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ISBN 978-981-16-4364-4 ISBN 978-981-16-4365-1 (eBook)
https://doi.org/10.1007/978-981-16-4365-1

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

The pharmaceutical industry has been experiencing a series of challenges with newly developed solid-state drugs because most of them are insoluble or poorly soluble in water or most of the pharmaceutically accepted organic solvents or agents. Other notable limitations with solid-state drugs are polymorphisms and their low bioavailability. As a potential alternative to conventional organic solvents/agents and water, ionic liquids have been used as solvents or materials in pharmaceutics and medicinal fields owing to their excellent properties, which include the combination of "green" properties and adjustable physicochemical and biological properties. Recent development of third-generation ionic liquids comprising biocompatible cations and anions creates innovative opportunities for the development of smart drug formulations and delivery systems.

Written by an international group of experts, this book summarizes the recent works that support the use of ionic liquids for various applications in pharmaceutics and medicine, with a particular emphasis on addressing their critical pharmaceutical challenges including the low solubility, polymorphism, and bioavailability of solid-state drugs. Readers will find diverse approaches to the application of ionic liquids in drug solubility, Active Pharmaceutical Ingredient (API) formulation, and drug delivery, such as topical, transdermal, and oral delivery, with a specific focus on the latest developments. This book also provides insights into the development of biologically functionalized ionic liquid-assisted biopolymers, surfactants, and nano/micro carriers for enhanced drug delivery systems/technologies.

The book contains valuable information and significant evidence on the potential use of biocompatible ionic liquids and/or ionic liquid-based materials/technologies in drug formulations and/or drug delivery systems. The broad coverage also provides a comprehensive resource for researchers and students from different disciplines, such as chemical engineering, chemistry, material science polymer science, and pharmaceuticals/medical fields, who are interested in both ionic liquids and their applications in pharmaceutics and medicine.

Design principles for ionic liquids in drug delivery systems are addressed in Chap. 1, which was written by Chowdhury et al. The authors focus on the design of the ionic liquids, rather than on their implementation in drug delivery systems, and particularly on their precursor selection, biocompatibility status for safety, and

potentiality for targeted drug delivery to achieve the maximum therapeutic efficacy with the fewest undesirable side effects. Chapter 2 was written by Moshikur and Goto, and it reviews the recent developments in ionic liquid-based API ingredient strategies to address the solubility and polymorphism challenges of crystalline APIs and explore their possible advantages in pharmaceutics by eliminating or at least minimizing common problems that are associated with solid APIs. The role of ionic liquids in transdermal delivery of APIs is described in Chap. 3 by Berton and Shamshina, where the authors focus on the Choline Geranate (CAGE) ionic liquid. Its scale-up and medical applications are also discussed. Chapter 4 by Moshikur et al. highlights the importance and advantages of ionic liquids as a potential solvent/agent for dissolving sparingly soluble drugs and explores the possible mechanism by which ionic liquids increase solubility during the preparation of drug formulations.

Chapter 5 by Shamshina and Rogers focuses on recent advances in the three-dimensional (3D) printing of cellulose and chitin from ionic liquids for drug delivery. There is a special focus on inkjet 3D printing and extrusion-based 3D printing of biopolymers from an ionic liquid. Recent advances in ionic liquid-based oral drug delivery systems are summarized in Chap. 6 by Islam and Goto. The authors highlight the potentials and limitations of oral therapy, and then they address the possible use of ionic liquids to bypass oral route constraints and enhance oral administration of many medicinal products. Chapter 7 by Pedro et al. reviews the latest applications of ionic liquids toward the development of polymer-based drug delivery systems. The authors also highlight the fundamental knowledge that is required to design multi-responsive copolymers from ionic liquid monomers to enhance the delivery of various drugs. Design and selection of potential ionic liquids for pharmaceutical applications are described using the Conductor-Like Screening Model (COSMO) in Chap. 8 by Khan et al., who highlight the advantages of COSMO-RS as a predictive tool.

Chapter 9 by Ali et al. presents Surface-Active Ionic Liquids (SAILs) as a potent biocompatible alternative to conventional surfactants and explores their pharmaceutical applications as promising surfactants/co-surfactants that help to form a stable formulation in aqueous or non-aqueous media. The authors also highlight why SAIL-based drug formulations represent favorable target drug delivery systems for pharmaceutical applications. Ionic liquid-based transdermal vaccination of drug molecules and antigen peptides is summarized in Chap. 10 by Tahara with a focus on how ionic liquid acts to enhance skin penetration. Chapter 11 by Elgharbawy et al. reviews ionic liquid-based antibiotics for resistant microbial strains and drug polymorphism, focusing on the antibiotics' solubility and bioavailability. Recent advances in ionic liquid-based microemulsions to enhance drug solubility and delivery are summarized in Chap. 12 by Salabat. The mechanism of enhancing the solubility of an active pharmaceutical ingredient and transdermal drug delivery using ionic liquid-based microemulsion is also highlighted.

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Contents

Chapter 1
Design Principles for Ionic Liquids in Drug Delivery Systems

Md. Raihan Chowdhury, Md Nurunnabi, and Masahiro Goto

Abstract Ionic Liquids (ILs) have been a topic of interest in many scientific areas since the mid-1990s and can be classified as potential "green solvents," especially for use in drug delivery systems (DDSs). Because of the "green" and "designer" properties of ILs, the use of ILs has escalated dramatically in pharmaceutics and medicine. Although virtually an unlimited number of ILs could be produced from diverse sources of organic and inorganic cations and anions, including IL precursors derived from biological sources, special consideration must be given for the implementation of ILs in DDSs. Herein, the focus is on the design of the ILs, rather than their implementation in DDSs, particularly the precursor selection, biocompatibility status for safety (biosafety), and potential for targeted drug delivery. It is possible to design an IL suitable for a DDS with synergistic benefits by achieving the maximum therapeutic efficacy of the drug with minimum undesirable side effects caused by the delivery systems or vehicles.

Keywords Ionic liquids · Drug delivery system · Biocompatibility · Designed principle

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M. Goto and M. Moniruzzaman (eds.), *Application of Ionic Liquids in Drug Delivery*,
https://doi.org/10.1007/978-981-16-4365-1_1

Abbreviations

ABDS	Affinity-Based Delivery Systems
API	Active Pharmaceutical Ingredients
BDOA	Benzyldimethyloctyl Ammonium
CAGE	Choline and Geranic Acid
COSMO-RS	Conductor-Like Screening Model for Real Solvents
DDS	Drug Delivery System
DHA	Docosahexaenoic Acid
IL	Ionic Liquids
siRNA	Small Interfering Ribonucleic Acid

1.1 Introduction

A drug delivery system (DDS) is an optimized formulation or device that can transport a therapeutic agent to a target site of action by avoiding or overcoming the biological barriers associated with cells, organs, and tissues. Some DDSs are simply engineered technologies that use various biocompatible materials for the targeted delivery and/or sustained release of therapeutic agents to maintain a desired level in the body (Erdine and De Andrés 2006; Kwon et al. 2008). New technologies are continuously being developed for use in DDSs, and current DDSs include liposomes, microemulsions, nanoparticles, niosomes, polymers, implants, and transdermal drug delivery systems (Vega-Vásquez et al. 2020). The design of optimized DDSs for particular purpose is challenging. Therefore, particular attention must be paid to the selection of the materials and the design of the vehicles to develop improved DDSs. In the last two decades, a new class of materials, the ionic liquids (ILs), has become popular for use in DDSs (Adawiyah et al. 2016a; Cabuy 2015; Huang et al. 2020; Karande et al. 2005; Pedro et al. 2020). ILs have been a topic of interest in many scientific areas since the mid-1990s, and can be classified as potential "green solvents," especially for use in DDSs (Moshikur et al. 2020b). ILs are the molten organic salts of unsymmetrical organic cations and inorganic or organic anions that have melting points barely above 100 °C (Marrucho et al. 2014; Moniruzzaman and Goto 2011; Shamshina et al. 2013). ILs are known as "designer solvents" because their physicochemical properties can be easily altered by simply changing the combinations of the cations and anions (Earle and Seddon 2007; Huang et al. 2020; Moshikur et al. 2020a). The designer and green solvent properties of ILs make them extremely useful materials for DDSs. The use of ILs has escalated dramatically, especially in the fields of pharmaceutics and medicine, in last two decades (Huang et al. 2020; Moshikur et al. 2020b). DDSs using either ILs or IL-based technologies, such as IL form of active pharmaceutical ingredients (IL-APIs), IL-in-oil microemulsions, IL-drug complexed

nanoparticles, IL-protein/peptide complexes, or drugs in IL/IL-water binary solvent systems, have been developed for use in synthetic and medicinal chemistry, especially in pharmaceutical formulations (Adawiyah et al. 2016a; Agatemor et al. 2018; Amaral et al. 2021; Applicable 2013; Chowdhury et al. 2019a). In DDSs, ILs have been mainly used as media, formulation components, polymerizable agents, and plasticizers. Virtually, an unlimited number of ILs could be produced from diverse sources of organic and inorganic cations and anions, including IL precursors derived from biological sources, but special consideration must be given for the implementation of ILs in DDSs (Adawiyah et al. 2016b; Anselmo et al. 2018; Gomes et al. 2019; Kumar et al. 2017; McQueen and Lai 2019; Omar 2016; Rodríguez et al. 2008; Uddin et al. 2020a). However, it is worth mentioning that not all ILs are suitable for DDSs. Currently, the design of ILs is more important than their implementation in DDSs (Huang et al. 2020; Karande et al. 2005; Nebgen et al. 2018). The design of a suitable IL for a DDS should particularly consider the following: (1) the selection of precursors; (2) the biological safety; and (3) the targeted delivery system. Figure 1.1 shows the exponential growth of publications related to the application of ILs or IL-related technologies in different facets of DDSs in the pharmaceutical field, as compiled by Pedro et al. (2020). The data clearly indicates that the use of ILs and IL-related technologies in DDSs is increasing year by year and almost reached a saturated level over the last decade. However, intensive investigations are still required before the regulatory approval of any ILs or IL-related technologies, particularly when used in a DDS, can be acquired. The design of ILs and IL-related pharmaceutics has already been approved by the FDA with a special consideration that must be acquired from the regulatory authorities before use in pharmaceutical applications (Moshikur et al. 2020b; Zandu et al. 2019).

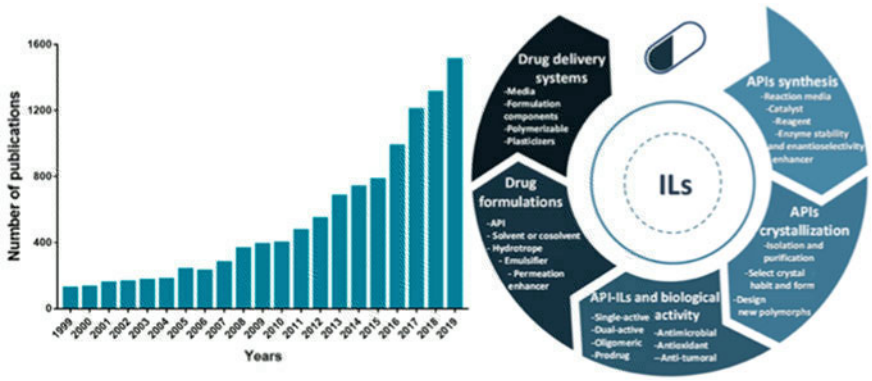

Fig. 1.1 Publications related to ILs or IL-related technologies used in DDSs over a 20-year period (left). An overview of the use of ILs in the pharmaceutical field (right). Reproduced from Pedro et al. (2020) with permission from the International Journal of Molecular Sciences and MDPI

1.2 Selection of Precursors

ILs consist of two precursor molecules, a cation and an anion, which can be derived from organic or inorganic sources (Welton 2018). According to the principal of green chemistry, an IL can be declared a "green" material/solvent/co-solvent only if it meets certain standards for toxicity and biodegradability (Gomes et al. 2019). An IL should be biocompatible if it is derived from biocompatible precursors. However, it has been demonstrated that the toxicity of ILs is an unpredictable parameter that does not follow any formal rules (Rodríguez et al. 2008). Several studies have investigated the relationship between the toxicity of an IL and its cation and anion precursors, but unfortunately no general correlations have been established yet (Chowdhury et al. 2018; Moshikur et al. 2020a). The accumulated toxicity and biodegradability data reported in the last few decades indicate that: (A) the ideal strategy for synthesizing biocompatible ILs is to use precursors from biocompatible sources; (B) the length of the alkyl side chain in the cations might have a strong influence on the toxicity; (C) the functional groups in the cations might contribute to the toxicity; (D) the nature of the cations and anions influences the toxicity; and (E) intermolecular interactions between the precursors also affect the toxicity (Egorova et al. 2017; Gomes et al. 2019; Marrucho et al. 2014; Omar 2016; Uddin et al. 2020b). As a result, third generation ILs have been designed with favorable biodegradable and biocompatible profiles especially for use in DDSs. The most common approach to design such ILs is to use biomolecules, such as amino acids, non-nutritive sweeteners, glucose, and carboxylic acids, as the precursors to minimize environmental, biochemical, and financial concerns (Egorova et al. 2017; Gomes et al. 2019; Rodríguez et al. 2008; Sivapragasam et al. 2020). Amino acids, which can be derived from protein hydrolysis and purification, can be considered as bio-renewable precursor molecules, and are also nontoxic, biodegradable, and biocompatible (Chowdhury et al. 2018, 2019b; Moshikur et al. 2018, 2019). To maintain the chirality of the ILs, natural α-amino acids and their ester salts have been extensively studied. To minimize the cation toxicity, naturally occurring sugars are an option, derived either from depolymerization or the direct refining of polysaccharides. Not only D-fructose monomers that have been converted into monosubstituted compounds, but also other fructose derivatives, such as isomannide, glucose, arabinose, and isosorbide are possible cation precursors (Adawiyah et al. 2016a; Huang et al. 2020; Moshikur et al. 2020b; Siegel et al. 2021). The cholinium ion and its derivatives are the most commonly reported biocompatible cations because of their biological source (Amaral et al. 2021; Moshikur et al. 2020b). The design of ILs with choline or its derivatives in combination with various active pharmaceutical ingredients (APIs), such as ampicillin, nalidixate, pyrazinoate, phenytoin, niflumate, picolinate, methotrexate, and 4-amino salicylate, has contributed to the improvement of pharmaceuticals, particularly pharmaceuticals used in DDSs (Amaral et al. 2021; Applicable 2013; Huang et al. 2020; Moshikur et al. 2020b; Pedro et al. 2020). In a recent study, according to the green chemistry metrics, a series of amino acid-derived surface active ILs with different head group precursors, including pyridium, imidazolium, and cholinium, has been investigated

to determine the effect of the chain length on the biocompatibility and toxicity of ILs and the subsequent effects in DDSs (Pedro et al. 2020). Anions derived from natural organic acids; such as malic acid, succinic acid, and tartaric acid, are also options for the production of biocompatible ILs suitable for DDSs in combination with appropriate cationic precursors (Amaral et al. 2021; Moshikur et al. 2020b; Pedro et al. 2020). In a recent study, Tanner et al. outlined the design principles for ILs used for transdermal delivery; 16 ILs were used to investigate the dependence of the skin penetration of a drug on the chemical properties of the IL (Tanner et al. 2019). The study revealed that the ability of an IL to enhance the transdermal drug delivery was inversely correlated with the inter-ionic interactions. Finally, using knowledge of the effect of the ion stoichiometry of ILs on the skin penetration of drugs and knowledge of the inter-ionic interactions obtained by 2D NMR spectroscopy, an IL was designed that provided the highest delivery of the drug of all the 16 ILs investigated. This study provided a generalized framework for optimizing ILs for enhanced skin permeation using the appropriate precursor molecules. However, only the delivery potency of the ILs was described in this study, and it was strongly emphasized that additional investigations were required to evaluate the biological safety.

To design the best possible sustainable ILs for DDSs, the conductor-like screening model for real solvents (COSMO-RS) has become a very popular tool for the effective prediction of the toxicity and biocompatibility of ILs for implementation in DDSs (Lotfi et al. 2016). COSMO-RS is a quantum chemistry-based equilibrium thermodynamics method used for predicting the chemical potential (μ) in liquids by processing the screening charge density (σ) on the surface of molecules to calculate the chemical potential (μ) of each species in a solution by considering the temperature and pressure at 25 °C and 1 atm, respectively. The surface chemical potential, μ, with screening charge density, σ, in bulk, can be calculated using the following equation (Eq. 1.1):

$$\mu s(\sigma) = -\frac{RT}{Aeff} ln\left[Ps(\sigma\prime) exp\left\{ \frac{Aeff}{RT} [\mu s(\sigma\prime) - Emisfit(\sigma, \sigma\prime) - EH.bonding(\sigma, \sigma\prime)] \right\} \right] d\sigma \tag{1.1}$$

where $Aeff$ is the effective contact area between two surfaces, $EH.bonding$ describes the energy share from H-bonding interactions, $Emisfit$ describes the electrostatic contact interaction energy, and $s()$ is the affinity of system S to the surface polarity σ measurement.

The ability of COSMO-RS to predict the solubility of chemicals in any pure or mixed solvents enables the program to be used to predict the solubilization of a drug in an IL, or mixture of ILs, as an effective pre-screening for ILs in DDSs. However, many other factors can have a detrimental effect on the toxicity and biocompatibility of ILs, and the exact mechanisms need to be investigated in detail in future ILs and IL-related research, especially for DDSs.

1.3 Biological Safety

Although ILs and IL-related techniques have tremendous potential for improving DDSs, as well as in drug development, their implementation is not always without problems. The main controversial issues with ILs and IL-related techniques in DDSs are the biological safety and biocompatibility, along with people's perceptions (Moshikur et al. 2020b). To develop a suitable IL or IL-related technique for DDSs, first, the biodegradability profile of the IL should be investigated using approved biodegradation methods to predict the minimum/maximum environmental effects upon direct/indirect interactions. However, the pharmaceutical application of ILs or IL-related techniques can only be approved upon satisfactory and detailed toxicological investigations, such as in vitro cytotoxicity assays using different human cell lines and in vivo cytotoxicity analysis using murine models (Petkovic et al. 2010a; b). In addition, the cumulative effect on biological systems needs to be investigated to determine the biocompatibility of an IL material. The 1st and 2nd generations of ILs were extensively studied regarding their cytotoxicity and environmental and microbial toxicity, which ultimately promoted the development of the 3rd generation of ILs that contain biocompatible precursors (Moshikur et al. 2020b). The 3rd generation ILs, which are most often nontoxic and readily biodegradable, could be appropriate materials for pharmaceutical applications, including DDSs. The addition of biological properties, along with the tunable physicochemical properties, is the main advantage of the 3rd generation of ILs that may direct them into biopharmaceutical applications, such as use as antibacterial, local anesthetic, anticholinergic, and antifungal agents. One of the best strategies to develop an IL-based biopharmaceutical is the use of an API or API precursor, either as the cation or anion or both, to achieve a pharmacologic effect (Egorova et al. 2017; Jordan and Gathergood 2015; Kumar et al. 2017). A few ILs are less toxic compared with their precursors, such as the IL from the venom of the fire ant, *Solenopsis* and formate from a different venom of its competitor *Nylanderia fulva.* Interestingly, the toxic effect of the precursor venom simply disappears in the synthesized IL (Moshikur et al. 2020b). In a study on the "design principals of ionic liquids for transdermal delivery," the IL based on choline and geranic acid (CAGE) was reported to have a lower dermal toxicity than that of its individual precursors (Tanner et al. 2019). However, it is not guaranteed that the final IL product will be safer compared with the precursors every time. Sometimes, a biocompatible IL or IL-drug formulation can be non-biocompatible at a higher concentration than the plasma isotonic level. The tolerable limit for plasma IV infusion is ~300–600 $mOsmL^{-1}$ (Moshikur et al. 2020b). Biological systems will treat an IL as a salt, as ILs consist of a cation and an anion, which can have considerable effects post-administration. A formulation of a biocompatible IL, cholinium dihydrogen phosphate, was considerably hypertonic when administered at 12%, w/v (~1520 $mOsmL^{-1}$) (Moshikur et al. 2020b). However, ILs can be designed based on their targeted route of administration, and any toxicological effects might be minimized by selecting the appropriate route of delivery. A database for

the biological safety of ILs and IL-related techniques could be established by investigating the molecular aspects behind the toxicity/biocompatibility of the precursors, which would assist in the development of subsequent ILs for future pharmaceutical applications, especially for DDSs.

1.4 Targeted Delivery Systems

The therapeutic effects of many drugs are limited by their poor solubility in biological fluids, *in vivo* instability, insufficient plasma concentration of the drug or the time at the site of action, and, in particular, a lack of targeted delivery that can often cause undesirable side effects and high plasma fluctuations during therapeutic applications (Applicable 2013; Karande et al. 2005; Nebgen et al. 2018). In the last few decades, targeted DDSs have been explored extensively to overcome these problems to ensure the targeted and controlled delivery of a high payload of a drug, and also to maintain the desired level of the drug in the body within the therapeutic window (Deng et al. 2019; Hwu et al. 2009; Medi and Singh 2006; Wayne et al. 2019; Zhang et al. 2019). Figure 1.2 shows some examples of targeted DDS vehicles composed of different materials, which can provide an extended period of action for a drug, optimized drug concentrations at a target site, reduced drug degradation and thus the dosage required, less undesirable side effects, less fluctuations in the drug concentration in the plasma, enhanced bioavailability, and improved patient compliance (Amaral et al. 2021).

Currently, ILs and IL-related techniques are being explored extensively in targeted DDSs. The solubilization of increased amounts of a drug through the interactions between IL ions and specific groups present in the drug allows the delivery of higher

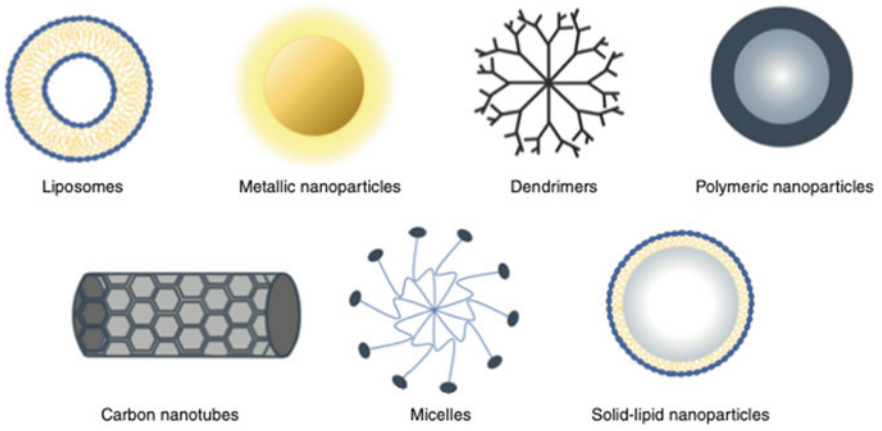

Fig. 1.2 Schematic illustration of targeted drug delivery systems for therapeutic applications. Reproduced from Amaral et al. (2021) with permission from Nanomedicine of Future Medicine Ltd

concentrations of the drug compared with the free drug (Islam et al. 2020a; b). The water solubility of paracetamol and diclofenac was reported to be enhanced significantly using *N*-acetyl amino acid *N*-alkyl cholinium-based ILs (Amaral et al. 2021). ILs based on choline and geranic acid (CAGE) successfully enabled the oral delivery of insulin with enhanced paracellular transport (Banerjee et al. 2018). The use of API-ILs offers enormous potential for promoting the dissolution of poorly soluble drugs. As a targeted delivery approach, the transdermal route has become very popular for delivering therapeutics, including small molecules and biologics (peptides and proteins), using ILs or IL-based techniques through and across the skin (Banerjee et al. 2017; Chowdhury et al. 2021; Tanner et al. 2018). The topical delivery and cellular internalization of RNAi (siRNA) were significantly enhanced using the IL, benzyldimethyloctyl ammonium-siRNA (Zakrewsky and Mitragotri 2016). ILs and IL-related techniques can deliver antigenic proteins and peptides to antigen presenting cells, such as Langerhans cells, in the dermis and epidermis by penetrating the lipid bilayers of the skin (Chowdhury et al. 2021; Tanner et al. 2019). It has been reported that the incorporation of ILs in transdermal and topical delivery systems could enhance the penetration and permeation of therapeutics into and across the skin in a non-invasive manner, upon the disruption of the lipid membranes (Anselmo et al. 2018). Nurunnabi et al. have shown that a CAGE IL could reduce body weight of treated mice by decreasing fat absorption through the intestine (Nurunnabi et al. 2019). The in vivo data showed 60–70% reduced absorption of the fat molecule, docosahexaenoic acid, in the intestine using CAGE. The mechanism for this effect could be that an interaction between CAGE and the fat molecules prevented the absorption of the fat by the intestinal tissue, which eventually provided a feeling of satiety. ILs have also been developed that incorporate metals to detect biomolecules, such as glucose in diabetic patients. Senthilkumar and coworkers have fabricated a metal-containing IL-based glucose sensor by immobilizing an IL containing Salophen on electrochemically reduced graphene oxide deposited onto a screen-printed carbon electrode (Amaral et al. 2021; Pedro et al. 2020). ILs can also be strategically designed for other targeted applications, such as anti-microbial agents, food preservatives, and stabilizing agents for proteins and enzymes.

1.5 Concluding Remarks

Much effort has already been devoted toward improving DDSs, but the incorporation of ILs or IL-related techniques provides a new dimension in the design of innovative, controlled, and targeted DDSs for therapeutics. It is possible to design an IL that is suitable for DDSs and has synergistic benefits by achieving the maximum therapeutic efficacy of a drug, with minimum undesirable side effects from the delivery systems or vehicles, by considering the biocompatibility of the precursors, and the safety and targeted delivery. The possible market for ILs in DDSs is large, provided these DDSs can gain regulatory approval. However, there is still a considerable amount of

research required before the potential application of ILs in DDSs can be realized. We thank Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

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Chapter 2
Ionic Liquids as Active Pharmaceutical Ingredients (APIs)

Rahman Md Moshikur and Masahiro Goto

Abstract The development of effective drug delivery systems for poorly water-soluble drugs remains a significant challenge for the pharmaceutical industry because of their limited solubility, bioavailability, permeability and stability and their polymorphic conversion. A well-established approach to address these limitations is to convert the active compounds to salts; however, the challenges related to bioavailability, permeability and polymorphic transformation of crystalline drugs remain. The incorporation of active pharmaceutical ingredients (APIs) into ionic liquids (ILs) has been shown to be an attractive method for resolving these challenges and/or significantly increasing the pharmacokinetic and pharmacodynamic properties of drugs. To date, API-ILs have been designed to enhance the solubility of poorly water-soluble drugs in both water and simulated fluids, and to disrupt physiological barriers to deliver drugs to target sites. This chapter highlights the progress of ILs in API-related research. The discussion is focussed on the importance and advantages of the API-IL approach for the development of novel drugs, considering not only the physicochemical properties but also the pharmacological profiles of the API-ILs.

Keywords Active pharmaceutical ingredients · Ionic liquid · Dissolution · Drug development · Biomedical activity

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M. Goto and M. Moniruzzaman (eds.), *Application of Ionic Liquids in Drug Delivery*,
https://doi.org/10.1007/978-981-16-4365-1_2

Abbreviations

[C_2MIM]	1-Ethyl-3-methylimidazolium
[C_{16}Pyr]	1-Hexadecylpyridium
[$N_{2,2,2,2}$]	Tetraethylammonium
[$N_{4,4,4}$]	Tributylammonium
[$N_{4,4,4,4}$]	Tetrabutylammonium
[$N_{1,1,10,10}$]	Didecyldimethylammonium
[$N_{6,6,6,6}$]	Tetrahexylammonium
[$P_{4,4,4,4}$]	Tetrabutylphosphonium
[$P_{6,6,6,14}$]	Tributyl(tetradecyl)phosphonium
[C_{16}Pyr]	Cetylpyridinium
[HMPyr]	1-Methylpyrrolidinium
[AAE]	Amino acid ester
[AlaEt]	Alanine ethyl ester
[ProEt]	Proline ethyl ester
[AspEt]	Aspartic diethyl ester
[PheEt]	Phenylalanine ethyl ester
[C_2OHMIM]	1-(2-Hydroxyethyl)-3-methylimidazolium
[mPEG3N_{444}]	Triethylene glycol monomethyl ether tributylammonium
[$(C_{10})_2(C_1)_2$ N]	Didecyldimethylammonium

2.1 Introduction

The pharmaceutical industry is facing unprecedented challenges related to the delivery of many solid active pharmaceutical ingredients (APIs) because of their limited solubility, insufficient bioavailability, polymorphism and poor stability, as well as formulation difficulties (Egorova et al. 2017; Ali et al. 2020). Approximately 40% of marketed drugs and up to 70% of drugs under development are poorly water-soluble, which leads to poor bioavailability and delivery difficulties, and thus causes them to fail in the later stages of development (Rodriguez-Aller et al. 2015; Moshikur et al. 2020b). Generally, the therapeutic efficacy of APIs is strongly influenced by their chemical structures, which contain various functional groups capable of forming strong inter/intramolecular interactions via hydrogen and/or halogen bonding, resulting in the formation of highly crystalline solids (Shamshina et al. 2015; Ali et al. 2021). These crystalline forms of APIs are accompanied by a suite of issues, such as lower aqueous solubility, irregular gastrointestinal absorption, pre-systemic metabolism, possible toxicity and side-effects of polymorphs and challenging particle size modification (Shamshina et al. 2015; Egorova et al. 2017). Large differences in bioavailability have been observed for different polymorphs of APIs,

leading to toxic or potentially lethal ramifications if the wrong polymorph is administered (Ghielmetti et al. 1976). Difficulty controlling the particle size of solid APIs is another common problem that is often critical to the development of formulations with therapeutic efficacy. Based on the structural diversity of drug molecules (ionisable or non-ionisable), several approaches such as salt formation, prodrug conversion, nanoemulsion formation, micellisation and nanoparticle formation, are now widely used to improve their aqueous solubility and bioavailability (Rodriguez-Aller et al. 2015; Egorova et al. 2017). However, these techniques often use large quantities of organic solvents, leading to concerns for human health and ecosystems (Clarke et al. 2018). Green techniques that do not compromise the therapeutic efficacy of drugs are therefore required for effective delivery.

The use of API-ionic liquids (API-ILs, organic salts prepared by pairing an ionisable API with an appropriate IL-forming counterion that melt below body temperature) is a promising tool for addressing the polymorphism and aqueous solubility of solid drugs. ILs comprising APIs are expected to provide many advantageous physicochemical and biopharmaceutical properties over solid or crystalline APIs (Egorova et al. 2017; Moshikur et al. 2020b). The strategic design and appropriate choice of IL-forming counterions have the potential to not only stimulate the synergetic actions of API-ILs, but to allow tuning of physico-thermal properties such as solubility, polymorphism, hygroscopicity, permeability and thermal stability. In addition, the scientific and technical advantages of APIs in liquid form could allow facile formulation and delivery via various routes of administration compared with the solid or crystalline drug. Therefore, the API-IL strategy is a potential opportunity for pharmaceutical companies as one of their options in a competitive market.

The research activity related to the use of ILs in drug formulation and delivery has significantly expanded over the last two decades (Egorova et al. 2017; Moshikur et al. 2020b). Figure 2.1a shows the number of research publications that have reported the application of ILs/IL technologies in the pharmaceutical field since 2000. Notably, the API-ILs approach is the most studied area among the IL-based drug delivery

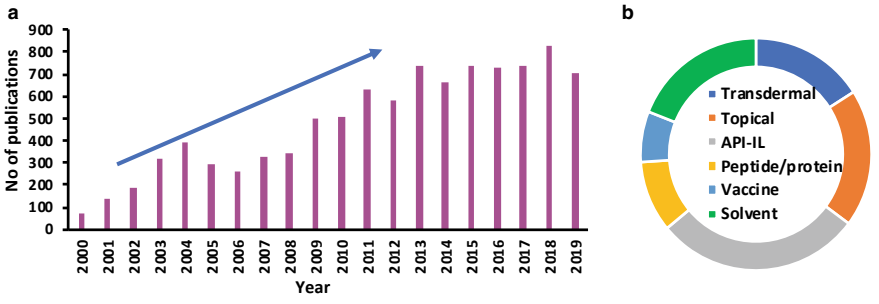

Fig. 2.1 **a** Publications related to ionic liquids (ILs)/IL technologies over the past two decades. **b** A comparison of the prevalence of API-IL technology and other commonly used IL-related technologies in the pharmaceutics literature, reproduced with permission from (Moshikur et al. 2020b)

strategies (Fig. 2.1b). Consequently, many companies that produce generic pharmaceuticals are increasingly motivated to design effective API-IL bearing drug delivery systems. However, the objective of this chapter is to summarise and further motivate biomedical application-driven exploration of API-ILs.

2.2 Design of API-ILs

The design of novel liquid forms of APIs is an appealing strategy for addressing the innate difficulties of many crystalline drugs. ILs derived from APIs may also provide new perspectives in terms of lowering the production costs or repurposing of classical drugs, and address the risk of toxicity arising from different undetected polymorphic phases that could cause harmful effects in patients. Converting solid drugs into API-ILs by pairing with tailor-made IL-forming counterions can lead to desirable physicochemical and biopharmaceutical properties. Their charged liquid state allows fine-tuning of their melting enthalpy barrier as well as the solubility/bioavailability. With effectively infinite options for design and flexibility, the use of the API-IL platform in drug delivery systems has already made advances through several approaches reported in the literature (Fig. 2.2). In this section, several implementation strategies for the API-IL platform developed over the last decade will be discussed.

2.2.1 Single-Active API-ILs

The combination of crystalline APIs with an appropriate IL-forming counterion is a promising technique for converting conventional pharmaceuticals into IL salts (Fig. 2.2a). These salts usually melt below body temperature and comprise one pharmaceutically active API and an IL-forming counterion. The appropriate selection of an IL-forming counterion allows control of the physicochemical and biological properties of the corresponding parent API, including the solubility, dissolution, permeability and bioavailability. API-ILs can reduce the issues of polymorphism and

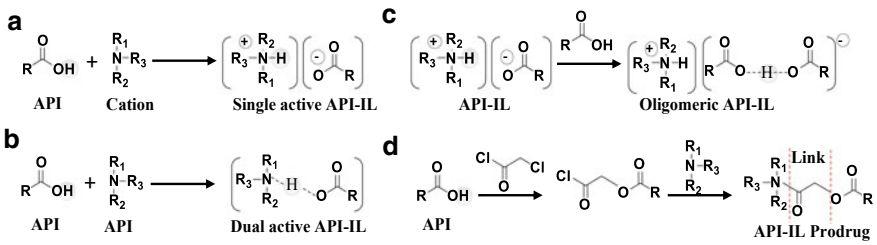

Fig. 2.2 Schematic examples of API-ILs in pharmaceutical approaches. **a** The preparation of a single-active API-IL, **b** dual-active API-IL, **c** oligomeric API-IL, and **d** API-IL prodrug

crystallinity that are related to the low aqueous solubility, poor therapeutic efficiency and thermal instability of drugs. A series of API-ILs with different pharmacological activities have been reported where solid APIs such as lidocaine, ibuprofen, sulfacetamide, sulfasalazine, indomethacin, procaine, aspirin, salicylic acid, methotrexate, piperacillin and penicillin are converted to the IL form by combining with IL-forming cations such as cholinium, amino acid ester, ammonium or phosphonium (Egorova et al. 2017; Moshikur et al. 2020b).

2.2.2 Dual-Active API-ILs

The dual-active API-IL strategy appears very attractive for the design of effective drug delivery systems owing to the dual-functional performances and possible synergistic effects beyond those of the parent APIs. Generally, any combination of two or more APIs is possible if both drugs form stable ions. Dual-active API-ILs are composed of an active cation and an active anion with different pharmaceutical activities (Fig. 2.2b). The role of the counterions is not only to influence the crystallinity of the drug molecules, but also to retain their own biomedical activity, resulting in dual-functional properties or providing new therapeutic properties not attainable with the two isolated APIs or known salt forms. Several notable examples of dual-active API-ILs have been reported to enhance their physicochemical and biomedical properties. A dual-functional API-IL was formed by the combination of acetylsalicylate with its main metabolite salicylic acid, resulting in the enhanced solubility of acetylsalicylate with minimal gastrointestinal distress (Endres 2010). Similar dual-active API-ILs were also formed from both salicylate and acetylsalicylate when paired with an analgesic tramadolium cation, antibacterial benzethonium cation, local anaesthetic lidocainium and procainium cations and an antiarrhythmic procainiumamide cation. Most of these API-ILs were liquids at room temperature and showed improved stability in air and moisture (Endres 2010). Antibacterial cations such as benzalkonium and didecyldimethylammonium were paired with the 'sweet' anions saccharinate (Sac) and acesulfame (Acesuf), which led to improved antimicrobial activity as well as good insect deterrent activity compared with the individual drugs. However, some of these API-ILs ($[(C_{10})_2(C_1)_2\ N][Sac]$ and $[(C_{10})_2(C_1)_2\ N][Acesulf]$) caused oral toxicity and skin irritation (Hough-Troutman et al. 2009). Ampicillin is a popular antibiotic that formed a dual-active API-IL when paired with the antiseptic cetylpyridinium ($C_{16}Pyr$), demonstrating significantly higher activity against several gram-positive and gram-negative bacterial strains compared with parent [Na][Amp] or $[C_{16}Pyr][Cl]$ (Ferraz et al. 2014, 2015). Notably, $[C_{16}Pyr][Amp]$ showed significantly higher growth inhibition in some tumour cell lines than [Na][Amp] (Ferraz et al. 2015). To improve the transdermal penetration, the nonsteroidal anti-inflammatory drugs, etodolac and ibuprofen, were combined with the local anaesthetic lidocaine, resulting in significant aqueous solubility as well as more efficient skin permeability. Although, the permeation of etodolac from lidocainium etodolac was significantly