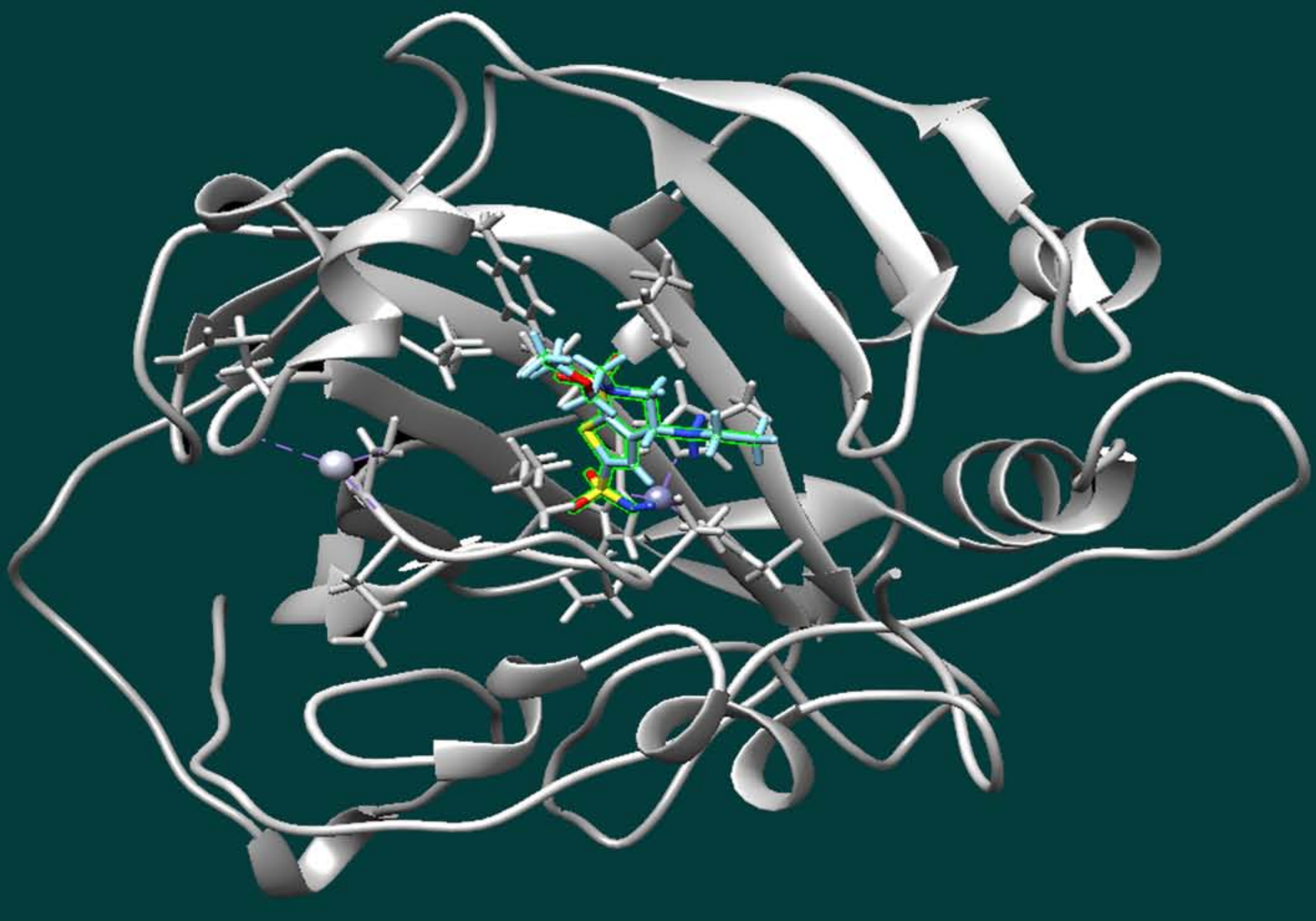
THIRD GENERATION IONIC LIQUIDS: SYNTHESIS TO APPLICATIONS



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Third Generation Ionic Liquids: Synthesis to Applications

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PREFACE

Ionic liquids (ILs) have emerged as a transformative approach with diverse applications in both academia and industry. Over the past two decades, extensive research has underscored the efficacy of ILs in various fields. Their unique properties, stemming from the combination of cation and anion charge carriers, distinguish them from traditional solvents. ILs offer promising advantages over conventional methodologies due to their high ionic conductivity, exceptional electrochemical stability, low vapor pressure, and non-flammability. These attributes have sparked significant interest globally, leading to their widespread adoption across disciplines such as organic synthesis, electrochemistry, biomass conversion, carbon dioxide fixation, energy storage, biomedical sciences, and pharmaceuticals.

In this book, we aim to provide a comprehensive overview of Ionic Liquids, focusing on their synthesis, characterization, and properties. Moreover, we delve into their diverse applications in advanced fields such as biomedical research, pharmaceutical formulations, advanced polymer composites, transdermal drug delivery systems, and heat transfer fluids. Our intent is to offer researchers, practitioners, and students alike a consolidated resource that not only summarizes the current state of IL research but also serves as a practical guide for exploring new avenues and applications. Each chapter is crafted to provide insights into the latest advancements, challenges, and potential future directions in the realm of Ionic Liquids.

We extend our sincere gratitude to all contributors and collaborators who have made this endeavour possible. Their expertise and dedication have enriched the content of this book, making it a valuable asset for the scientific community.

We invite you, as a reader, to explore the intricacies of Ionic Liquids presented in these pages and to engage actively with the material. Your feedback and observations will be invaluable in shaping future editions and advancing our collective understanding of this dynamic field.

Thank you for joining us on this journey through the world of Ionic Liquids. We trust that this book will serve as a beacon of knowledge and inspiration in your research pursuits.

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CHAPTER 1

Ionic Liquids: History, Properties & Applications

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Abstract: Since the energy and chemical industries have been contributing to environmental pollution for a number of decades, society has come to expect scientists and engineers to try to create sustainable chemical processes that produce fewer harmful substances and more environmentally friendly energy sources. Ionic liquids are becoming more and more well-known in the research industry because of their unique properties and characteristics. Ionic liquids have been applied in both commercial and educational applications. Because of their special thermal, physical, chemical, and biological characteristics, they have the potential to be a clean, efficient, and environmentally friendly alternative source of volatile organic solvents, which could help solve some of the biggest problems society is currently facing. They also have many other important advantages. Furthermore, by changing the ratio of cations to anions, their qualities could change according to how they are used. Thus, a great deal of basic and applied study has focused on them due to their special qualities. Actually, compared to the standard way, ionic liquids are more exciting and effective. As a result, their uses in organic synthesis have expanded greatly because of their increased diversity and adaptability. We have concentrated on the background, properties, and uses of ionic liquids in this book chapter, particularly in the context of organic synthesis. The physicochemical qualities that are important for their usage in industrial applications are therefore measured in a number of ways and reviewed.

Keywords: Application, Characterization, History, Ionic liquid, Properties.

INTRODUCTION

Sustainable practices are essential now more than ever since environmental concerns from the chemical and traditional energy sectors are intensifying. An increasing number of scientists and engineers are looking for creative ways to reduce pollution and provide ecologically acceptable energy sources. Because of their remarkable qualities and wide range of uses, ionic liquids have been a focus

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of study and development among these solutions. Ionic liquids have attracted a lot of interest from the academic and industrial communities because of their distinctive thermal, physical, chemical, and biological properties. Their ability to replace volatile organic solvents in a more effective, efficient, and ecologically responsible manner holds hope for resolving modern social issues. Ionic liquids' characteristics may be customized to meet the needs of various applications by varying the proportion of cations and anions, which has led to a great deal of research and use in a variety of disciplines [1]. Organic synthesis has been transformed by the development of ionic liquids, which provide a more dynamic and efficient way than traditional techniques. Their range of uses has expanded due to their increasing diversity and flexibility; this is especially true in organic synthesis, where their versatility is most evident. This chapter explores the background, inherent characteristics, and many uses of ionic liquids, with an emphasis on their use in organic synthesis. Ionic liquids play a key role in promoting sustainable chemical processes, as demonstrated by the careful examination and evaluation of their physicochemical properties that are essential for industrial use. This chapter attempts to clarify the revolutionary potential of ionic liquids in promoting sustainable chemical practices and innovation in the field of organic synthesis by utilizing a thorough examination of their history, characteristics, and uses [2]. A broad variety of features, such as variable solvation properties, great thermal stability, minimal vapor pressure, and large liquidus range, define ionic liquids. Their distinct molecular structure, which consists of inorganic or organic anions and organic cations, gives them these characteristics. They are perfect candidates for many applications because they lack a definite crystal structure, which allows them to stay in the liquid form at or close to ambient temperature.

Ionic liquids have been the subject of a recent study that has centered on examining their unique characteristics and identifying potential uses. The creation of task-specific ionic liquids for certain purposes is one subject of great interest. Through meticulous selection of component ions and structural modifications, scientists have developed ionic liquids with improved characteristics including conductivity, solubility, and catalytic activity. In addition, developments in computer modelling and simulation methods have yielded important new understandings of molecular interactions in ionic liquids. Ion transport and solvation dynamics have been clarified by molecular dynamics simulations, which have also provided insight into the behaviour of ions at the liquid interface [3]. The logical design of ionic liquids with enhanced performance in a variety of applications, such as energy storage, catalysis, and separation processes, has been made easier by these ideas.

Definition of Ionic Liquid

Liquids that are virtually entirely made up of ions are known as ionic liquids. Ionic conductivity is so displayed by them. With high melting points, these liquids are also included in the definition of molten salts or fused salts. For the last twenty years or so, the phrase “Ionic liquids” has mostly been used to refer to liquids that meet the preceding definition and have melting points or glass-transition temperatures below 100 °C. An ionic liquid is an organic molten salt consisting of a large cation and a charge-delocalized anion. Because the noncovalent interaction lies between the cation and the anion of an ionic liquid, an ionic liquid usually has a low melting point (below 100 °C) and is usually in a liquid state.

Ionic liquids are defined as those that contain essentially solely cations and anions and very few molecular species, such as ethyl ammonium nitrate.

Ionic liquids, like the halo aluminate systems, are binary mixes that are liquid and made completely of ions. “Room-temperature ionic liquids” is a term frequently used to describe tonic liquids that are liquid at or near room temperature.

Classification of Ionic Liquid

Ionic substances with a melting point below 100 °C are referred to as ionic liquids, or ILs. Their chemical and physical characteristics make them appealing for a range of uses. Even as early as the middle of the 19^{th} Century, a number of organic substances that are today categorized as ionic liquids were described. Three generations of ILs have been gradually developed and applied as a result of the hunt for novel and distinctive ILs.

First-Generation Ionic Liquids

The first generation concentrated primarily on their distinct inherent chemical and physical characteristics, including strong chemical and thermal stability, dissolved state, conductivity, thickness, and stickiness. The first generation was water and air delicate, and it mostly consisted of dialkyl imidazolium and alkylpyridinium cations coupled with metal halide anions (Fig. **1**). These ILs drew interest primarily because of their physical characteristics. These ILs have the potential to replace volatile organic solvents/agents that are harmful to the natural world. The majority of first-generation ILs, including [C4MIM][BF4] and [C4MIM][PF6] are poorly degradable and harmful to aquatic ecosystems. Their setup is extremely costly because of the inclusion of the indirect high E factor. Some typical anions, such as [BF4] and [PF6], are unstable because they are hydrolyzed when exposed to water from hazardous volatiles like HF and phosphate oxyfluoride [1]. Other

CHAPTER 2

Characterisation and Properties of Third Generation Ionic Liquids

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Abstract: Introducing biological and pharmaceutical perspectives into ionic liquids leads to the formation of a third generation of ionic liquids with lower toxicity and high biodegradability. These 3rd generation ionic liquids overcome the limitations of low thermal stability, solubility, and aggregation often associated with pharmaceutics. In this milieu, the 3rd generation of ionic liquids provides tailor-made biological properties in addition to the conventional ionic liquids (ILs) properties. This chapter provides a concise overview of the basic characterization and a discussion on the extraordinary physicochemical properties of the third generation of ILs/active pharmaceutical ingredients (API)-based ILs in this field. This paper strategically addresses the tuning of molecules to get the desired properties, thermal behavior to determine the transitional of the solid biological component into the liquid, and polymorphism in the field of pharmaceutics. An in-depth view of the nano-structuring phenomena, revealing the insights from structural characterization by NMR and EPR spectroscopy, and also a theoretical understanding of ILs using computational techniques have been discussed. Also, this chapter fosters the understanding of the solubility profiles and surface activity of API-ILs in water to overcome the inadequate biopharmaceutical properties with reference to parent API. This chapter highlights their enhanced biological properties such as antimicrobial, pharmacokinetics, antibacterial activity, *etc.,* and the various literature available on the different API-ILs. This will also include the biomedical perspective, for transport and toxicity studies. The effect of various anions and cations on the various biological and physiochemical properties will be discussed. Overall, the chapter aims to create a comprehensive understanding of the properties and characterization of 3rd generation ILs to pave the way for diverse biological and chemical applications.

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Keywords: Antimicrobial activity, Antibacterial properties, API ionic liquids, Biological applications, Characterization, Green solvent, Low melting point, Pharmaceutical activity, Pharmacokinetics, Permeability, Polymorphism, Thermal stability, Third-generation ionic liquids.

INTRODUCTION

The growing population and urbanization drive the need for industrial demand and supply, resulting in a high risk to human health and the environment. Besides the useful outputs, industries also generate a high volume of hazardous industrial waste containing harmful contaminants due to Volatile Organic Compounds (VOCs), organic toxins, and petroleum-based chemicals or solvents. The rapid process of industrialization has resulted in severe environmental consequences that may increase in the future [1]. It has ratified many international and regional environmental conventions and enacted several provisions to regulate the potential harm caused by chemical contamination and safeguard humans and environmental health [2, 3]. Overall, the negative effect can be minimized. The prime concern is to replace these toxic organics with alternative routes, green solvents, and processes without creating an adverse impact on nature and human health.

Ionic liquids (ILs) have gained interest and shown substantial growth over the last two decades. ILs have been considered molten salts and composed entirely of ions, whose melting point is below the boiling point of the water, with extraordinary unique properties such as high thermal stability (up to 300°C), a wide electrochemical window, non-volatility towards lowering the environmental impacts of volatile organic solvents, and most importantly the tuning ability to change the cation or anion as required [4 - 6]. The liquid properties of ILs are attributed to the presence of electrostatic, van der Waals, and hydrogen bonding interactions. ILs have been utilized in multifaceted applications in the fields of solvents and catalysts for chemical synthesis, and electrochemical, analytical, environmental, and biological contexts [7, 8].

Progress in Ionic Liquids

The evolution in the discovery of ionic liquids has progressed through over three generations: The first generation has been used as the tailored solvent with unique properties, but is limited by their air and moisture-sensitive nature, the second generation has been considered as more stable liquids and used for energetic material, lubricants, synthesis, but exhibits high toxicity and low biodegradability [9]. To overcome the limitations of previous generations and to find sustainable solutions, a series of bio-based ILs using important pharmaceutical molecules were prepared by Rogers and his group in 2007 and declared the "3rd generation of ILs" [10]. The basis of the third generation was a bioactive compound, biological resources, or their derivatives used as precursors in the synthesis. The third generation of ILs is about including active pharmaceutical ingredients (APIs) and enhancing the biological activity of ILs for biomedical applications like antimicrobial behavior, cytotoxicity assays, antibacterial, *etc.*, and other applications in catalysis, separation, and purification [11]. The majority of pharmaceutical drugs exist in their salt forms, the third generation of ILs has the capability to address high biodegradability and low toxicity but is also able to resolve the challenges associated with pharmaceutical ingredients such as low solubility in water, polymorphism, and stability issues in the organic solvents [12]. ILs have been made impactful solutions for the limitations shown by the FDA/WHO for the drugs to *"Exist in different crystalline forms which differ in their physical properties"*. The adsorption of oral drugs is influenced by their aqueous solubility, dissolution rate, and permeation into the intestinal barrier. (Fig. **1**) [13, 14].

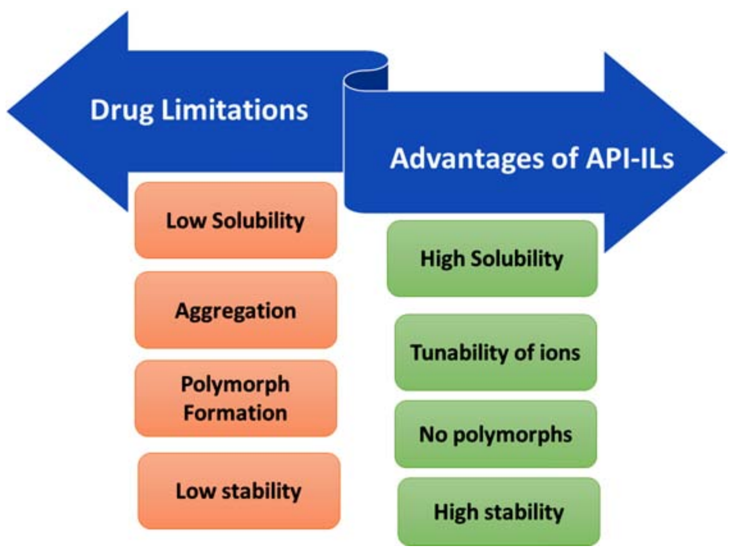

Fig. (1). Advantages of using API-ILs to overcome the drug-related limitations.

Additionally, there are different drug-related issues such as pH degradation, hygroscopicity in the presence of moisture, co-crystallization, prodrugs, and formulation difficulties in acidic and basic forms. API-ILs can provide a distinct strategic choice for selecting cations and anions to form ionic liquids associated with drug properties and also deliver diverse functionalities. It has shown tremendous potential to overcome such drawbacks, and some specific examples of the tuning of the cations and anions are shown in Fig. (**2**).

CHAPTER 3

Ionic Liquids: Versatile Solutions for Catalysis, and other Applications

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Abstract: Ionic liquids (ILs) of the third generation have become known to be adaptable substances with prospective applications in numerous scientific domains. They are attractive options for application in catalysis, separations, and energy storage due to their unique physicochemical characteristics, which include low volatility, excellent thermal stability, and variable polarity. The application of ILs as environmentally friendly solvents for chemical reactions, effective electrolytes for batteries, and new materials for the production of nanoparticles are all covered in this chapter. It also emphasizes its potential for environmentally friendly processes and environmental cleanup. In general, third generation integrated light bulbs represent a significant advancement in material science, offering remedies for present challenges in the chemical, energy, and environmental sectors.

Keywords: Catalysis, Energy storage, Green solvents, Ionic liquids.

INTRODUCTION

Background on Ionic Liquids

With melting temperatures usually below 100°C, ionic liquids (ILs) are an intriguing family of molten salts made entirely of ions. ILs have unique characteristics because they are composed of large organic cations and inorganic or organic anions, as opposed to conventional molecular solvents, which are primarily composed of neutral molecules. A vast library of potential ILs with a variety of physicochemical properties can be produced due to the broad range of combinations that can be made possible by the design and synthesis of ILs [1 - 6].

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Although ILs were originally mentioned in publications in the early 20th century, their potential as reaction media and solvents was not fully realized until the late 20th century. Conventional ionic liquids, sometimes referred to as first-generation ILs [7, 8], were mostly made up of large organic cations like imidazolium, pyridinium, and phosphonium mixed with various anions like chloride, bromide, and tetrafluoroborate. These early ILs are attractive for certain applications because of their special qualities, which include low vapor pressure, excellent thermal stability, and superior solvating ability.

With further research, second-generation ILs were developed to address some of the shortcomings of first-generation ILs, such as their limited biodegradability and toxicity. The goal of creating these new ions was to make them more biocompatible and environmentally benign. This led to the creation of ILs that are based on natural carboxylates, amino acids, and choline. Their potential applications were expanded by the switch to greener ILs, especially in the fields of biotechnology, medicines, and food processing [9 - 14].

The creation of third-generation ILs was a significant turning point in the field, demonstrating that IL advancements went beyond the second generation. These enhanced ILs were designed with specific features to fit certain uses, such as enhanced conductivity for electrochemical devices or modified polarity for particular chemical reactions. By changing the structure of the cation and/or anion, the modular architecture of ILs allows for precise property change, opening up new possibilities for customization and creativity [5, 8, 10, 12].

Numerous scientific fields, including chemistry, materials science, and engineering, have expressed a great deal of interest in ILs due to their inherent diversity and tunability. Catalysis, separations, energy storage, and biomedicine are a few of their potential uses. The fact that many modern ILs are ecologically friendly and sustainable also aligns with the increased demand for environmentally friendly substitutes for conventional solvents and materials.

Evolution to Third-Generation Ionic Liquids

In recent years, ILs have become widely recognized and explored for their distinctive characteristics and wide-ranging uses in different scientific fields. From starting as simple molten salts, ILs have gone through notable advancements to become the advanced materials we know today. In this opening, we examine the evolution from traditional ILs to advanced third-generation ILs, emphasizing important achievements and new directions in IL research and innovation [10, 11, 15]. ILs were first explored in the early 20th century, mainly studying inorganic salts with low melting points. However, it was not until the late 20th century that ILs were widely acknowledged as unique solvents and reaction environments. Paul Walden's groundbreaking research in the 1910s established the basis for comprehending the distinct characteristics of ILs, such as their low vapor pressure, elevated thermal stability, and adjustable polarity.

The introduction of initial ILs, which are mainly composed of large organic cations combined with different inorganic or organic anions, rekindled enthusiasm for IL studies. Imidazolium, pyridinium, and quaternary ammonium salts were utilized as the foundation for creating ILs with customized characteristics for particular purposes. These initial ILs proved to be useful in fields like catalysis, separations, and electrochemistry, prompting more research into their possibilities.

As research advanced, new ILs known as second-generation ones were developed to overcome the drawbacks of the initial ones. Efforts to create more environmentally friendly options were sparked by worries regarding the harmful effects of specific ILs on the environment and health. This resulted in the creation of ILs using ions that are more suitable for biological applications, such as choline, amino acids, and natural carboxylates. The emergence of these eco-friendly ILs broadened their use in areas such as biotechnology, pharmaceuticals, and green chemistry.

Even with the progress made in second-generation ILs, scientists acknowledged the necessity of additional improvement and tailoring to fully unleash ILs' capabilities in different uses. This led to the development of third-generation ILs, known for their enhanced features and customized properties for specific purposes. The move to third-generation ILs signifies a fundamental change in IL chemistry, highlighting the importance of precise design and specific applications.

One of the main characteristics that set third-generation ILs apart is their improved performance, which is achieved by making changes to both the cation and anion components at a structural level. This modular method enables researchers to adjust the physicochemical characteristics of ILs to accommodate various needs in different applications. For instance, adding functional groups or heteroatoms to the cation or anion can give them certain qualities like increased conductivity, better solubility, or specific interactions with substances.

Additionally, third-generation ILs show better performance in various important aspects when compared to earlier versions. They provide increased stability in challenging conditions, wider compatibility with solvents, and enhanced selectivity in different processes. Such progress has driven their use in new areas like energy storage, biomedicine, and nanotechnology, where accurate management of molecular interactions is crucial.

CHAPTER 4

Third-Generation Ionic Liquids in Biomedical and Pharmaceutical Applications

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Abstract: In recent years, research in the field of ionic liquids (ILs) has discovered several aspects of their 3rd generation derivatives, such as tuneable physicochemical properties (viscosity, polarity, hydrophobicity), green synthesis, and biocompatibility, making them promising agents in different applications for example clean energy, drug delivery, and other various industrial applications. 3rd Generation ILs have a unique modular architecture that can be modified independently, allowing the design of a range of functional materials while retaining the inherent features of ionic liquids. This chapter explores the application of third-generation ILs in the biomedical and pharmaceutical sectors to solve solubility, polymorphism, and bioavailability challenges. They serve as agents for poorly soluble drugs, modulate polymorphic formations of pharmaceutical compounds, and act as carriers for hydrophobic drugs, respectively. Other applications include drug formulation, delivery, and synthesis owing to their physicochemical properties, which have opened new doors for pharmaceutical research and development. We conclude by exploring the future opportunities that can be realized from integrating ILs into the biomedical and pharmaceutical sectors.

Keywords: Biomedical, Ionic liquids, Pharmaceutical, Polymorphism.

INTRODUCTION

Ionic liquids refer to salts in a liquid phase below 100°C. They are composed of bulky, asymmetric organic cations (such as alkylpyridinium [RPy], alkyl

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imidazolium [R_1R_2IM], tetraalkyl-phosphonium [PR_4] or tetraalkylammonium [NR_4]) and weakly coordinating anions. Paul Walden reported the first ionic liquid, ethyl ammonium nitrate, in 1914. In the later years, first-generation ionic liquids of alkyl imidazolium halogenoaluminates were reported by mixing imidazolium halides with aluminum halides. Since their discovery, ionic liquids have evolved through three generations, each with unique characteristics, properties, and applications (Fig. **1**) [1, 2]. The First-generation ionic liquids exhibit physical properties such as high thermal stability, decreased vapor pressure, a wider range of liquidity, and low melting point. The second-generation ILs are superior and a bit more advanced than their predecessors. They can be modified at a molecular level, independently altering cation and anion properties, thus tuning them into new functional materials without affecting the core characteristics. Chemical properties of these liquids, for example, energy density, reactivity, chiral induction, *etc*, can be targeted as desired and integrated with the necessary physical properties [3 - 5]. The third-generation ILs will be discussed in detail in the later sections. ILs have become a topic of interest due to their attractive physicochemical properties, which have found their way into various applications in biotechnology, chemical engineering, biomedicine, separation science, pharmaceutical ingredients, *etc*. A large number of ILs (approximately 1018 ILs) broaden their scope for scientific innovation. Ionic liquids can be classified as protic (proton-donating), aprotic (non-proton-donating), hydrophobic (water immiscible), hydrophilic (water miscible), chiral ILs (presence of stereogenic groups), and achiral ILs (absence of stereogenic groups). Many more classes of ILs have been reported over the years, given the diverse research in this field. Other interesting classes of ILs are Room Temperature Ionic Liquids (RTILs) [6] with extremely low vapor pressure and Task-Specific Ionic Liquids (TSILs) [7], mainly tuned for specific applications or tasks.

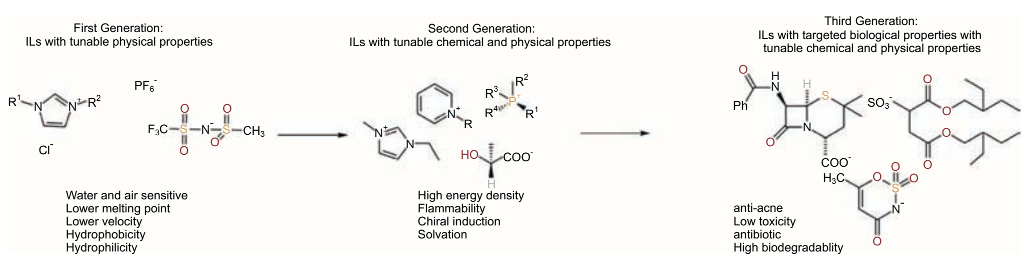

Fig. (1). Evolution of ionic liquids.

Third-Generation Ionic Liquids

Third-generation ILs are closely related to second-generation ILs with a significant complement of their tuneable biological, physical, and chemical properties, which allows them to be utilized in various biological, biomedical, and pharmaceutical applications (Fig. **2**) [8, 9].

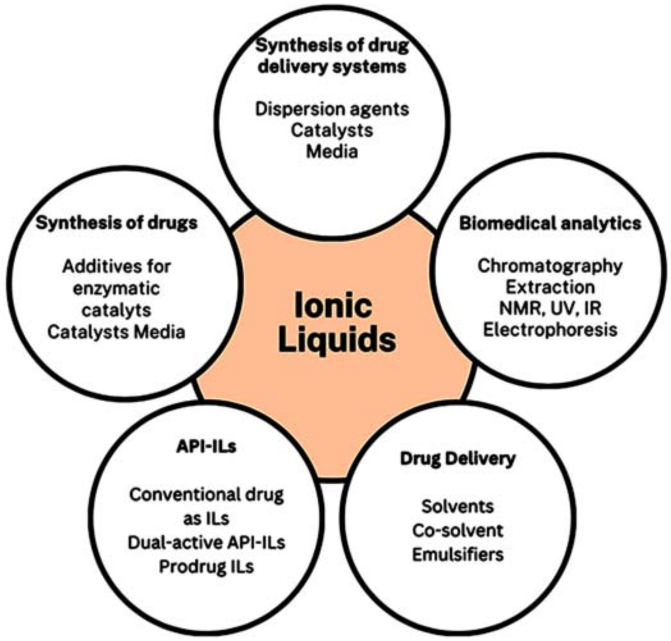

Fig. (2). Pharmaceutical and biomedical applications of ionic liquids.

Properties of Third-Generation Ionic Liquids

- *Solubility:* Third-generation ILs can dissolve a wide range of organic and inorganic compounds owing to their unique molecular structure, polarity, charge density, hydrogen bonding capacity, *etc*.
- *Thermal Stability:* Third-generation ILs exhibit a stable liquid state over a broad temperature range and do not deteriorate in performance and efficiency. Hence, they are ideal when working under harsh conditions.
- *Conductivity:* Third-generation ILs are highly conductive due to mobile ions within their liquid matrix. Their high conductivity facilitates rapid electron transfer at electrode interfaces, resulting in sensitive and selective sensor application detection.

Characteristics of Third-Generation Ionic Liquids

- *Biocompatibility:* Third-generation ILs exhibit little or no cytotoxicity with living tissues or cells, which makes them suitable candidates for applications like tissue engineering, biosensing, and drug delivery. Hydroxyl-functionalized imidazolium ILs are used in cell culture and tissue engineering applications. Due to their biocompatibility, these ILs do not induce immune responses or

CHAPTER 5

Third Generation Ionic Liquids: New Forms of Active Pharmaceutical Ingredients

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Abstract: The pursuit of innovative and unique ionic liquids (ILs) has led to the gradual development and implementation of three generations of ILs. The first generation concentrated mostly on the inherent chemical and physical characteristics of these materials, while the second generation offered the chance to modify these characteristics and create "task-specific ILs," which can be employed as greener or more ecologically friendly solvents. Utilising the active pharmaceutical ingredients (API) for creating ILs with biological activity, the third and most recent generation of ILs is currently being developed. The incorporation of biomolecules with API-based IL involves the protein stability as well as solubility of the drug molecules. By interacting with biomolecules, ILs can be used for drug delivery, drug carrier, and biomolecular stabilisation applications. To explore the molecular properties of these biomolecular complexes, the combined electronic structure calculations and molecular dynamics simulations are widely used. In this chapter, we intend to explore the molecular-level interaction of this innovative generation of a mixture of ILs/water with biomolecules.

Keywords: Active pharmaceutical ingredients, Density functional theory, Drug delivery, Ionic liquids, Molecular dynamics simulations, Molecular hydration, Non-covalent interactions.

INTRODUCTION

Origin of Third-Generation ILs in Therapeutics

The pharmaceutical business is facing numerous challenges, and we urgently require fresh scientific discoveries that lead to new, effective medicines and treatments. Not many drugs that are tested in clinical trials make it to market. This

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makes it harder for people who need effective treatments to get them [1]. About half of the available drugs are given as salts. By pairing a drug with different counter ions, its physicochemical and biopharmaceutical qualities can be fine-tuned [2]. They are easily changed by adding ionizable functional groups to get rid of bad things about the parent drug. The salt structure affects the performance, safety, and quality of a drug, and the choice of ion pair can have a big effect on how the drug works in the body [3]. The third version of ILs was just released. They are made from biocompatible compounds that have biological activity. A lot of research has been done on the chemical and physical properties of ILs. Recently, more studies have also been performed on how toxic they are and how they affect living things. Novel ILs have been made using biologically active ions, but most of these studies have been focused on using well-known less toxic ions [4 - 6]. As a specific type of ILs with unique physicochemical characteristics and concurrent promise for pharmaceutical applications, Active Pharmaceutical Ingredient-Ionic Liquids (API-ILs), are attracting more and more attention [7].

Significance of Liquid Salts of APIs

A different approach that can circumvent the problems associated with solid pharmaceuticals and the limitations on bioavailability is to convert API-ILs from solid-state to liquid salt forms, or their Deep Eutectic Solvent (DES) equivalents. With the appropriate choice of IL-forming ions, solid-state medication problems can be resolved and a variety of functions can be delivered while maintaining the fundamentally desired features of the IL state of matter on the innovative platform that API-ILs offer. With the appropriate choice of IL-forming ions, solid-state medicine problems can be resolved and several functions can be delivered while maintaining the fundamentally desirable features of the IL on the innovative platform provided by API-ILs [8 - 13]. They allow modifying physicochemical properties (such as stability, hydrophilicity, and liquid range) and give researchers more creative freedom when creating novel functional medications. Furthermore, choosing counter ions with the appropriate physical properties enables the creation of hydrophilic-lipophilic balanced ion pairs for the administration of drugs. They might also have complementary therapeutic effects, like using "dual-functional" API-ILs [14 - 16].

Similarly, hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) are mixed to form DES at room temperature. Because several HBA/HBD pairings are available, it is also feasible to easily change the properties of DES by varying the HBDs/HBAs [17]. By addressing problems with solubility and bioavailability and enabling adjustments to pharmacokinetics and pharmacodynamics without compromising the effectiveness of the API itself, DES systems and liquid salts can generate the required biopharmaceutical properties [18]. Certain DESs and API-ILs have demonstrated improved biological activity, longer and more noticeable therapeutic effects, better drug delivery across the skin barrier, quicker absorption and transdermal transport, improved skin retention, *etc* [19 - 22]. In a nutshell, the pharmaceutical industry may find the API-IL strategy to be advantageous in a competitive market. This approach can recover unsuccessful candidates, prolong the patent life of existing APIs, repurpose traditional medications, or offer a substitute for polymorph patents [23].

OVERVIEW OF CURRENT SYNTHESIS AND CHARACTERIZATION OF API-ILS

A necessary condition for the synthesis of salts, acidic or basic functional groups is present in a large number of APIs. Since the pharmaceutical industry depends so heavily on solid salts, the specifications needed to produce crystalline salts have previously been established [24]. It is believed that the amount of proton transfer can be predicted based on the pKa difference between an acid and a base [25]. The "pK_a rule-of-thumb" is widely used to pick counter ions. This rule originally proposed that for proton transfer to occur, the pK_a difference between a base and an acid should be more than or equal to 3 ($\Delta pK_a = pK_a$ (protonated base) $- pK_a$ (acid) > 3). However, when ΔpK_a values were computed for a considerably larger data set of crystalline salts from the Cambridge Structural Database in 2012, it was found that $\Delta pK_a > 4$ forms completely ionized acid-base pairs, while $\Delta pK_a \leq -1$ forms non-ionized acid-base complexes. A linear correlation was found between the value of ΔpK_a and the likelihood of crystalline salt production in the circumstances where $-1 \leq \Delta pK_a \leq 4$ [26]. Furthermore, the "pK_a rule-of-thumb" only applies to aqueous solutions, a substantially bigger ΔpK_a, more than roughly 8-10, is required for pure acids and bases. Acid-base neutralization techniques have been shown to provide API-ILs with an almost optimal ionic nature when there is a comparable variation in ΔpK_a [13]. As evidenced by the speciation of oligomeric ILs and liquid co-crystals, the liquid nature of ILs and their moderate ΔpK_a levels (<8 for eatable ILs and <4 for aqueous solutions) provide a broad range of speciation [27, 28]. For instance, lidocaine-diclofenac, which has a ΔpK_a of 3.7, is only 6% ionized API, but procainium diclofenac ($\Delta pK_a = 4.8$) is 99% ionized [29].

Employing ion exchange resin is an alternative method of creating API-ILs without creating an insoluble solid residue [30]. One technique is to make a [OH^-] resin and then feed free acid through it in a suitable solvent to immobilize the carboxylate on the resin support. After that, the column is washed with a solution of the matching halide in the appropriate solvent [31]. Nevertheless, the

CHAPTER 6

Ionic Liquids in Polymer Composites: Enhancing Performance and Functionality

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Abstract: Ionic Liquids have shown new developments in materials chemistry research. ILs combined with polymers allow the development of smart materials and the fabrication of high-performance polymer composites. ILs are formed from different combinations of anions and cations, providing infinite possibilities for tuning their properties. Nanofillers like carbon nanotubes and graphene often need surface modification to improve dispersion in polymer matrices, as they tend to aggregate. ILs can help disperse these fillers by reducing inter-molecular interaction. ILs interact with carbon nanofillers *via* carbon- π and π-π interactions with the graphitic structures. This builds a strong interface between the filler and polymer. IL applications in polymers are expanding into areas like vulcanization accelerators, dispersants, plasticizers, and modifiers to improve membrane selectivity and electrolytes. Porus polymers with IL monomers may enable new battery/fuel cell membranes, field-responsive gels, *etc*. Due to the sensitivity of the ionic group to stimuli, polymer-supported ILs show significant early applications in areas like catalysis, nanofluids, and proton conduction. More development is expected around stabilizing dispersions, plasticization, and interpenetrating networks. Solvent-free nanofluids utilizing IL-functionalized surfaces to generate supra-molecular ILs may proliferate. These could produce new resin classes and hybrid materials. Anti-static agents are essential additives for plastics to avoid issues like sparking, dust, buildup, and fire hazards. Anti-static agents work through various mechanisms, allowing flexibility to tune their performance for different applications and meet industry standards. ILs have properties like electric conductivity, viscosity reduction, lubrication, and corrosion inhibition that make them promising anti-static polymer additives. Using lower levels of ionic liquids can minimize costs and environmental impacts while still enhancing polymer properties. Recent literature shows ionic liquids being increasingly utilized in elastomer composites in various roles, including dispersants fillers, crosslinkers, catalysts, and solvents. Their uses will likely continue rising.

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Keywords: Ionic liquids (ILs), Nanofillers, Polymer composites, Smart materials.

INTRODUCTION

As pollution from chemical and energy industries has increased over the years, there's a growing expectation for scientists and engineers to develop chemical processes that are sustainable and produce less harmful substances. Solvent losses significantly contribute to environmental waste, with about 60% of energy in pharmaceutical production and 50% of greenhouse gas emissions coming from solvent use. To tackle this, it is crucial to choose solvents systematically. To address this, scientists are exploring alternative solvents like water, supercritical fluids, and ionic liquids (ILs) [1].

Ionic liquids, in particular, have gained attention as replacements for traditional solvents. They offer advantages in terms of reaction speed, specificity, and product yield, rather than just replacing VOCs(volatile organic compounds). Room-temperature ionic liquids are special types of salts that stay liquid even at room temperature. There are lots of studies on their use in catalysis and as support for catalysts. People are also using them as environmentally friendly solvents for separating different substances. Recent studies have analyzed the properties of pure ionic liquids and how they mix with other liquids, like common organic solvents. While some properties match up well, others are quite different [2].

Ionic liquids- which are molten salts at room temperature are made of cations and anions. If a salt melts at a temperature below the boiling point of water, it is called an ionic liquid. They have many physical and chemical properties, like very low vapor pressure, and good thermal stability, and they can be used as environmentally friendly solvents or catalysts. Because of their wide range of properties, they are used in various fields like biochemistry, engineering, and physics [3].

Chemists discovered the first ionic liquid while performing a chemical reaction called Friedel-Crafts alkylation with $AlCl_3$ in the mid-1800s. They noticed a red-colored oil formed during the reaction, which they later found out, through a technique called NMR spectroscopy. It was synthesized of a positively charged carbon atom (carbocation) and a negatively charged tetrachloroaluminate ion. In the later part of the 20^{th} century, scientists started combining different ions like pyridinium and imidazolium to make new types of ionic liquids [4].

Ionic liquids were mainly developed as solvents for chemical reactions. Many studies have focused on their use as reaction solvents, but only a few types of ionic liquids have been thoroughly studied. Some researchers have explored the use of enzymes in ionic liquids for reactions, particularly hydrolytic enzymes as catalysts in water-free environments. In the field of biology, there's growing interest in using ionic liquids to dissolve bio-derived materials and proteins. Ionic liquids are also being investigated for their ability to dissolve gas molecules, with some being used as absorbents, particularly for carbon dioxide. They have been explored for gas separation and concentration, with certain ionic liquids designed to have an affinity for specific gases. Combining ionic liquids with supercritical fluids shows promise for various chemical processes, including reactions and separation. Ionic liquids, made of ions, can replace electrolyte solutions because they don't evaporate easily, making them safer for energy devices like batteries. They have unique properties compared to regular liquids such as water and organic solvents, opening up new areas of technology. Despite lots of research, only a few types have been used. To understand them better, we need to study different kinds. By using synthetic chemistry, we can make new functional ionic liquids faster. This involves designing and testing various types for different uses [5].

Some uses of ionic liquids (IL) involve removing pollutants from wastewater. For this, we need ILs which can form a separate layer from water because they are hydrophobic. However, some IL can dissolve in water, potentially spreading in wastewater. They may also end up in soil or accumulate in living organisms, posing risks to the environment. Ionic liquids (ILs) are important for various kinds of polymerization. Recently, there's been a focus on using ILs in ionic polymerizations and attaching atom transfer radical polymerization (ATRP) catalysts to ILs, making them easier to recover during living polymerizations. The number of polymerizable ILs is increasing [6].

Some ILs are found to be toxic and non-biodegradable based on their life cycle assessments (LCA). Besides toxicity and biodegradability, other factors make them environmentally friendly. There are studies that show how ILs are made, used, and broken down in the environment after being used. Life cycle assessment (LCA) is a method used to analyze the environmental impact of ILs throughout their entire life cycle, including the raw materials used for making them, their applications, and how they are recycled or disposed of. Many questions remain about how to produce and use them on a large scale, including their toxicity, hazards, cost, purity, and stability. To determine how green ionic liquids are, we need to assess their impact on the environment compared to other liquid products or processes [7].

Compared to other actuation technologies, ionic polymer membrane actuators have several advantages. For example, they can be implanted in the human body due to their flexibility and hydration, making them very promising for biomedical

CHAPTER 7

Ionic Liquids for Application as Heat Transfer Fluids for Solar Thermal Energy

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Abstract: The feasibility of using ionic liquids (ILs) in solar thermal power plants as heat transfer fluids (HTFs) and liquid thermal storage media has been investigated. Thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR), viscometry, and other pertinent techniques were used to synthesize and thoroughly characterize a number of IL variants, including [C_4min][PF_6], [C_8mim][PF_6], [C_4min][bistrifluoromethane sulflonimide], [C_4min][BF_4], and [C_4min][bistrifluoromethane sulflonimide]. Important parameters were carefully determined, including density, heat capacity, viscosity, melting point, decomposition temperature, and thermal expansion coefficient. To evaluate the thermophysical properties of basal ILs and nanoparticle-enhanced ILs (NEILs), experiments were carried out. Because solar thermal energy (STE) is more effective than photovoltaic solar cells, energy researchers have been paying close attention to it lately. Heat transfer fluids (HTFs), a secondary medium, are used in STE to transport heat. As such, the thermophysical characteristics and thermal behaviour of the HTFs determine the overall performance of STE systems. High melting point, high decomposition temperature, and high vapor pressure are problems for conventional HTFs. To overcome these constraints, scientists have started working on creating new HTFs specifically designed for STE applications. Because of their improved thermophysical characteristics, such as their strong ionic conductivity, low vapor pressure, and thermal stability at high temperatures, ionic liquids (ILs) have become intriguing candidates for the next generation of HTFs. Moreover, adding nanoparticles to ILs can improve their thermophysical characteristics and thermal performance even more. This is a rapidly developing field of study that aims to increase the effectiveness of solar thermal systems. An overview of recent studies using IL-based nanofluids as HTFs is also given in this study.

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Keywords: Heat transfer fluids (HTFs), Ionic liquids (ILs), Solar thermal energy (STE), Thermophysical properties.

INTRODUCTION

As societies worldwide work on reducing their carbon footprint, it is crucial to emphasize the importance of collective efforts. Governments, industries, and individuals all play pivotal roles in promoting sustainable practices and adopting cleaner energy sources. This collaborative approach is essential for achieving meaningful progress in the global fight against climate change and ensuring a more sustainable future for generations to come [1]. Recognizing these challenges, the environmental community and energy researchers are actively seeking sustainable solutions to transition away from fossil fuels. This involves a multi-faceted approach that includes renewable energy adoption, energy efficiency measures, policy initiatives, and technological innovations. Certainly, addressing global warming and reducing carbon dioxide (CO_2) emissions from fossil fuel combustion is a critical concern for energy researchers. Energy researchers focus on developing and improving technologies that contribute to cleaner energy production, storage, and distribution. This includes advancements in renewable energy sources, energy efficiency, and carbon capture technologies. The impact of climate change, driven by the accumulation of greenhouse gases like CO_2 in the atmosphere, has led to a growing emphasis on finding environmentally friendly and energy-efficient alternatives. Some potential solutions, such as Solar Power, are utilizing sunlight to generate electricity through photovoltaic cells [2].

The rapid development of the economy has brought energy and environmental concerns to the forefront. In this context, finding alternative energy sources, utilizing clean working fluids, and optimizing current energy technologies are crucial strategies to address these issues effectively. Absorption heat pumps (AHPs), absorption heat transformers (AHTs) and absorption refrigeration systems play significant roles in energy conservation and cost reduction. These devices can recover low-temperature exhaust heat from various processes and reuse it for heating or air-conditioning purposes. Traditionally, AHPs and absorption refrigeration systems have relied on specific working pairs to function effectively. The most common pairs include water–ammonia and lithium bromide–water. Each pair has its advantages and applications, but they share the common goal of efficiently transferring heat and providing cooling or heating as needed. Water–ammonia systems, for example, are well-suited for medium to high-temperature applications and are widely used in industrial and commercial settings. On the other hand, lithium bromide–water systems are often employed in air conditioning and refrigeration applications due to their ability to operate at lower temperatures. By utilizing absorption heat pumps and absorption refrigeration systems, industries and households can significantly reduce their energy consumption and greenhouse gas emissions. These technologies offer a sustainable solution for utilizing waste heat and improving overall energy efficiency, contributing to both economic and environmental sustainability. Continued research and development in this field are essential for advancing these technologies and maximizing their potential in addressing energy and environmental challenges.

However, they have great disadvantages such as toxicity, high operating pressure, corrosion, and crystallization. Therefore, it is necessary to explore new working pairs to overcome these shortcomings in industrial applications [3, 4].

Ionic liquid's (ILs) have emerged as versatile solvents composed of organic cations and either organic or inorganic anions. One of their most notable characteristics is their ability to remain in the liquid state at room temperature. Research has demonstrated that ILs offer a wide range of actual and potential applications across various fields. In electrochemical processes, ILs serve as electrolytes or solvents due to their unique properties, such as high conductivity and wide electrochemical stability window. This makes them valuable in applications like batteries, fuel cells, and electroplating. In solar collecting processes, ILs can be utilized as heat transfer fluids or as components of advanced materials for solar cells. Their thermal stability and ability to retain a liquid state over a wide temperature range make them promising candidates for improving the efficiency of solar energy conversion systems. ILs also find applications in extraction and separation processes, where their selectivity and tunable properties make them suitable for extracting specific compounds from mixtures or separating complex chemical mixtures. Carbon dioxide capture is another area where ILs have garnered attention. Their ability to selectively capture CO_2 from gas streams, combined with their low vapor pressure and recyclability, makes them potential candidates for mitigating greenhouse gas emissions from industrial processes. ILs play a significant role in organic synthesis and catalysis, offering unique reaction environments and catalytic properties. Imidazolium-based ILs, in particular, are known for their high thermal stability, low vapor pressure, wide temperature range, and compatibility with water and alcohols, making them especially valuable in various applications. Overall, the diverse properties and potential applications of ILs make them attractive candidates for addressing challenges in energy, environmental, and chemical processes. Continued research into their synthesis, characterization, and application will likely lead to further advancements and wider adoption in these areas [5, 6].

CHAPTER 8

Third Generation Ionic Liquids and Deep Eutectic Solvents in Advanced Transdermal Drug Delivery

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Abstract: Ionic liquids (ILs) have emerged as promising chemical compounds with extensive applications in drug delivery due to their unique and tunable biological and physicochemical properties. Researchers are continually advancing new generations of ILs, and recently, third-generation ILs and Deep Eutectic Solvents (DESs) have exhibited greater efficiency, increased biocompatibility, and enhanced chemical stability compared to their predecessors. This chapter explores the advancements in the generations of ILs followed by DESs and their impacts on enhancing transdermal drug delivery (TDD). TDD is a topic of significant interest in drug delivery due to its potential for directly dosing drugs and other bioactive molecules without invasiveness. Over the past two and a half decades, ILs and DESs have significantly improved TDD by serving as skin permeation enhancers, solvents, and surfactants to regulate skin permeability and pharmacokinetic behavior of drugs and biomaterials. The chapter will focus on highlighting the roles of third generations of ILs and DESs in advancements of TDD.

Keywords: Biodegradable, Carriers, Drug delivery, Evolution, High molecular weight, Ionic liquids, Low solubility, Skin permeability, Transdermal drug delivery, Third-generation.

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INTRODUCTION

Recent decades have witnessed efficacious developments in transdermal drug delivery systems (TDDS), offering direct bloodstream access, bypassing first-pass metabolism, ensuring non-invasiveness, and enhancing patient compliance [1 - 3]. Following oral administration and injection, it is considered the third most significant method for delivering drugs, playing a pivotal role in the current field of pharmaceuticals [4]. However, this field has significant limitations because of poor drug solubility and limited permeability across the stratum corneum (SC), poor stability of the formulations, and inadequate control over drug release kinetics [5]. These challenges hinder TDD's efficacy and practical application, especially for therapeutic compounds with a molecular weight exceeding 500 Da, melting point surpassing 200 °C, and a dosage requirement greater than 10 mg per day [6, 7]. To overcome the challenges, the advancing carriers in TDD are crucial for ensuring safe and enhanced skin permeation for a diverse range of active pharmaceutical ingredients (APIs) [8].

Ionic liquids (ILs) have emerged as a promising solution due to their unique physicochemical properties, making them effective permeation enhancers for TDD [9, 10]. ILs, molten organic salts that remain liquid at ambient temperatures with melting points below 100 °C have garnered attention in TDDS due to their non-volatile, non-flammable, and thermally stable properties [10, 11]. ILs can be synthesized by the combination of numerous cations and anions, allowing for their tuning to meet specific requirements [5, 12, 13]. Incorporating ILs into TDD has shown potential for enhancing drug loading, release profiles, and drug permeability across biological membranes, enhancing therapeutic efficacy [14]. However, the scenario was not always like this, as the first-generation conventional ILs could not be used extensively in TDD because of their inherent toxicity [15]. To improve their efficacy, the second-generation ILs, characterized by their stability in both water and air, were developed to replace volatile organic compounds with ILs owing to their minimal vapor pressure, and soon after this, they became recognized as 'green solvents' for chemical reactions [16, 17]. Then, at the end of the 20th century, the third generation of ILs evolved, incorporating biocompatible ions to develop ILs as biodegradable carriers in drug delivery [18]. These biodegradable ILs are now being extensively used in TDD for their biocompatibility and multifunctional properties compared to previous generations [5]. Researchers are presently more focused on developing new generations of ILs, aiming to optimize the stability and longevity of transdermal drug formulations to ensure patient comfort while also reducing toxicity for managing various diseases in pharmaceutical industries [19, 20].

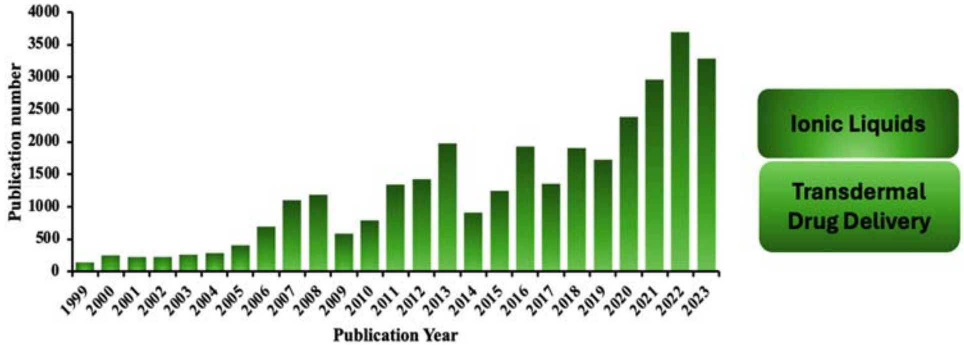

Fig. (1). Publications related to ILs and Transdermal drug delivery over the last 25 years.
Data source: Digital Science. (2018-) Dimensions [Software] available from https://app.dimensions.ai. Accessed on (15^{th} May 2024), under license agreement.

This review article aims to summarize recent advancements in utilizing new-generation ILs for TDD. The aim is to reach and attract scientists focusing on improving TDD applications of a diverse range of drugs by discussing the factors necessary to consider from the perspective of IL advancements and their progressive role in TDD.

TDDS AND ILS

ILs have undoubtedly become one of the most studied and major topics of research in the era of modern chemistry, and they can be found in almost every aspect of various fields, including pharmaceuticals, catalysis, electrolytes, CO_2 capture, and separation [21 - 23]. Publications on this topic are increasing each year, revealing the extended applications of ILs across various sectors [16] (Fig. **1**). The evolution of ILs can be traced through independent discoveries and evolving perspectives, beginning with the exploration of molten liquid salts [24, 25]. Paul Walden's discovery of ethyl ammonium nitrate in 1914 marked the first protic IL in the field of chemistry [26]. Research on ionic liquids (ILs) surged in the 1980s, led by Ken Seddon and Tom Welton. Presently, ILs can be classified into three generations, which are mainly based on their toxicity and diversity in functional properties [27]. The brief discussion about the generations of ILs has already been covered in the previous chapters. In this chapter, I will provide a concise discussion on them to understand the significance of their evolution in TDDS. For TDDS, third-generation biocompatible ILs are the best possible choice to ensure skin permeation with safety [5].

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