Chapter

Applications of Ionic Liquids in Pharmaceuticals

Sadia Rani, Ali Irfan, Samina Aslam, Gamal A. Shazly, Huma Hameed, Muhammad Zaman, Noreen Samad and Yousef A. Bin Jardan

Abstract

Ionic liquids (ILs) have emerged as a cutting-edge frontier in the realm of science and technology, offering a unique blend of tunable physicochemical and biological features with eco-friendly characteristics. Thus, ILs exhibit a broad spectrum of applications in pharmacology, pharmaceuticals, medicine, and pharmaceutical fields, providing solutions to challenges in drug formulation and delivery. The focus of this chapter is on the application of IL methodologies and strategies to resolve critical issues within the pharmaceutical field, such as polymorphism, low solubility, stability, and bioavailability, which are problems with solid-state pharmaceuticals. The innovative use of ILs as carriers for active pharmaceutical ingredients (APIs) presents a highly promising avenue for addressing these challenges. In conclusion, this chapter detailed the utilization of ILs in pharmaceutical applications, and the strategic design of liquid salts has the potential to revolutionize the way we address critical issues in drug development, manufacturing, and developing biocompatible ILs.

Keywords: ionic liquids (ILs), ILs as solvent, ILs in drug delivery, ILs in drug formulations, API-ILs, ILs in drug extraction, toxicity & biodegradability of ILs

1. Introduction

The current challenging task for the pharmaceutical industries is the development of safe, effective and smart chemotherapeutic formulations, and delivery systems for the management of various diseases [1]. Pharmaceutical industry portfolios are facing an ever-increasing issue with the limited aqueous solubility of active pharmaceutical ingredients (APIs) in biopharmaceutical classification system class II drugs [2]. The difficulties encountered in the development of new drug formulations are mainly associated with the slow dissolution of APIs in biological fluids, which leads to insufficient and irregular systematic exposure, resulting in suboptimal clinical efficacy. The pharmaceutical companies are actively exploring various strategies to surmount these challenges, recognizing them as pivotal for enhancing drug performance. Some of the approaches under investigation include prodrug [2, 3], micellar system [4], salt formation [5], solid dispersions [6], and crystal engineering [7].

The pharmaceutical sector was initially motivated to investigate ILs due to their distinct characteristics and potential as environmentally friendly solvents. Ionic liquids (ILs) are defined as solvents with a 1:1 ratio of bulky, asymmetric cations and anions that are shaped by non-directional ionic interactions and exist as liquids below 100°C [8]. Other names for ILs include ionic glasses, ionic melts, designer solvents, fusion salts, green solvents, ionic fluids, liquid electrolytes, and solvents of the future [9].

These solvents belong to a unique class that is ideal for biological material formulation and development while also being environmentally benign. Paul Walden developed ethylammonium nitrate, the first ionic liquid, in 1914 [10]. Because of how difficult it was to handle and how sensitive it was to moisture and air, this initial ionic liquid was not employed much. This was altered in 1992 when Wilkes and Zaworotko provided the first set of imidazolium cation-based air- and moisture-stable ionic liquids [11]. Since then, these have found widespread application in a number of interdisciplinary domains, including biomedicine, engineering, and material chemistry [8, 12–14]. With the expansion of their chemical diversity, ILs have been further subdivided into numerous types, such as supported IL membranes (SILMs) [15] that comprise composites of ILs supported on metal–organic frameworks (MOFs) [16], task-specific ILs (TSILs) [17], room-temperature ILs (RTILs) [18], polyionic liquids (PILs) [19], and so on. It is frequently necessary for scientists and engineers to swiftly screen for appropriate ILs for a particular process. Ionic liquids often consist of inorganic anions and organic cations that include nitrogen [20]. **Figure 1** illustrates a few typical cation and anion structures [8, 21, 22].

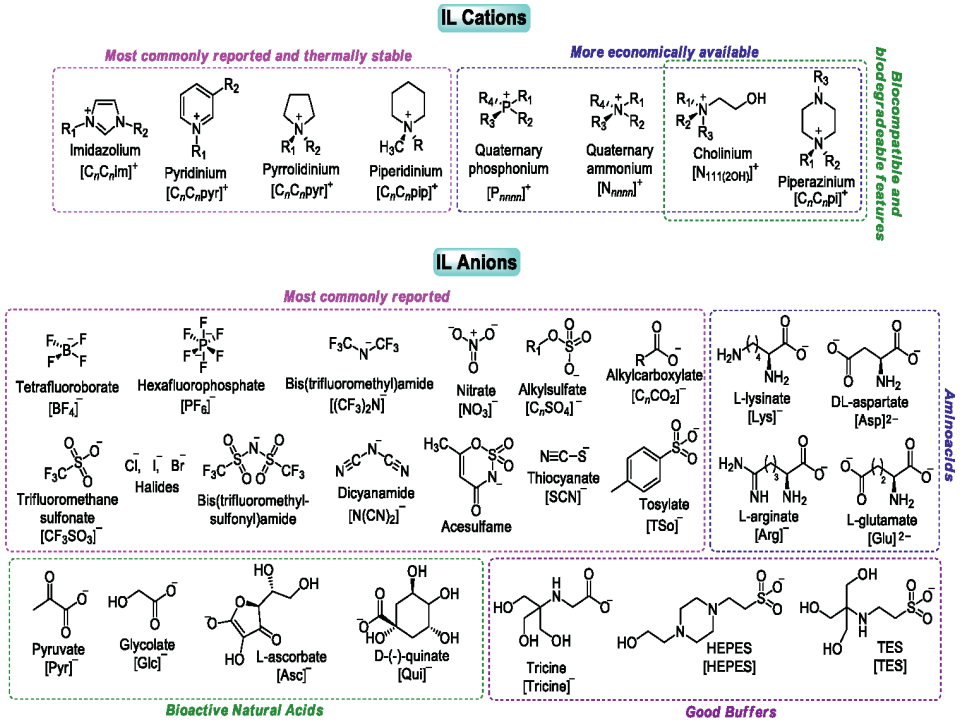


Figure 1.
Examples of IL cations and anions' chemical structures.

2. Evolution of ionic liquids

Four generations of ILs are currently on the market for different purpose (**Figure 2**) [1, 25].

2.1 Generation 1

Particular physical characteristics of the first generation of ILs include a low melting point, good thermal stability, reduced vapor pressure, and increased fluidity [26–28]. These ILs could take the place of organic solvents and agents that are flammable and bad for the environment. The majority of first-generation ILs, including $[C_4MIM][BF_4]$ and $[C_4MIM][PF_6]$, are aquatic ecotoxic and poorly biodegradable. But the first-generation ILs are also linked to additional weakly coordinating anions such as methylsulfate TFA, triflate, and TFSA [26, 27].

2.2 Generation 2

With their customizable physical and chemical characteristics, second-generation ILs are particularly useful in metal ion complexation, lubricants, and energetic materials [23, 26, 27]. These ILs have higher concentrations of biocompatible cations and anions that come from naturally occurring, reasonably priced, environmentally benign sources such as amino acids and carbohydrates. For instance, cholinium ILs can be made by reacting a number of naturally available carboxylic acids with cheap choline hydroxide to generate carboxylate salts and water as the only byproduct [27].

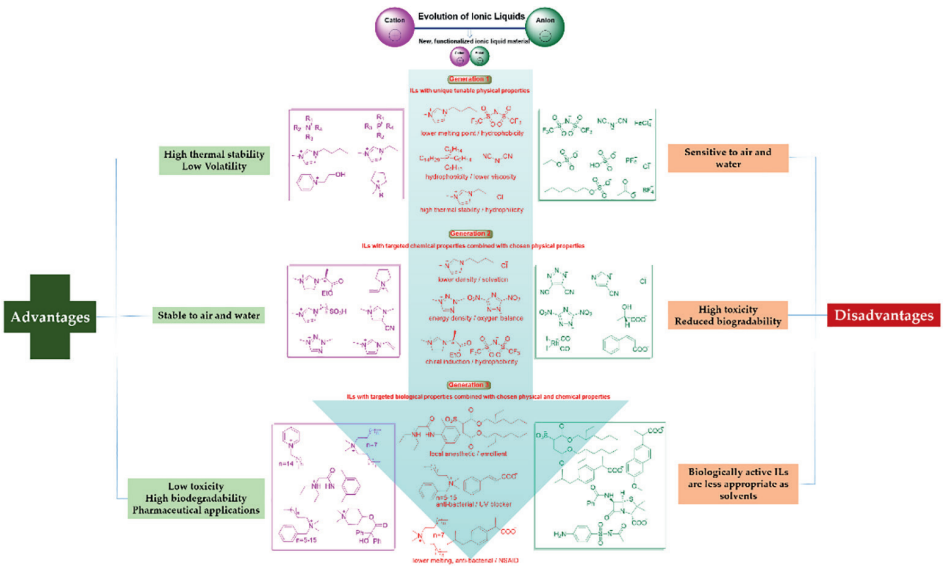


Figure 2.
Generations of ionic liquids: the evolution through time highlighting their characteristics, benefits, and drawbacks [23, 24].

2.3 Generation 3

Third-generation ILs have a biological feature added to their tunable chemical and physical properties, making them suitable for use in biological and pharmaceutical applications [23, 26, 29, 30]. Their suitability for biopharmaceutical applications, including local anesthetic, antifungal, antibacterial, and anticholinergic drugs, is mostly due to biologically active ions derived from recognized biocompatible sources. To fabricate various kinds of ILs, active pharmaceutical ingredients (APIs) or API precursors are primarily utilized as cations, anions, or both cations and anions [26, 29]. For biological uses, ILs in this group can also be easily biodegraded [31]. In comparison to the first- and second-generation ILs, the third-generation ILs also have some noteworthy advantages, including low production costs, an easy tunability of anions and cations, the structural and functional integrity of API, and controllable polymorphism [26].

In particular, the pharmaceutical industry is making more and more use of ILs because of their advantages in terms of drug delivery (oral, transdermal, and topical), stability, and solubility. Finally, by converting solid-state APIs into the IL form, potential issues with solid-state APIs can be easily overcome [32, 33]. Over the past 20 years, there has been a notable rise in the quantity of research publications concerning the incorporation of ILs in therapeutic formulations and administration [8, 34, 35]. In particular, the third generation of ILs has been used extensively to create ILs with desirable biological activity as active pharmaceutical ingredients (APIs) [36].

2.4 Generation 4

In 2018, the fourth generation of ionic liquids came out. These ionic liquids, whether in solution or after combining with other molecular liquids, had distinct and unanticipated properties and were biocompatible [25].

3. Applications of ionic liquids in pharmaceuticals

The primary areas of research for the next decade years will be the use of ILs in biomedicine [37]. In addition to their particular features and application as solvents, tunable ionic liquids (ILs) have enabled the emergence of novel, important topics. It is remarkable considering how many IL studies are now shifting their attention toward the biological sciences and medicine. Because of its unique attributes, the pharmaceutical industry is increasingly employing IL as a solvent [38]. Researchers can alter their characteristics to develop effective ILs that may be used in biomedical research. The uses of ILs in biomedicine have grown to include biosensors, drug delivery carriers, and other applications because of their structural tunability and biocompatibility [8, 10]. **Figure 3** shows examples of IL applications in each of these fields.

In order to increase a drug molecule's solubility, pharmacokinetic and pharmacodynamic capabilities, skin and intestinal permeability, formulation stability, and other attributes, ILs have been widely utilized in recent years to modify the physicochemical and biopharmaceutical properties of a therapeutic molecule [1, 8, 10]. The type of the cation and anion as well as the substituents on the cation or anion determine the biological and physicochemical properties of ILs.

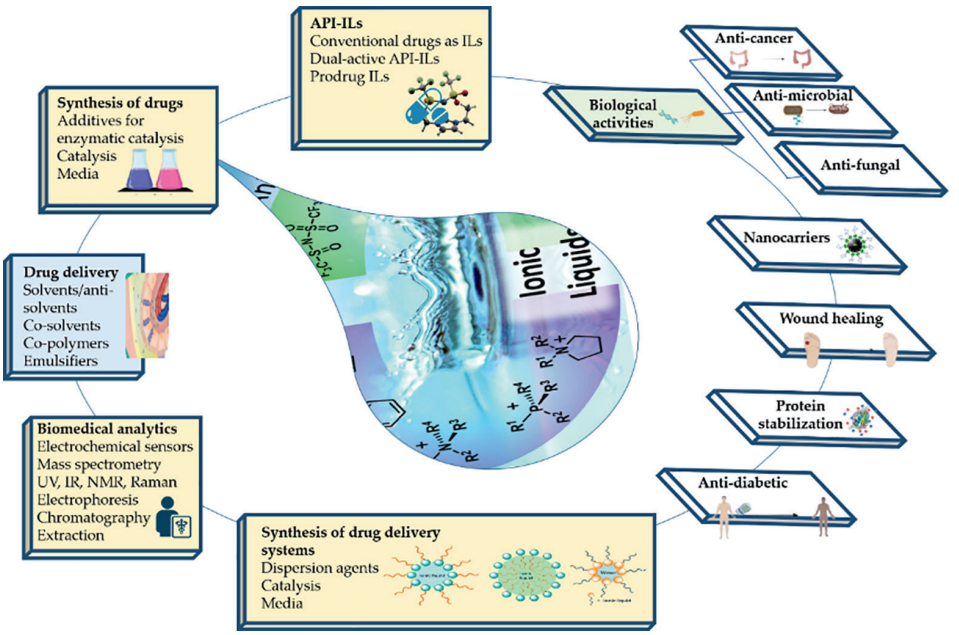


Figure 3.
Biomedical applications of ionic liquids in biomedicines.

Ionic liquids have been employed in biological applications since the late 1990s and early 2000s. They have been used to increase enzymatic catalytic efficiency and improve the thermostability of model proteins and enzymes (**Figure 4b**) [40, 41]. ILs were also employed as formulation excipients [42] for small compounds with poor water solubility and in controlled release systems [43]. Because of their basic chemical characteristics, which set them apart as particularly potent molecules for biomedical applications, ILs have gradually extended out into several domains over the years. Moreover, ILs have become a cutting-edge drug delivery platform [44–46]. ILs have the potential to increase the permeability of small and macromolecular drugs across biological barriers [10, 47], as well as to boost the solubility of poorly water-soluble pharmaceuticals by several to thousand folds [21]. Certain ILs are bioactive, showing antimicrobial (**Figure 5**) [49], anti-oxidant [8, 50], anti-cancer potential (**Figure 4a**) [51], anti-proliferative [52], anti-biofilm activities [53], and anti-diabetic (**Figure 6**) [54].

Levodopa is a widely used medicine for Parkinson's disease. ILs facilitated in the development of levodopa. IL was thought to be a more economical solvent than methanol, which was the typical solvent in the process but had the drawback of requiring higher pressure [1, 39]. Furthermore, ILs may be employed as a medium for the tailored synthesis of pharmaceutical nanocrystals. The use of nanocrystals in the delivery of poorly soluble drugs is very beneficial since it allows for improved bio-availability and solubility [55]. Ionic liquids were first employed in biomedical nano-carriers when they were used to synthesize and template silica nanoparticles for drug release [56], gene transfection [57], and antimicrobial applications. Subsequently, they were employed as emulsifiers [58] in nanocarriers as well as in nanocomposite systems [59] and the fabrication of nanoparticles using non-silica materials [60]. In order to enhance many of the properties of nanocarriers, such as biocompatibility,

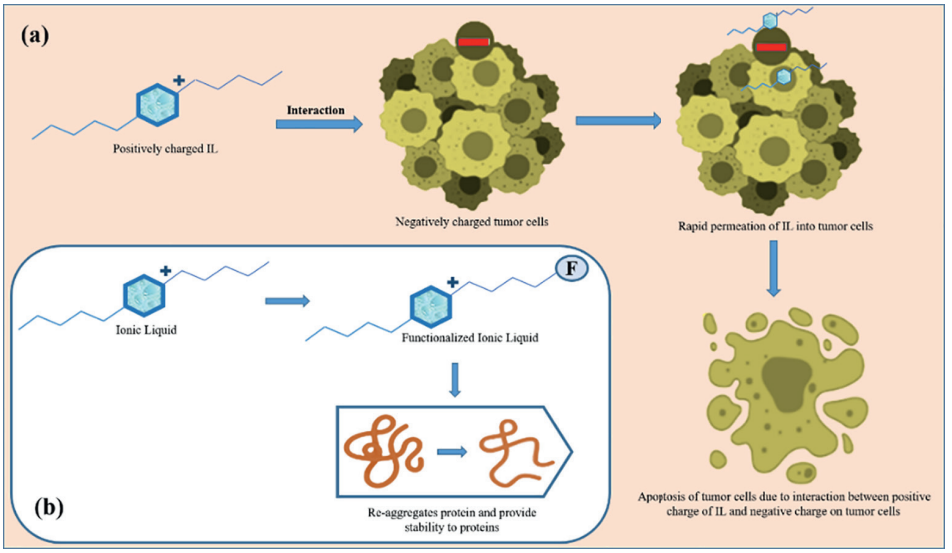


Figure 4.
(a) Schematic representation of ionic liquid demonstrating anticancer activity. (b) Diagram showing how the stability of proteins is affected by ionic liquid [39].

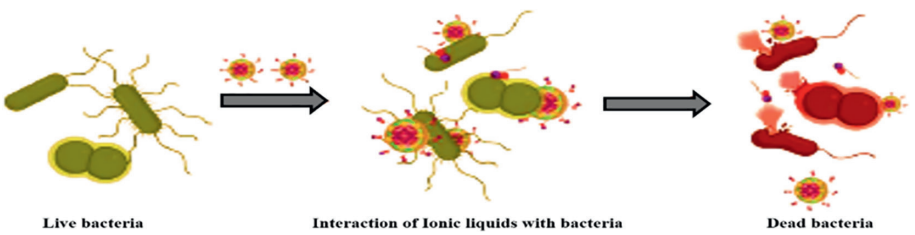


Figure 5.
Antibacterial activity of ionic liquids [48].

stability, and drug loading, ILs have also lately been utilized in their synthesis [61]. Use of ionic liquids in drug delivery system is displayed in **Table 1**.

3.1 Ionic liquids in drug synthesis

Ionic liquids in drug production have thereby started a new era. The use of ILs in a variety of chemical processes associated with the synthesis of medicines, their precursors or intermediates, and other substances with proven or potential biological activity has been documented by numerous research groups over the past 15 years. ILs are used in the synthesis of heterocyclic compounds that are used in biology and medicine, including imidazoles, furans, oxazoles, thiazoles, and quinolones [66]. These heterocyclic compounds are API's precursors with extensive biological activities, due to their high applicability in many chemical processes [67]. Ionic liquids have exciting applications in the manufacture of medicinal compounds and pharmaceuticals, among their many other uses in chemical processes. For example, the NSAID pravadoline was synthesized using $[C_4MIM][PF_6]$ as the media, signifying the first high-yield synthesis of a drug in an ionic liquid medium, as reported in 2000 [68]. By heating the IL to

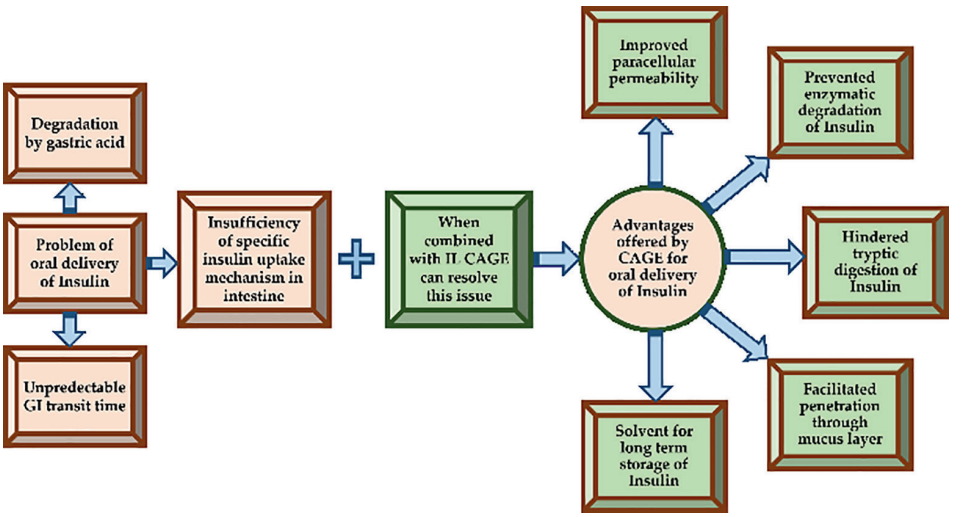


Figure 6.
An illustration showing the benefits of ionic liquid for diabetes [39].

IL used	Description	Application	Advantage	Ref.
Choline amino acid IL	The IL system boosted rutin's bioavailability and expanded its use in the treatment of cancer	To increase rutin's anticancer potential	Provided improved solubility of rutin (a poorly soluble drugs) and regulated drug delivery	[62]
1-Dodecyl-3-methylimidazolium bromide	One of Quercetin's problems is its solubility. The solubility issues can be resolved by surface active IL (SAILS). The non-ionic polymers' interaction with SAILs allowed for effective drug delivery	Anti-tumorous and anti-inflammatory actions	High anti-tumor effectiveness, improved hydrophobic drug solubility, and prolonged release	[63]
Choline and geranic acid	Enhancing the solubility of diabetes medications is crucial for augmenting their bioavailability. The CAGE IL system increased nobiletin's solubility	Antidiabetic potential	Enhanced drug permeability and prevented enzymatic breakdown	[64]
Lidocaine docusate	Lidocaine docusate, an API in its IL form, exhibited greater solubility than the parent molecule	As an analgesic	Increased solubility, effectiveness, and thermal stability	[23]
1-Methyl-3-butyl-imidazolium ibuprofenate and lidocainium ibuprofenate	The release pattern of API-IL increased as a result of its integration into the polymer voids	To enhance drug delivery	Enhanced pattern of drug release	[65]

Table 1.
Applications of ionic liquids in drug delivery systems.

150°C for 2 minutes, the proposed reaction, which uses potassium hydroxide as the base and IL as solvent, was able to improve the typical reaction yield (70–91%) to 95%. This approach results in an aqueous potassium chloride solution as the only chemical waste produced during the process, and it is simple to extract the API product and recycle and reuse the solvent (**Figure 7a**) [67]. The hydrogenation of 2-arylacrilic acids in [C_4MIM][BF_4] medium was published in 1997. The method to manufacture the nonsteroidal anti-inflammatory drug (NSAID) (S)-naproxen was used by the authors [69]. The electrosynthesis of naproxen by the electrocarboxylation of 2-(1-chloroethyl)-6-methoxynaphthalene using CO_2 employed [C_4C_1im][BF_4] as a reaction media (**Figure 7b**). When the solvent recovery was taken into account, this process produced high yields (89%) and conversion rates (90%), with 65% of atom economy. Even though the newly modified synthesis routes also enable the attainment of comparable high yields, the process in IL media employs CO_2 rather than CO, a well-known pollutant, and less expensive and more readily available catalysts (electron), which helps to develop "greener" routes for the synthesis of APIs [70]. Because of their special solvent qualities, ILs can act as both media and catalysts at the same time. For, example, a straightforward and effective iodination technique has been used to generate antifungal and antiprotozoal drugs, such as iodoquinol and clioquinol, respectively. In the absence of any oxidant, catalyst, or base, the IL ([C_4C_1py][DCI]) was utilized as both a solvent and an iodinating agent. By adding ICl (1.2 eq.), it is possible to regenerate the IL for up to five runs without losing its iodinating activity with a yield of >90% (**Figure 7c**) [71]. ILs can produce rapid microwave heating because of their charged composition, which leads to rapid and more efficient reactions. In a one-pot reaction, for instance, this method has been effectively used to directly lactamize lactones with >80% yields (**Figure 7d**) [72].

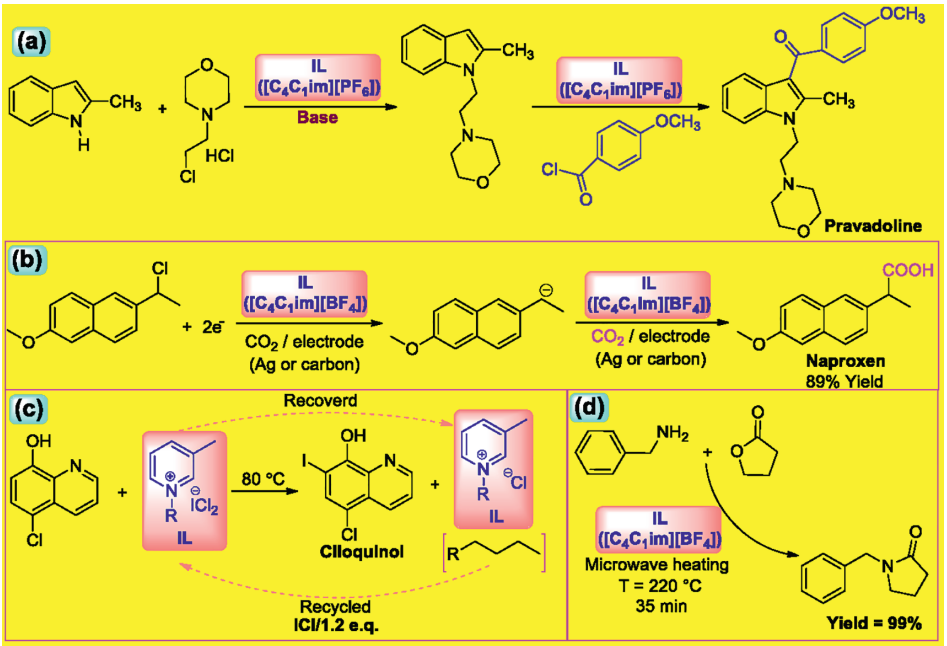


Figure 7.
(a) Synthesis of pravadoline in an IL media; (b) IL-based electrochemical production of naproxen; (c) synthesis of clioquinol in IL media; and (d) rapid and acid-free one-pot IL-based microwave methodology for direct synthesis of lactams.

Imidazolium salts are the most commonly utilized ionic liquids (ILs). **Table 2** shows that ILs are typically used as reaction media, which frequently functions as catalysts. Thus far, there have been descriptions of the synthesis of several NSAIDs [69, 71, 87], cholinesterase inhibitors [88], antiviral agents [73, 89], antimalarial [74], anticancer (**Figure 4a**) [89], antibacterial agents (**Figure 5**) [71, 90, 91], and radiolabeled molecular imaging and therapeutic agents [92]. Important examples of innovative medicinal compound synthesis using IL medium are displayed in **Table 2**.

3.2 Active Pharmaceutical Ingredient-Ionic Liquid (API-IL)

Active Pharmaceutical Ingredient-Ionic Liquids (API-ILs) are ionic liquids made from drug molecules, which are a novel approach to addressing the issues of bioavailability, low solubility, and thermal stability associated with traditional pharmaceutics. The idea of API-ILs is to preserve the drug's profile while giving it access to the advantageous characteristics of the solvent class and the counter-ion. The primary goal of the first wave of API-ILs was to synthesize these novel liquid salts and add well-known pharmacophores into them [23, 93]. Some examples of API-ILs are given in **Table 3**. Comparing IL-APIs to crystalline or solid pharmacological forms can reveal a number of benefits. One of the main issues in modern science is polymorphism, which can be resolved via IL-APIs [32]. Three methods exist for introducing API into IL systems (**Figure 8**). Type I involves utilizing API as an anion or cation through ionic binding; Type II requires covalent linkage; and Type III includes combining the two methods to create API-ILs with dual activity, allowing for the combination of comparable or different APIs in a single IL [33, 94]. The great majority of API-ILs that are currently on the market are Type I, meaning they have easily ionizable API moieties that can be utilized as IL anions or cations.

3.3 Application of ILs to drug extraction from natural products

Drug extraction from natural products uses a lot of volatile organic compounds (VOCs), which poses a major risk to the environment [95]. However, using ILs in place of conventional solvents may be able to reduce VOC emissions [96]. There have been numerous reports of recent attempts to use ILs as drug extraction solvents [97]. Protic ILs (PILs) were used to extract artemisinin, a strong naturally occurring antimalarial chemical, with water serving as the antisolvent [98]. Freire et al. have successfully carried out comprehensive extractions of prototypical alkaloids employing IL-based aqueous biphasic systems [97]. The findings indicate that the impact of impurity-causing agents (ILs) on the overall extraction of alkaloids is mostly determined by the characteristics of the cations rather than the anions. Materials that worked particularly well include $[C_2OHMIM]Cl$ (increased hydrogen-bonding capabilities) and $[C_7H_7MIM]Cl$ (improved aromatic interactions). The technique offers novel prospects for the concentration and isolation of other bioactive pharmaceuticals.

3.4 Toxicity and biocompatibility of ILs

The biodegradability and biocompatibility of ILs are generally unknown, which presents a challenge for their biological applications in pharmaceutics and the utilization of ILs as highly promising solvents for pharmaceutical and biological

IL	Role of IL	Compound	Activity	Ref.
$[C_1OC_2MIM][Ms]$, $[C_1OC_2$ MIM] [TFa], $[C_4MIM]$ [TFa]	Media	Stavudine	Anti-HIV drug	[73]
$[C_1C_1MIM]$ $[C_1SO_4]$	Dehydrating agent	Hydrazinyl phthalazines	Anti-malarial agents	[74]
$[C_1OC_2MIM][Ms]$, $[C_1OC_2$ MIM] [TFa], $[C_4MIM]$ [TFa]	Media	Trifluridine	Anti-HSV drug	[73]
$[C_2Py][BF_4]$ $[MCl_m]$ (MCl_m = $AlCl_3$, $FeCl_3$, $ZnCl_2$, $SnCl_2$, $SnCl_4$, CuCl)	Catalyst	1-[*(E)*-3-methyl-4-benzenesulfonyl-3-methylbut-2-enyl]-2,3,4,5-tetramethoxy-6-methylbenzene	Coenzyme Q_{10} intermediate	[75]
$[C_2MIM][Br]$	Media for enzymatic enantioselective esterification	*(R)*-modafinil	Wakefulness-promoting agent	[76]
$[C_4MIM][PF_6]$	Media	Pravadoline	NSAID	[68]
$[C_4C_1Py][ICl_2]$	Iodinating reagent	Clioquinol	Antifungal drug	[71]
$[C_4MIM][PF_6]$	IL phase, whole-cell catalysis	*(R)*-1-trimethylsilylethanol	Vital synthon for different silicon-containing drugs	[77]
$[C_4MIM][NTf_2]$	IL phase, whole-cell catalysis	(S)-3-chloro-1-phenyl-1-propanol	Precursor of antidepressant drugs	[78]
$[C_4C_1Py][ICl_2]$	Iodinating reagent	Iodoquinol	Antiprotozoal drug	[71]
$[C_4MIM][PF_6]$	Media for enzymatic enantioselective esterification	11α-hydroxy-16α,17-epoxyprogesterone	Intermediate in the steroidal drug-synthesis process	[79]
$[C_4MIM][BF_4]$	Media	Isoxazolines	Precursor of antimicrobial agents	[80]
$[C_4MIM][NTf_2]$	Media	3-phenylglycidol	Precursor of various drugs, e.g., tomoxetine and reboxetine	[81]
$[C_4MIM][PF_6]$, $[C_8C_1Py][BF_4]$	Media for enzymatic enantioselective esterification	*(R,S)*-1-chloro-3-(3,4-difluorophenoxy)-2-propanol	Intermediate in the synthesis of *(S)*-lubeluzole	[82]
$[C_4MIM][PF_6]$	IL phase, whole-cell catalysis	*(R)*-phenyl-acetylcarbinol	Precursor of (1*R*,2S)ephedrine and (1S,2S) pseudoephedrine	[83]
$[C_4MIM][PF_6]$	Media	Modafinil and its derivatives	Stimulant for treatment of sleep disorders	[84]

IL	Role of IL	Compound	Activity	Ref.
$[C_4MIM][BF_4]$	Media	*(S)*-naproxen	NSAID	[69]
$[C_5MIM][NO_3]$	Catalyst, media	α-tocopherol succinate	Vitamin E ester	[85]
Various imidazolium and pyridinium ILs	Media	Dronedarone intermediates	Anticardiac arrhythmia drug	[86]

Table 2.
Application of ILs in the synthesis of drugs and their intermediates.

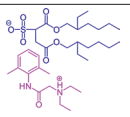
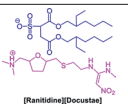
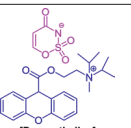
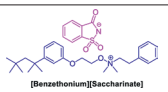
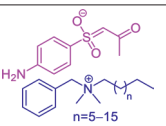
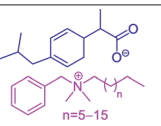
IL-APIs		
 [Lidocainium][Docustae] Emollient, pain reliever	 [Ranitidine][Docustae] Histamine H_2-receptor antagonist, emollient	 [Propantheline] [Acesulfamate] Antimuscarrinic, sweetener
 [Benzethonium][Saccharinate] Antiseptic, sweetener	 n=5–15 [Benzaalkoium] [Sulfacetamide] Antibacterial, anti-acne	 n=5–15 [Benzaalkoium][Ibuprofenate] Antibacterial, anti-inflammatory

Table 3.
Some examples of IL-APIs with their biological properties.

applications [99]. In order to be employed in biological applications, particularly for medicinal purposes, as solvents, co-solvents, or reagents, ILs should ideally have strong biodegradability and non-toxicity. Therefore, it is critical to evaluate the effects of ILs with respect to their environmental fate, ecotoxicity, bioaccumulation, and biodegradability [100–103].

To find non-toxic ILs, one approach is to modify the anion/cation combination of ILs, which can be utilized to fine-tune their chemical and biological properties. Fortunately, biocompatible organic cations and inorganic anions can be used to synthesize non-toxic ILs [104–106]. According to Amde and colleagues [103], the relative toxicity of the cationic head groups often follows the following trend:

Phosphonium > ammonium > imidazolium = pyridinium > morpholinium > pyrolidinium > piperidinium > choline.

There is still room for more research on the general toxicity, particularly cytotoxicity. Instead of restricting their usefulness, some ILs' high toxicity may make them promising antitumor and anticancer medicines, giving new opportunities in a variety of medical specialties.

3.5 Biodegradability and biocompatibility of ILs

The synthesis of biodegradable ILs has garnered more attention from researchers recently. The design of biocompatible ILs naturally coincides with the objective of biodegradability [107]. For instance, despite demonstrating low toxicity, ILs with a short alkyl chain attached to the cation have demonstrated resistance to

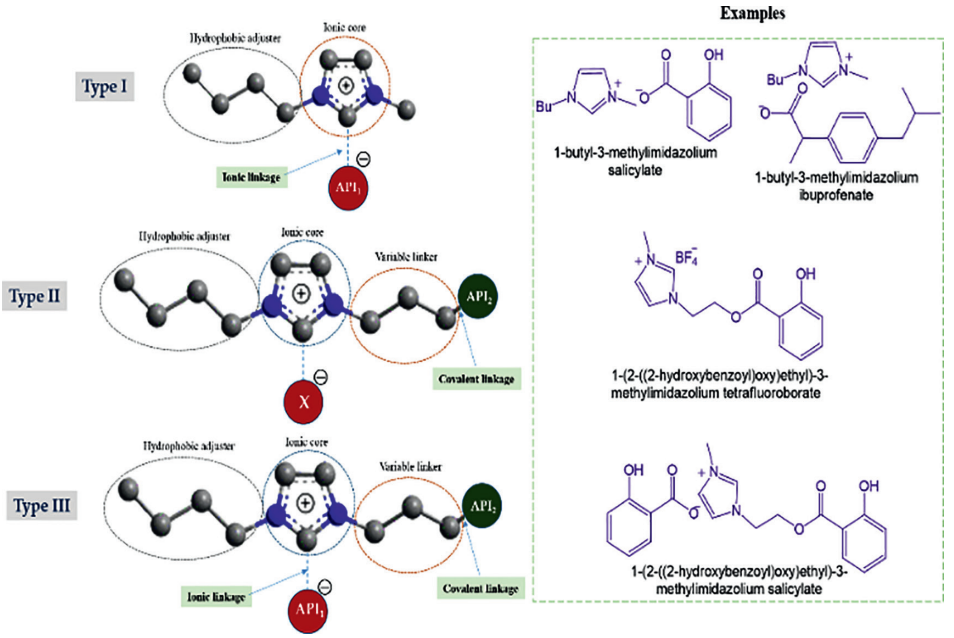


Figure 8.
Type I API-ILs contain ionic API as the anion; type II API-ILs comprise covalently coupled API as the cation; and type III API-ILs combine both possibilities. It should be noted that covalent binding to the anion is also plausible in type II (omitted for clarity) [8].

biodegradation [108]. It has been demonstrated that ILs with cationic groups (such phosphonium, pyridinium, ammonium, and imidazolium) that are especially toxic to microbes also degrade very quickly in the environment [109].

ILs with longer alkyl side chains (>C6) in the cationic core have been revealed to be biodegradable, while the same head group with shorter side chains is very weakly biodegradable. When it comes to their fundamental structure, imidazolium-based ILs generally show lower biodegradability, while 1-alkyl-3-methylpyridinium-based ILs have a higher potential for biodegradation [110].

On the other hand, the biodegradability of pyridinium ILs with linear alkyl chains is noticeably reduced [111]. The biodegradability of ILs is influenced not only by the cations but also by the nature of the anions. In contrast to ILs with shorter linear-chain anions (ethanoate and propanoate) those with longer linear-chain anions (butanoate, pentanoate, hexanoate, and octanoate) were found to be entirely biodegradable. On the other hand, it is known that anions like $[NTf_2]$, $[N(CN)_2]$, and $[B(CN)_4]$ cannot be hydrolyzed or biodegraded in the environment.

4. Conclusions

The significance and benefits of ILs as feasible solvents in pharmaceutical applications have been emphasized in this chapter in comparison to traditional organic solvents. By taking advantage of their diverse ionic structures, basic characteristics of ILs can be altered and customized to meet desired requirements in biomedical applications. Developments in this area have shown that ILs can enhance

the penetration of small and macromolecular pharmaceutical compounds through physiological barriers and solubilize water-insoluble or sparingly soluble drug molecules. In order to increase the stability of formulations and the transportation of drugs to the targeted site of action, ILs are showing as important components and drug binders. The solubility and polymorphism issues with solid drugs which were significant obstacles to the development of adaptive drug delivery methods have been effectively resolved by ILs with APIs. To address a number of problems and difficulties in the formulation and administration of IL-based therapeutic formulations, more research is necessary. We firmly believe that the tunability that is inherent in the realm of ILs is perfectly suitable and relevant to the pharmaceutical industry. In addition to offering remedies to issues that solid drugs frequently encounter, ILs can offer novel therapeutic or delivery possibilities that cannot be achieved by using solid APIs or conventional methods. A variety of IL-APIs that can be tailored to meet specific requirements while adjusting the chemical and physical characteristics of these ILs should be able to be prepared using such a modular design. Importantly, one may be able to solve the particular issue that caused this molecule to fail (such as poor solubility) by matching a failed API with a suitable cation or anion. Because of their inherent toxicity, lack of biodegradability, and detrimental effects on the environment, the therapeutic application of ILs is still unknown. Though the toxicity and biodegradability of ILs as green solvents remain unclear, a great deal of work has been made in the understanding and manufacture of biocompatible ILs for biological and pharmaceutical purposes. It has been discovered that a number of naturally occurring cations and anions that generate ILs, such as fatty acids, choline, and amino acids, are preferable to ammonium, imidazolium, and phosphonimum ILs. Further knowledge of ILs' structural characteristics and interactions with biosystems, particularly the coexistence of ILs and other living forms in an ecosystem, may also help to lessen their toxicity. In order to avoid having any effect on non-target areas or living forms, ILs must be designed with target specificity.

5. Future perspectives

Since structural features of ILs have been demonstrated to play a significant and often unexpected role in a variety of circumstances, developing pharmaceutical applications utilizing IL-based methodologies necessitates a thorough understanding of ILs both at the molecular and macroscopic levels. Furthermore, effective medications based on ILs might be given FDA approval in the near future. Even though ILs are no longer an innovative field, it is nevertheless remarkable how many different ways cations and anions can be combined to generate unique ILs with exciting new features. There has not been much work done to move the majority of IL examples from the laboratory to the bench scale; they are still proofs of concept. While the traditional pharmaceutical industry relies heavily on solids and solids processing, the use of ILs should be promoted as a way to recycle many of the drugs that have been shelved due to limited aqueous solubility or polymorphic conversion, giving these products a new market value. The pharmaceutical sector can undergo unexpected changes if a modular IL approach is implemented. This strategy can offer a foundation for enhanced performance with novel therapeutic approaches or even individualized drug regimens. New and fascinating findings will continue to be produced by the knowledge foundation created by international efforts in IL research as well as the research community's openness to explore new things. We propose that

pharmaceutical companies should follow the increasing number of industries that are thinking about using ILs for more than simply solvents in their processes. We think that in the near future, clinical trials involving green and biocompatible ILs to advance IL-based medication delivery technology will be carried out, which will stimulate the usage of ILs in commercial applications.

Conflict of interest

The authors declare no conflict of interest.

List of abbreviations

ILs	ionic liquid
DDSs	drug delivery systems
PILs	protic ionic liquid
TSILs	task-specific ILs
HIV	human immunodeficiency virus
$[C_1SO_4]$	methyl sulfate
[C2Py]	1-ethylpyridinium
[Lac]	lactate
$[BF_4]$	tetrafluoroborate
$[PF_6]$	hexafluorophosphate
[Ms]	methanesulfonate
[TFa]	trifluoroacetate
[Pro]	propanoate
[Br]	bromide
$[ICl_2]$	dichloroiodate
$[(C_2)_3NH]$	triethylammonium
RTILs	room-temperature ILs
[OAc]	acetate
$[NO_3]$	nitrate
PIL	polyionic liquids
ST	surface tension
CAGE	choline-geranate
[IBut]	isobutanoate
$[C_1C_1MIM]$	1,2,3-trimethylimidazolium
APIs	active pharmaceutical ingredients
VOCs	volatile organic compounds
SILMs	supported IL membranes
MOFs	metal-organic frameworks
HSV	herpes simplex virus
NSAID	nonsteroidal anti-inflammatory drug
$[C_2MIM]$	1-ethyl-3-methylimidazolium
$[C_1OC_2MIM]$	1-methoxyethyl-3-methylimidazolium
$[C_7H_7MIM]$	1-benzyl-3-methylimidazolium
$[C_2OHMIM]$	1-hydroxyethyl-3-methylimidazolium
$[C_5MIM]$	1-pentyl-3-methylimidazolium
$[(C_1)_2(C_1)_2G]$	1,1,3,3-tetramethylguanidine

[Cl]	chloride
[C_4C_1Py]	1-butyl-3-methylpyridinium
[NTf_2]	bis(trifluoromethylsulfonyl)amide
[HDBU]	1,8-diazabicyclo[5.4.0]undec-7-en-8-ium
[$N(CN)_2$]	dicyanamide
[HSO_4]	hydrogensulfate
[C_8C_1Py]	1-octyl-3-methylpyridinium
TFA	trifluroacetic acid
TFSA	trifluoromethanesulfonic acid
[C_4MIM]	1-butyl-3-methylimidazolium
([C4C1py][DCI])	1-butyl-3-methylpyridinium dichloroiodate

Author details

Sadia Rani[1], Ali Irfan[2*], Samina Aslam[1*], Gamal A. Shazly[3], Huma Hameed[4], Muhammad Zaman[4], Noreen Samad[5] and Yousef A. Bin Jardan[3*]

1 Department of Chemistry, The Women University Multan, Pakistan

2 Department of Chemistry, Government College University Faisalabad, Faisalabad, Pakistan

3 Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

4 Faculty of Pharmaceutical Sciences, University of Central Punjab, Lahore, Pakistan

5 Department of Biochemistry, Bahauddin Zakariya University, Multan, Pakistan

*Address all correspondence to: raialiirfan@gmail.com, drsamina.chem@wum.edu.pk and ybinjardan@ksu.edu.sa

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