.*, Enhanced Drug Skin Permeation by Azone-Mimicking Ionic Liquids: Effects of Fatty Acids Forming Ionic Liquids, *Pharmaceutics*, 2025, **17**, 41.
83 A. B. P. Silva, *et al.*, Using dicationic ionic liquids to upgrade the cytotoxicity and solubility of poorly water-soluble drugs, *J. Ionic Liq.*, 2023, **3**, 100052.
84 Y. Huang, D. Ouyang and Y. Ji, The role of hydrogen-bond in solubilizing drugs by ionic liquids: A molecular dynamics and density functional theory study, *AIChE J.*, 2022, **68**, e17672.
85 Y. Zhuo, H. L. Cheng, Y. G. Zhao and H. R. Cui, Ionic Liquids in Pharmaceutical and Biomedical Applications: A Review, *Pharmaceutics*, 2024, **16**, 151.
86 S. Akkineni, M. Rawas-Qalaji, S. A. Kouzi, C. Chbib and M. N. Uddin, Exploring the Biological Activities of Ionic Liquids and Their Potential to Develop Novel Vaccine Adjuvants, *Vaccines*, 2025, **13**, 365.
87 H. E. Rasmy, S. A. Abouelmagd and E. A. Ibrahim, New Ionic Liquid Forms of Antituberculosis Drug Combinations for Optimized Stability and Dissolution, *AAPS PharmSciTech*, 2025, **26**, 27.
88 M. Khavani, A. Mehranfar and M. R. K. Mofrad, Effects of Ionic Liquids on the Stabilization Process of Gold Nanoparticles, *J. Phys. Chem. B*, 2022, **126**, 9617–9631.
89 G. Hema, N. Giri Lakshman, K. Palanisamy and M. Prakash, Hydration Pattern of Ionic Liquids in the Stabilization of Insulin Dimer: A Computational Perspective, *Adv. Theory Simul.*, 2025, **8**, 2400943.
90 S. Selvam, *et al.*, Photophysical study on synthesized triazolium ionic liquids and their stabilizing effect on native state of serum albumin, *J. Mol. Liq.*, 2024, **409**, 125463.
91 F. F. Magalhães, *et al.*, Tailoring the partitioning of proteins using ionic liquids as adjuvants in polymer-polymer aqueous biphasic systems, *Green Chem. Eng.*, 2022, **3**, 328–337.
92 A. M. Rashid and M. M. Ghareeb, Using ionic Liquids-Based Surfactant in formulating Nimodipine Polymeric Nanoparticles: A Promising Approach for Improved Performance, *Iraqi J. Pharm. Sci.*, 2025, **34**, 203–217.
93 B. Wang, Z. Zhu, J. Yin and X. Lu, Microemulsion system formed with new piperazinium-based surface-active ionic liquid, *J. Mol. Liq.*, 2023, **371**, 121103.
94 V. P. Priyanka, A. S. Harikrishna, V. Kesavan and R. L. Gardas, Synergistic interaction and antibacterial properties of surface-active mono- and di-cationic ionic liquids with ciprofloxacin, *J. Mol. Liq.*, 2024, **399**, 124359.
95 D. Baghel and M. K. Banjare, Influence of phosphonium-based ionic liquid on the micellization behavior of surfactants system and potential application in paracetamol drug aggregation, *J. Indian Chem. Soc.*, 2023, **100**, 101077.
96 V. P. Priyanka and R. L. Gardas, Unraveling the impact of mono- or di-cationic ionic liquids on sodium deoxycholate aggregation and their interactions with ciprofloxacin, *Colloids Surf., A*, 2024, **680**, 132698.
97 L. Li, *et al.*, Ionic Liquids: Momentous Tools in Transdermal Delivery of Biomacromolecules, *Adv. Ther.*, 2023, **6**, 2200332.
98 Z. Wang, Phase behavior of multi-stimuli-responsive ionic liquids-based micro-emulsion and its application in nano silica synthesis and curcumin encapsulation, *J. Mol. Liq.*, 2024, **393**, 123588.

99 R. Patel, *et al.*, Ionic liquid-Tween-20 based biocompatible microemulsion for the encapsulation of rifampicin, *J. Dispersion Sci. Technol.*, 2025, 100181.
100 Y. Shu, R. Xue, Y. Gao, W. Zhang and J. Wang, A thermo-responsive hydrogel loaded with an ionic liquid microemulsion for transdermal delivery of methotrexate, *J. Mater. Chem. B*, 2022, **11**, 5494–5502.
101 F. H. Nabila, *et al.*, Ionic liquid-mediated ethosome for transdermal delivery of insulin, *Chem. Commun.*, 2024, **60**, 4036–4039.
102 D. Zhang and H. Zhang, Highly sensitive SERS platform on isotropic ionic liquid-based liposome, *J. Mol. Liq.*, 2023, **391**, 123311.
103 M. K. Mandal, *et al.*, Investigations on the role of ionic liquid on the physicochemical characteristics and toxicological consequences of liposomes, *JCIS Open*, 2022, **6**, 100050.
104 X. Lin, *et al.*, Oil-in-ionic liquid nanoemulsion-based adjuvant simultaneously enhances the stability and immune responses of inactivated foot-and-mouth disease virus, *Int. J. Pharm.*, 2022, **625**, 122083.
105 F. Althobaiti, *et al.*, New Ionic Liquid Microemulsion-Mediated Synthesis of Silver Nanoparticles for Skin Bacterial Infection Treatments, *Antibiotics*, 2023, **12**, 247.
106 Z. Wang and H. Song, Phase behaviors, properties and potential application of temperature-responsive microemulsions based on tropine ionic liquids, *J. Mol. Liq.*, 2022, **368**, 120624.
107 A. Poustforoosh, The impact of cationic/anionic ratio on the physicochemical aspects of catanionic niosomes as a promising carrier for anticancer drugs, *J. Mol. Liq.*, 2024, **408**, 125338.
108 R. S. A. Solita, *et al.*, Inhibiting Stenotrophomonas maltophilia, a Pathogenic Bacterium Responsible for Kernel Rot Disease in Pili nut (Canarium ovatum Engl.) with Ionic Liquid-loaded Nanoemulsions, *Appl. Sci. Eng. Prog.*, 2025, **18**, 7417–7417.
109 H. Beitollahi, S. Tajik, M. R. Aflatoonian and A. Makarem, Glutathione detection at carbon paste electrode modified with ethyl 2-(4-ferrocenyl-[1,2,3]triazol-1-yl)acetate, ZnFe2O4 nano-particles and ionic liquid, *J. Electrochem. Sci. Eng.*, 2022, **12**, 209–217.
110 S. Uddin, *et al.*, Transdermal Delivery of Antigenic Protein Using Ionic Liquid-Based Nanocarriers for Tumor Immunotherapy, *ACS Appl. Bio Mater.*, 2022, **5**, 2586–2597.
111 D. Işın, E. Eksin and A. Erdem, Graphene-Oxide and Ionic Liquid Modified Electrodes for Electrochemical Sensing of Breast Cancer 1 Gene, *Biosensors*, 2022, **12**, 95.
112 A. Siddiquee, *et al.*, Binding Study of Antibacterial Drug Ciprofloxacin with Imidazolium-Based Ionic Liquids Having Different Halide Anions: A Spectroscopic and Density Functional Theory Analysis, *ACS Omega*, 2023, **8**, 42699–42710.
113 Z. Zhang, *et al.*, Antibacterial, anti-inflammatory and wet-adhesive poly(ionic liquid)-based oral patch for the treatment of oral ulcers with bacterial infection, *Acta Biomater.*, 2023, **166**, 254–265.
114 Z. Liu, X. Liu, B. Zhu, G. Wang and Y. Diao, The Antibacterial Activity and Mechanism of Imidazole Chloride Ionic Liquids on Staphylococcus Aureus, *Front. Microbiol.*, 2023, **14**, 1109972.
115 F. Faísca, *et al.*, Enhanced In Vitro Antiviral Activity of Hydroxychloroquine Ionic Liquids against SARS-CoV-2, *Pharmaceutics*, 2022, **14**, 877.
116 T. Gundolf, R. Kalb, P. Rossmanith and P. Mester, Bacterial Resistance Toward Antimicrobial Ionic Liquids Mediated by Multidrug Efflux Pumps, *Front. Microbiol.*, 2022, **13**, 883931.
117 M. Kuddushi, *et al.*, Temperature-Responsive Low Molecular Weight Ionic Liquid Based Gelator: An Approach to Fabricate an Anti-Cancer Drug-Loaded Hybrid Ionogel, *ChemSystemsChem*, 2020, **2**, e1900053.
118 I. Rivero Berti, *et al.*, Assessment of: In vitro cytotoxicity of imidazole ionic liquids and inclusion in targeted drug carriers containing violacein, *RSC Adv.*, 2020, **10**, 29336–29346.
119 A. Kumar, K. Kumari, S. Singh, I. Bahdur and P. Singh, Noscapine anticancer drug designed with ionic liquids to enhance solubility: DFT and ADME approach, *J. Mol. Liq.*, 2021, **325**, 115159.
120 Y. Shi, *et al.*, Enhancement of Anticancer Efficacy and Tumor Penetration of Sorafenib by Ionic Liquids, *Adv. Healthcare Mater.*, 2021, **10**, 2001455.
121 R. M. Moshikur, M. K. Ali, R. Wakabayashi, M. Moniruzzaman and M. Goto, Methotrexate-based ionic liquid as a potent anticancer drug for oral delivery: In vivo pharmacokinetics, biodistribution, and antitumor efficacy, *Int. J. Pharm.*, 2021, **608**, 121129.
122 A. R. Dias, J. Costa-Rodrigues, M. H. Fernandes, R. Ferraz and C. Prudêncio, The Anticancer Potential of Ionic Liquids, *ChemMedChem*, 2017, **12**, 11–18, DOI: 10.1002/cmdc.201600480, Preprint.
123 Y. Li, *et al.*, Enhanced transdermal delivery of insulin by choline-based ionic liquids, *Int. J. Pharm.*, 2024, **667**, 125006.
124 D. Satheesh and A. Rajendran, Anti-inflammatory and Anti-diabetic Activity of N1-(4-substitutedbenzyl)/Butyl-2-methyl-4-nitro-3-imidazolium (E)-3-(4-hydroxy-3-methoxyphenyl) acrylates, *J. Ionic Liq.*, 2025, 100148, DOI: 10.1016/j.jil.2025.100148.
125 N. A. Saqa, S. Khalil-Moghaddam and A. S. Shahvelayati, DABCO-based ionic liquid-promoted synthesis of indeno-benzofurans derivatives: Investigation of antioxidant and antidiabetic activities, *Heterocycl. Commun.*, 2022, **28**, 164–173.
126 E. Judy and N. Kishore, Prevention of insulin fibrillation by biocompatible choline-amino acid based ionic liquids: Biophysical insights, *Biochimie*, 2023, **207**, 20–32.
127 M. Asad, *et al.*, Colorimetric acetone sensor based on ionic liquid functionalized drug-mediated silver nanostructures, *J. Pharm. Biomed. Anal.*, 2022, **221**, 115043.

128 V. Vanik, *et al.*, Modulation of Insulin Amyloid Fibrillization in Imidazolium-Based Ionic Liquids with Hofmeister Series Anions, *Int. J. Mol. Sci.*, 2023, **24**, 9699.
129 B. Liu, *et al.*, Ionic liquid-based non-releasing antibacterial, anti-inflammatory, high-transparency hydrogel coupled with electrical stimulation for infected diabetic wound healing, *Composites, Part B*, 2022, **236**, 109804.
130 Y. Zong, *et al.*, An ionic liquid-functionalized near-infrared fluorescent hydrogel dressing for promoting wound healing and real-time monitoring hypochlorous acid at the diabetic wound site, *Sens. Actuators, B*, 2023, **394**, 134405.
131 J. Wang, *et al.*, An ionic liquid functionalized sericin hydrogel for drug-resistant bacteria-infected diabetic wound healing, *Chin. Chem. Lett.*, 2024, 109819, DOI: 10.1016/j.cclet.2024.109819.
132 W. S. He, *et al.*, Novel Synthesis of Phytosterol Ferulate Using Acidic Ionic Liquids as a Catalyst and Its Hypolipidemic Activity, *J. Agric. Food Chem.*, 2024, **72**, 2309–2320.
133 S. Tang, *et al.*, Environmentally Adaptable Organo–Ionic Gel-Based Electrodes for Real-Time On-Skin Electrocardiography Monitoring, *Adv. Healthcare Mater.*, 2023, **12**, 2300475.
134 Z. Poorshaab-Fallah, S. A. Shahidi, M. Baghayeri, A. Ghorbani-HasanSaraei and F. Kiani, Two Fold Amplification of Paste Electrode with Pt/Graphene Nanocomposite and Room Temperature Ionic Liquid to Monitoring of Vitamin B6 in Environmental and Food Samples, *Top. Catal.*, 2025, **68**, 510–518.
135 A. Holden, M. Krauss, R. O'Hara, J. Jones and D. K. Smith, A First-in-Human Trial of a New Aqueous Ionic Liquid Embolic Material in Distal Embolization Applications, *J. Vasc. Interv. Radiol.*, 2024, **35**, 232–240.e1.
136 A. Bekdemir, *et al.*, Ionic Liquid-Mediated Transdermal Delivery of Thrombosis-Detecting Nanosensors, *Adv. Healthcare Mater.*, 2022, **11**, 2102685.
137 T. M. Abdelghany, *et al.*, Potential for cardiac toxicity with methylimidazolium ionic liquids, *Ecotoxicol. Environ. Saf.*, 2023, **249**, 114439.
138 T. Fukuta, M. Ikeda-Imafuku and Y. Iwao, Development of Edaravone Ionic Liquids and Their Application for the Treatment of Cerebral Ischemia/Reperfusion Injury, *Mol. Pharmaceutics*, 2023, **20**, 3115–3126.
139 M. Bagheri, F. Ghaffari, H. Shekaari, M. Mokhtarpour and B. Golmohammadi, Molecular interactions between surface-active ionic liquids based on 2-hydroxyethylammonium laurate with gabapentin: electrical conductivity and surface tension studies, *RSC Adv.*, 2025, **15**, 26–37.
140 H. Tanigawa, N. Suzuki and T. Suzuki, Application of ionic liquid to enhance the nose-to-brain delivery of etodolac, *Eur. J. Pharm. Sci.*, 2022, **178**, 106290.
141 W. Wang, *et al.*, Conductive ionic liquid/chitosan hydrogels for neuronal cell differentiation, *Eng. Regener.*, 2022, **3**, 1–12.
142 S. Mutić, *et al.*, Electrochemical sensing platform for anticonvulsant drug carbamazepine detection based on graphitic carbon nitride and tetrabutylammonium chloride ionic liquid, *Electrochim. Acta*, 2024, **500**, 144755.
143 Z. Fan, W. Yu and Z. Liu, Ultra performance liquid chromatography with ultrasound assisted magnetic ionic liquid dispersive liquid liquid microextraction for determination of 20 neurotransmitters in spinal cords, *Sci. Rep.*, 2025, **15**, 5151.
144 X. Ding, C. Liu, W. Yu and Z. Liu, Magnetic ionic liquid-based liquid-liquid microextraction followed by ultra-performance liquid chromatography coupled with triple-quadrupole tandem mass spectrometry for simultaneous determination of neurotransmitters in human cerebrospinal fluid and plasma, *Talanta*, 2023, **262**, 144755.
145 F. Yin, *et al.*, A wearable device based on the ionic liquid decorated sponge-like ultraviolet-curable resin for recognizing human mental health conditions, *Nano Energy*, 2023, **118**, 109039.
146 H. Wang, *et al.*, Long-term exposure to ionic liquid [C8mim]Br induces the potential risk of anxiety and memory deterioration through disturbing neurotransmitter systems, *Neurotoxicology*, 2024, **104**, 66–74.
147 W. Ding, *et al.*, Neurotoxicity of Chronic Co-Exposure of Lead and Ionic Liquid in Common Carp: Synergistic or Antagonistic?, *Int. J. Mol. Sci.*, 2022, **23**, 6282.
148 J. C. Bastos, N. S. M. Vieira, M. M. Gaspar, A. B. Pereiro and J. M. M. Araújo, Human Cytotoxicity, Hemolytic Activity, Anti-Inflammatory Activity and Aqueous Solubility of Ibuprofen-Based Ionic Liquids, *Sustainable Chem.*, 2022, **3**, 358–375.
149 J. Klebeko, O. Krüger, M. Dubicki, P. Ossowicz-Rupniewska and E. Janus, Isopropyl Amino Acid Esters Ionic Liquids as Vehicles for Non-Steroidal Anti-Inflammatory Drugs in Potential Topical Drug Delivery Systems with Antimicrobial Activity, *Int. J. Mol. Sci.*, 2022, **23**, 13863.
150 D. Datta, S. P. Bandi and V. V. K. Venuganti, Ionic Liquid-Mediated Transdermal Delivery of Organogel Containing Cyclosporine A for the Effective Treatment of Psoriasis, *ACS Omega*, 2024, **9**(40), 41565–41582, DOI: 10.1021/acsomega.4c05346.
151 M. J. Goetz, *et al.*, An ionic liquid-based adjuvant for modulating cellular and humoral immune responses, *J. Controlled Release*, 2024, **376**, 632–645.
152 A. B. Santamarina, *et al.*, Supplementation of carotenoids from peach palm waste (Bactris gasipaes) obtained with an ionic liquid mediated process displays kidney anti-inflammatory and antioxidant outcomes, *Food Chem.: X*, 2022, **13**, 100245.
153 T. Li, *et al.*, Ionic liquid microwave-assisted hydrodistillation extraction of Angelica sinensis essential oil and its own anti-inflammatory and antioxidant activities, *J. Appl. Res. Med. Aromat. Plants*, 2024, **39**, 100538.
154 M. T. García, E. Bautista, A. de la Fuente and L. Pérez, Cholinium-Based Ionic Liquids as Promising Antimicrobial Agents in Pharmaceutical Applications: Surface Activity,

Antibacterial Activity and Ecotoxicological Profile, *Pharmaceutics*, 2023, **15**, 1806.

155 Y. Sheng, *et al.*, Ionic co-aggregates based intravenous drug delivery: Evaluation on kinetics and distribution of the drug payloads and nanocarriers, *Int. J. Pharm.*, 2024, **665**, 124657.

156 A. C. Leitch, T. M. Abdelghany, A. Charlton, M. Cooke and M. C. Wright, Ionic Liquid 1-Octyl-3-Methylimidazolium (M8OI) Is Mono-Oxygenated by CYP3A4 and CYP3A5 in Adult Human Liver, *J. Xenobiot.*, 2024, **14**, 907–922.

157 K. M. Docherty, M. V. Joyce, K. J. Kulacki and C. F. Kulpa, Microbial biodegradation and metabolite toxicity of three pyridinium-based cation ionic liquids, *Green Chem.*, 2010, **12**, 701–771.

158 S. Stolte, *et al.*, Primary biodegradation of ionic liquid cations, identification of degradation products of 1-methyl-3-octylimidazolium chloride and electrochemical wastewater treatment of poorly biodegradable compounds, *Green Chem.*, 2008, **10**, 214–222.

159 I. L. Gonçalves Pereira, A. L. Ziulkoski, K. M. Zepon, L. A. Kanis and H. S. Schrekker, Ionic Liquids in Pharmaceuticals: A Scoping Review of Formulation Strategies, *ACS Omega*, 2026, **11**, 260–303, DOI: 10.1021/acsomega.5c08558, Preprint.

160 M. R. Chowdhury, *et al.*, In vivo biocompatibility, pharmacokinetics, antitumor efficacy, and hypersensitivity evaluation of ionic liquid-mediated paclitaxel formulations, *Int. J. Pharm.*, 2019, **565**, 219–226.

161 Y. Zhang, *et al.*, Ionic liquids in transdermal drug delivery system: Current applications and future perspectives, *Chin. Chem. Lett.*, 2023, **34**, 107631.

162 S. Passerini and G. B. Appetecchi, Toward more environmentally friendly routes to high purity ionic liquids, *MRS Bull.*, 2013, **38**, 540–547.

163 J. L. Ferguson, *et al.*, A greener, halide-free approach to ionic liquid synthesis, *Pure Appl. Chem.*, 2012, **84**, 723–744.

164 M. Torkzadeh and M. Moosavi, Multiscale modeling of CO2 capture in dicationic ionic liquids: Evaluating the influence of hydroxyl groups using DFT-IR, COSMO-RS, and MD simulation methods, *J. Chem. Phys.*, 2024, **160**, 154701.

165 A. Yazdani, M. Sivapragasam, J. M. Leveque and M. Moniruzzaman, Microbial Biocompatibility and Biodegradability of Choline-Amino Acid Based Ionic Liquids, *J. Microb. Biochem. Technol.*, 2016, **8**, 446–452.

166 M. M. Fernandes, *et al.*, Ionic Liquids as Biocompatible Antibacterial Agents: A Case Study on Structure-Related Bioactivity on Escherichia coli, *ACS Appl. Bio Mater.*, 2022, **5**, 5181–5189.

167 R. A. Dee, *et al.*, NTP Technical Report on the Toxicity Studies of Select Ionic Liquids (1-Ethyl-3-Methylimidazolium Chloride, 1-Butyl-3-Methylimidazolium Chloride, 1-Butyl-1-Methylpyrrolidinium Chloride, and N-Butylpyridinium Chloride) Administered in Drinking Water to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats and B6C3F1/N Mice, *NTP Developmental and Reproductive Toxicity Technical Report Series*, 2022, pp. 1–209, DOI: 10.22427/NTP-TOX-103.

168 X. He, *et al.*, Comparison of Eco-Friendly Ionic Liquids and Commercial Bio-Derived Lubricant Additives in Terms of Tribological Performance and Aquatic Toxicity, *Molecules*, 2024, **29**, 3851.

169 D. V. Sowbhagyam, Ionic Liquids as Green Solvents: A Comprehensive Review, *Int. Res. J. Adv. Eng. Hub*, 2024, **2**, 220–224, https://irjaeh.com.

170 B. Roy, U. Pal, M. Kar and D. R. MacFarlane, Recent strategies for improving the performance of ionic liquids as battery electrolytes, *Curr. Opin. Green Sustainable Chem.*, 2022, **37**, 100676.

171 J. M. Andanson, X. Meng, M. Traïkia and P. Husson, Quantification of the impact of water as an impurity on standard physico-chemical properties of ionic liquids, *J. Chem. Thermodyn.*, 2016, **94**, 169–176.

172 Z. Fei, T. J. Geldbach, D. Zhao and P. J. Dyson, From dysfunction to bis-function: On the design and applications of functionalised ionic liquids, *Chem. – Eur. J.*, 2006, **12**, 2122–2130.

173 A. D. Sawant, D. G. Raut, N. B. Darvatkar and M. M. Salunkhe, Recent developments of task-specific ionic liquids in organic synthesis, *Green Chem. Lett. Rev.*, 2011, **4**, 41–54.

174 R. R. Reddy, J. G. Reddy and B. P. Kumar, NMR investigations on binding and dynamics of imidazolium-based ionic liquids with HEWL, *Phys. Chem. Chem. Phys.*, 2020, **22**, 23824–23836, DOI: 10.1039/D0CP04584E, https://pubs.rsc.org/en/content/articlehtml/2020/cp/d0cp04584e.

175 S. Farooq and Z. Naureen, Potential hazards of ionic liquids: a word of caution, in *Advanced Applications of Ionic Liquids*, 2023, pp. 497–521, DOI: 10.1016/B978-0-323-99921-2.00017-3.

176 F. Al-Akayleh, M. Al-Remawi, A. S. A. Ali Agha and E. S. M. Abu-Nameh, Applications and Risk Assessments of Ionic Liquids in Chemical and Pharmaceutical Domains: An Updated Overview, *Jordan J. Chem.*, 2023, **18**, 53–76.

177 K. S. Egorova and V. P. Ananikov, Toxicity of Ionic Liquids: Eco(cyto)activity as Complicated, but Unavoidable Parameter for Task-Specific Optimization, *ChemSusChem*, 2014, **7**, 336–360.

178 Y. Fang, *et al.*, Synthesis of Low-Viscosity Ionic Liquids for Application in Dye-Sensitized Solar Cells, *Chem. – Asian J.*, 2019, **14**, 4201–4206.

179 L. K. S. Gujjala, *et al.*, Advances in ionic liquids: Synthesis, environmental remediation and reusability, *J. Mol. Liq.*, 2024, **396**, 123896.

180 F. Nardelli, *et al.*, Thermal Stability of Ionic Liquids: Effect of Metals, *Appl. Sci.*, 2022, **12**, 1652.

181 M. Choi, *et al.*, Economically Viable Process for Synthesizing and Purifying Ionic Liquids: 1-Butyl-3-methyl

Imidazolium Tetrafluoroborate, *Ind. Eng. Chem. Res.*, 2024, **63**, 10373–10379.
182 M. Lejeune, *et al.*, Easy to scale up synthesis of a high-purity piperidinium based ionic liquid combining both sustainability and cost-effectiveness, *J. Ionic Liq.*, 2024, **4**, 100076.
183 R. Islam, *et al.*, Ionic Liquid-Based Immunization Patch for the Transdermal Delivery of Antigens, *Molecules*, 2024, **29**, 2995.
184 B. Gorain, *et al.*, Drug–Excipient Interaction and Incompatibilities, *Dosage Form Des. Parameters*, 2018, **2**, 363–402.