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RECENT ADVANCES AND APPLICATIONS OF IONIC LIQUIDS IN THE PHARMACEUTICAL INDUSTRY

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ABSTRACT:

Ionic liquids are ionic compounds that possess a melting temperature below 100°C. The physical and chemical properties of ionic liquids are attractive for various applications—the several organic materials classified as ionic liquids were described as far back as the mid-19th century. The development and application of new and different ionic liquids have progressed. The aim of the first generation was mainly on their unique characteristics and intrinsic physical and chemical properties; such as density, viscosity, conductivity, solubility, and high thermal and chemical stability. This review focuses on the applications of ionic liquids methodologies to solve critical pharmaceutical problems, such as the low solubility and thus the bioavailability of pharmaceutical compounds and the presence of polymorphs, which hamper the efficacy of important commercially available drugs. The development (mendeley) Strategy to use ionic liquids as carriers of pharmaceutically active compounds is an extremely promising and wide avenue. The synthesis of liquid salts through the discerning combination of cations and anions with several distinct pharmaceutical roles answers some of today's pharmaceutical challenges.

KEYWORDS: Ionic Liquids, Solvents, Bioavailability, solubility

INTRODUCTION:

Ionic liquids (ILs), defined as salts that are liquid at relatively low temperatures, have gained significant traction in the pharmaceutical industry due to their unique physicochemical properties[1]. These non-volatile, thermally stable solvents can be designed with specific functionalities, making them highly versatile tools in drug development and formulation. Recent advancements in the understanding of ionic liquids have revealed their potential to address some of the critical challenges faced by the pharmaceutical sector, such as poor solubility of active pharmaceutical ingredients (APIs), stability issues, and environmental sustainability[2]. Their ability to enhance solubility, stabilize sensitive compounds, and essential components in the development of new drug formulations and delivery systems. Furthermore, their tunability allows for the customization of properties to meet specific therapeutic needs, supporting the growing trend toward personalized medicine. As the landscape of pharmaceutical research evolves, ionic liquids are emerging as pivotal players, promising to revolutionize drug development and delivery paradigms[3].

The pharmaceutical industry is at a crossroads, facing growing pressure from a range of environmental issues, major losses of revenue owing to patent expirations, increasingly cost-constrained healthcare systems, lengthening of drug development cycles, and more demanding regulatory requirements[3,4]. Performance indicators reveal that pharmaceutical research and development is focusing on fewer new molecular entities and at an increasing cost. However, the possibility of producing pharmaceutical materials by design, i.e., the knowledge of quantitative structure activity relationship (QSAR) that enables the control of the biological and chemical properties by precise changes in the chemical structure, brought to the pharmaceutical industry portfolios an increasing pharmaceutics classification system[5]. The challenging aspects of new formulations of such drug molecules are associated with their slow dissolution in biological fluids, and thus insufficient and inconsistent systemic exposure and consequent suboptimal clinical efficacy. Pharmaceutical companies are pursuing strategies to overcome this limitation as the key to these challenges. Among the many strategies attempted are pro-drug salt formation, crystal engineering, solid dispersion, and micellar systems.

In particular, ionic liquids are found to play a special role in the pharmaceutical industry[4,6]. And some have gained increasing attention as clean, multifunctional solvents for a variety of applications[7]. This neoteric class of solvents generally presents interesting properties, namely, negligible vapor pressure at relatively ambient conditions, high thermal, chemical, and electrochemical stability, and widely tunable properties concerning polarity, hydrophobicity, and solvent miscibility[8]. These properties result from the matchless combination of molecular characteristics of their constitutive ions[9]. Moreover, many types can be regarded as nano-segregated fluids with polar networks permeated by polar domains[10]. This enables the understanding of their particular solvent behavior at a molecular level and the numerous applications to solve classical problems[11].

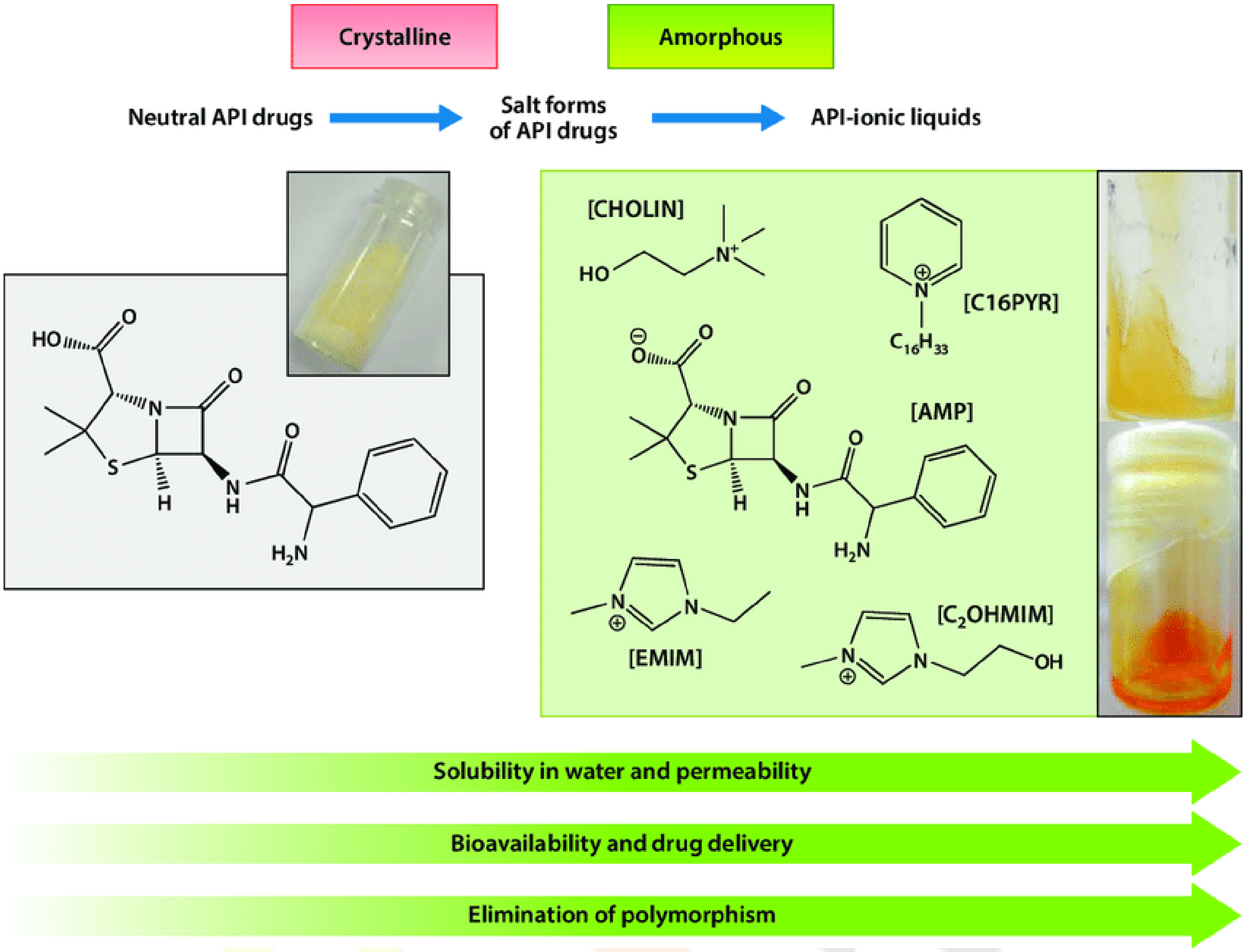


Fig.1: Active pharmaceutical ingredients ionic liquids perspectives

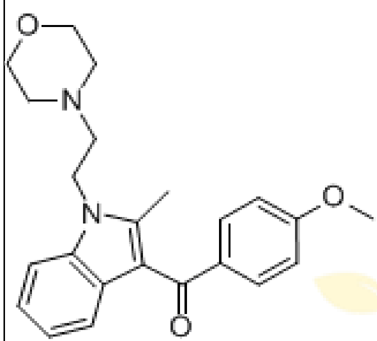
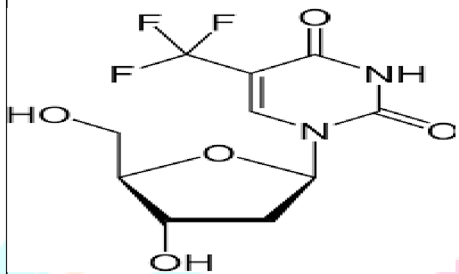
In this review, we will explore the recent advances and applications of ionic liquids in the pharmaceutical industry[4,12]. We will examine their role in improving drug solubility and bioavailability, enhancing the stability of sensitive compounds, enabling sustainable synthesis, and offering innovative extraction and purification methods[13]. This review is then divided into two main parts, of which the first highlights the many uses of ILs as solvents in the synthesis of APIs, providing novel drug-delivery options and serving as a solution for polymorphic molecules[14]. The second describes the use of APIs as cations or anions combined with counter from the IL toolbox so that liquid APIs can be obtained and their bioavailability-related properties evaluated[15]. Interestingly, in chronological terms, this last part was the first to be developed, owing to the vast pharmaceutical industry knowledge of salt formulations and the vision of some members of the IL community, as illustrated[16].

IONIC LIQUID AS SOLVENT

In the late 1980s, Sheldon proposed the introduction of the environmental factor, defined as kg waste/kg product, to assess the environmental impact of waste generation in manufacturing processes[17]. This parameter has played a major role in focusing the attention of the chemical industry worldwide, and particularly the pharmaceutical industry, on waste minimization[18]. The pharmaceutical industry has the highest Sheldon E-factor, as compared with the oil-refining. For this reason, the improvement of waste minimization in the pharmaceutical industry is mandatory so that its status in the broad context of green chemistry and sustainability can be revised[19]. Organic hazardous solvents should be replaced by greener solvents showing lower volatility and flammability[20]. In this context, ILs are especially useful because they present, in most cases, negligible vapor pressure. Further, the rigorous choice of cations and anions can provide special interactions with specific groups of the solute, which are essential in the solubilization of complex molecules, such as APIs and their precursors[21].

Synthesis of Pharmaceutical Drugs Using Ionic Liquids

Industrial synthesis of pharmaceutical compounds frequently involves the use of organic solvents that are responsible for organic contamination of the final product and, many times, it consists of residual impurities[22]. Ionic liquids have been explored as alternative and sustainable reaction media for several organic transformations, including the preparation of pharmaceutical drugs. Reactions in ILs are often faster and easier to carry out compared to those in conventional organic solvents and usually require no special apparatus or methodologies[23]. Despite the large array of different cation and anions available in the IL toolbox, the [C4MIM] cation combined with the [BF4], [PF6], or [NTf2] anions have been used most often as solvents in the synthesis of APIs[24]. Recent publications showed the possibility of performing the synthesis of nucleoside-based antiviral drugs (brivudine, stavudine, trifluridine)[25], using ILs such as 1-methoxyethyl3-methylimidazolium methanesulfonate, 1-methoxyethyl-3-methylimidazolium trifluoroacetate, and 1-butyl-3-methylimidazolium trifluoroacetate as reaction media. For instance, trifluridine (5- trifluoromethyl-2 -deoxyuridine) (see Figure 2) was produced, in high yield (90– 91%) and short reaction time (20–25 min), as a single product using these ILs as reaction media. Essentially, the IL methodology resulted in a higher-purity product and a tenfold decrease[26].

Antiviral Drug Trifluridine TFT (5- trifluoromethyl-2 deoxyuridine)	**Non-Steroidal Anti-Inflammatory Drug pravadoline**
 **Fig. 2: TFT**	 **Fig. 3: Pravadoline**

IONIC LIQUIDS AS ADJUVANT COMPOUNDS IN DRUG DELIVERY

Ionic liquids (ILs) are organic salts that exist in a liquid state at room temperature and have garnered interest in the pharmaceutical field as potential adjuvants in drug delivery systems[27]. Their unique properties, including low volatility, high thermal stability, and tunable solubility, make them ideal candidates for increasing drug delivery efficacy[28].

Mechanisms of Action

1. For Solubility Enhancement: ILs can significantly enhance the solubility of poorly soluble drugs, facilitating better absorption rate and bioavailability of the drug[28,29].

2. For Stabilization of Active Ingredients: ILs can stabilize drugs, particularly sensitive biologics, by preventing degradation during formulation and storage[30].

3. For Controlled Release: By incorporating ILs into drug delivery systems, the release of drugs can be modulated, allowing for sustained or targeted release[31].

4. Bioavailability Improvement: ILs can improve the permeability of drugs across biological membranes, and it will lead to increased bioavailability[32].

APPLICATIONS IN DRUG DELIVERY SYSTEMS

1. Nanoparticle Formulations:

ILs can be used to create nanoparticles that encapsulate drugs, providing controlled release and improving solubility. For instance, IL-based nanoparticles have been explored for effectively delivering anticancer agents[32,33].

2. Hydrogels:

ILs can be incorporated into hydrogel matrices, improving the mechanical properties and drug-loading capacity. This is particularly useful for local drug delivery applications, such as wound healing[34].

3. Microneedles:

ILs can improve the performance of microneedle patches by enhancing drug solubility and stability, making them easier for transdermal drug delivery of vaccines and therapeutics[35].

4. Liposomes and Nanocarriers:

The incorporation of ILs into liposomal formulations can enhance the drug encapsulation efficiency and release kinetics properties, particularly for lipophilic drugs[36].

CASE STUDIES

1. Cancer Therapy:

ILs have been investigated as adjuvants in delivering chemotherapeutic agents. Studies show that ILs can improve the solubility and stability of drugs like paclitaxel, resulting in improved therapeutic outcomes[37].

2. Vaccine Delivery:

ILs can act as adjuvants in vaccine formulations, improving immune responses. For example, ILs have been used to improve the stability and release of antigens, potentially improving vaccine efficacy[38].

ADVANTAGES OF DRUG DELIVERY

- Customizability: The physical and chemical properties of ILs can be tailored to specific drug delivery needs[39].
- Reduced Toxicity: Many ILs are less toxic than traditional organic solvents, providing a safe alternative for drug formulation[40].
- Enhanced Patient Compliance: By enhancing bioavailability and providing controlled release, ILs can lead to more effective treatments and improved patient adherence[41].

CHALLENGES AND CONSIDERATIONS

- Toxicity and Biocompatibility: While many ILs are considered safe, thorough evaluations are necessary to ensure biocompatibility for specific applications[42].
- Regulatory Hurdles: The unique characteristics of ILs may pose challenges in regulatory approval processes, requiring extensive safety studies[43].
- Cost and Scalability: The production and formulation costs of ILs may impact their commercial viability compared to traditional excipients[44].

Ionic liquids present a promising avenue for enhancing drug delivery systems through their multifunctional properties[45]. As research continues to uncover their potential, ILs could significantly enhance the efficacy and safety of pharmaceutical formulations. Ongoing studies and clinical evaluations will be critical in establishing their role in the future of drug delivery.

When ILs are used as solvents in drug synthesis, ionic liquid–organic systems are formed. Firstly, volatile components, such as organic solvents in the reaction, are removed through vacuum distillation using the low vapor pressure of the ILs in the Purification procedure[46]. Conventional NSAIDs or drugs are prepared to use as ILs as the alternative media. It is used as an alternative solvent for the preparation of different pharmaceutical drugs. Organic solvents replaced by ILs can provide and enhance better reaction conditions and accelerate more problematic reactions, as well as fascinate the isolation and purification of the desirable product[47].

Table 1: Composition of the organic solvents with ionic liquids

Property	**Organic solvents**	**Ionic liquids**
Number of solvents	Less than 1,000	Less than 1,000,000
Applicability	Single function	Multifunction
Catalytic ability	Rare	Common and tunable
Chirality	Rare	Common and tunable
Vapor pressure	Obeys the Clausius-Clapeyron equation	Negligible vapor under normal condition
Flammability	Usually flammable	Usually nonflammable
Salvation	Weakly solvating	Strongly solvating
Polarity	Conventional polarity	Polarity concepts questionable

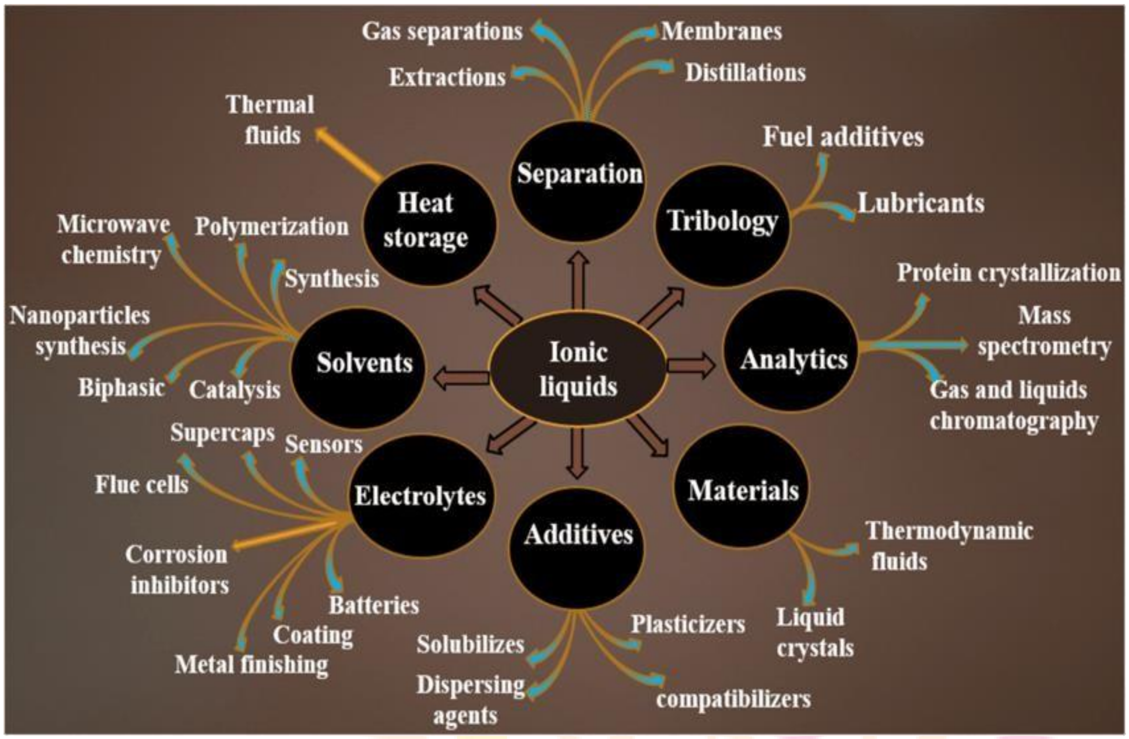


Fig.4: Ionic liquids

IONIC LIQUIDS IN DRUG DELIVERY

An ionic liquid is a salt in which the ions are poorly coordinated which results in these solvents being liquid below 100°C or even at the room temperature[48]. E.g.: The methylimazolidine and pyridinium ion have proven to be good starting points for the development of ionic liquid. For the solvent used for processing of API, a solubility greater than 1mg/ml must be attained.

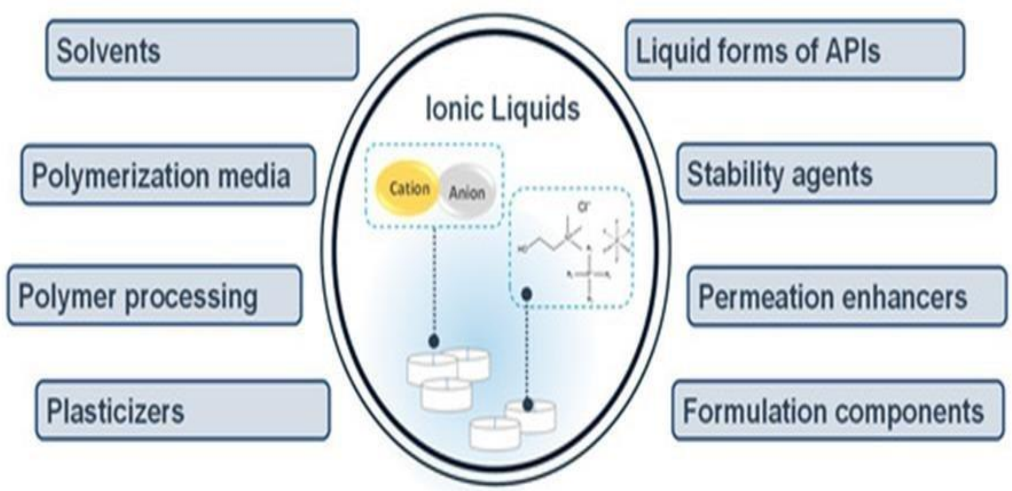


Fig. 5: Ionic Liquids

For enhancing and improving drug delivery, the design of novel systems with polymers and biopolymers has also been attempted by using Ionic liquids as media for polymerization processes, and processing of the polymers[49].
Because of the advantageous properties of ionic liquids, they have different components in drug delivery systems. The solubility of drugs like amphotericin-B, itraconazole, and etodolac, which are sparingly soluble in water.[6]

Here are some key aspects of ionic liquids in drug delivery:

1. Enhanced Solubility and Bioavailability

Many therapeutic agents or drugs, particularly poorly soluble drugs, these agents or the drugs face challenges in achieving adequate bioavailability[50]. Ionic liquids can improve or enhance the solubility of these compounds by modifying their chemical structure or by forming salts with the drug[51]. This enhancement leads to increased dissolution rates and good absorption in the gastrointestinal tract.[4,6]

2. Controlled Release Systems

Ionic liquids can be incorporated into drug delivery systems which can offer controlled or sustained release of active pharmaceutical ingredients (APIs). By encapsulating drugs in ionic liquid matrices, researchers can modulate the release profile based on the formulation's specific design. This capability is particularly valuable for managing chronic conditions requiring consistent drug levels [52]. The ionic liquid can also be used to improve the solubility of the drug that is not soluble in water.

3. Targeted Delivery

The tunable nature of ionic liquids allows for the functionalization of drug carriers that can selectively target specific tissues or cells[53]. By attaching targeting moieties to ionic liquid-based nanoparticles or other carriers, researchers can increase the localization of therapeutics, reducing side effects and enhancing efficacy, especially in cancer therapies.

4. Nanoparticle Formulations

Ionic liquids can be used to create nanoparticles for drug delivery. These nanoparticles can encapsulate drugs which improve their stability and protect them from degradation[54]. Additionally, ionic liquid-based nanoparticles can facilitate the release of drugs in response to specific stimuli (e.g., pH or temperature changes), providing a dynamic delivery system.

5. Improved Stability of Biologics

Ionic liquids have shown promise in stabilizing biologics such as proteins and peptides, which are often sensitive to environmental factors. By formulating these compounds in ionic liquids, researchers can enhance their stability during storage and administration, potentially improving their therapeutic outcomes.[38,54]

6. Formulation Flexibility

The versatility of ionic liquids allows for the formulation of various dosage forms, including oral, injectable, and transdermal systems.[6,55] Their ability to modify viscosity and solubility enables the development of formulations that cater to different routes of administration, enhancing patient compliance and therapeutic effectiveness.[55]

7. Green Drug Delivery Systems

As the pharmaceutical industry moves towards more sustainable practices, ionic liquids provide an environmentally friendly alternative to traditional solvents in drug formulation.[56] They can be recycled and often require milder conditions for processing, aligning with the principles of green chemistry.

Ionic liquids represent a significant advancement in drug delivery systems, offering Innovative solutions to common pharmaceutical challenges[56] Their ability to enhance Solubility, provide controlled and targeted delivery, and stabilize sensitive compounds positions them as vital tools in modern medicine. Continued research and development in this area will likely yield even more sophisticated applications, ultimately improving Patient outcomes and expanding therapeutic options.

RECENT ADVANCES AND APPLICATIONS OF IONIC LIQUIDS IN THE PHARMACEUTICAL INDUSTRY

Ionic liquids (ILs) have gained significant attention in the pharmaceutical industry due to their unique properties, such as low volatility, high thermal stability, and tunable solubility. Their ability to dissolve a wide range of compounds makes them valuable for various applications, from drug formulation to extraction processes[57]. Following this is an overview of recent advances and applications of IL:

1. Drug Solubility Enhancement

ILs can enhance the solubility of poorly soluble drugs through solubilization and complexation. This is particularly beneficial for oral drug delivery systems. Recent studies have explored the use of specific ILs to improve the bioavailability of drugs like curcumin and many anti-cancer agents[58].

2. Green Solvents for Extraction Processes

ILs are increasingly being used as solvents in the extraction of bioactive compounds from natural sources. Their tunable polarity allows for selective extraction of desired compounds, making them an excellent alternative to traditional organic solvents. Applications include the extraction of photochemical and antioxidants from plant materials[59]

3. Drug Delivery Systems

Innovative drug delivery systems utilizing ILs are emerging. For instance, ILs can be incorporated into nanoparticles or hydrogels, providing controlled release profiles and improving drug stability[60]. Recent research has focused on IL-based nanocarriers for targeted drug delivery, particularly in cancer therapy.

4. Synthesis of Active Pharmaceutical Ingredients (APIs)

ILs facilitate various chemical reactions used in the synthesis of APIs. Their unique properties can enhance reaction rates and yields while minimizing by-products[6]. Recent advances include the use of ILs in catalytic processes and as reaction media in organic synthesis.

5. Stability and Formulation of Biologics

ILs can improve the stability of biologics, such as proteins and peptides, during formulation and storage. They can help maintain the active conformation of these molecules, thus enhancing their efficacy and shelf life[61]. This has implications for the development of biological drugs and vaccines.

6. Crystallization and Polymorphism Control

ILs play a crucial role in controlling the crystallization of pharmaceutical compounds. By modifying the crystallization environment, ILs can help produce desired polymorphs with improved solubility and stability, which is essential for drug formulation.[6,62]

7. Antimicrobial and Antiviral Applications

Research has shown that certain ILs possess antimicrobial and antiviral properties, making them candidates for pharmaceutical applications. Studies have explored their efficacy against various pathogens, contributing to the development of new antimicrobial agents.[56]

8. Drug Formulation for Parenteral Administration

ILs have been investigated as excipients in parenteral formulations. Their ability to solubilize drugs and provide stability makes them suitable for injectable formulations. Recent work focuses on developing IL-based formulations that enhance patient compliance and therapeutic efficacy[59].

9. Waste Reduction and Process Intensification

The adoption of ILs can lead to greener processes by reducing waste and energy consumption in pharmaceutical manufacturing. Their reusability and ability to dissolve multiple reactants or products in one phase streamline processes, making them more efficient and sustainable.

The integration of ionic liquids in the pharmaceutical industry is advancing rapidly, driven by their versatile properties and potential to improve drug formulation, synthesis, and delivery[6,1]. Continued research will likely yield novel applications and further enhance the efficiency and sustainability of pharmaceutical processes. As regulatory frameworks adapt to these innovations, ILs may play an increasingly prominent role in the future of drug development and manufacturing.

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DRUGS SOLUBILITY ENHANCEMENT USING IONIC LIQUIDS:

Drugs' poor solubility affects their bioavailability and therapeutic efficacy, making it a significant hurdle in pharmaceutical development. A variety of medicinal substances can now have their solubility improved thanks to the special qualities of ionic liquids (ILs), which have made them viable solubilizing agents. When it comes to poorly soluble medications, ionic liquids are thought to be the most efficient drug delivery method. Ionic solutions increase the solubility of drugs and should also improve transdermal administration. The active components of pharmaceuticals, Ionic liquids are utilized to improve the way that drugs are delivered[64].

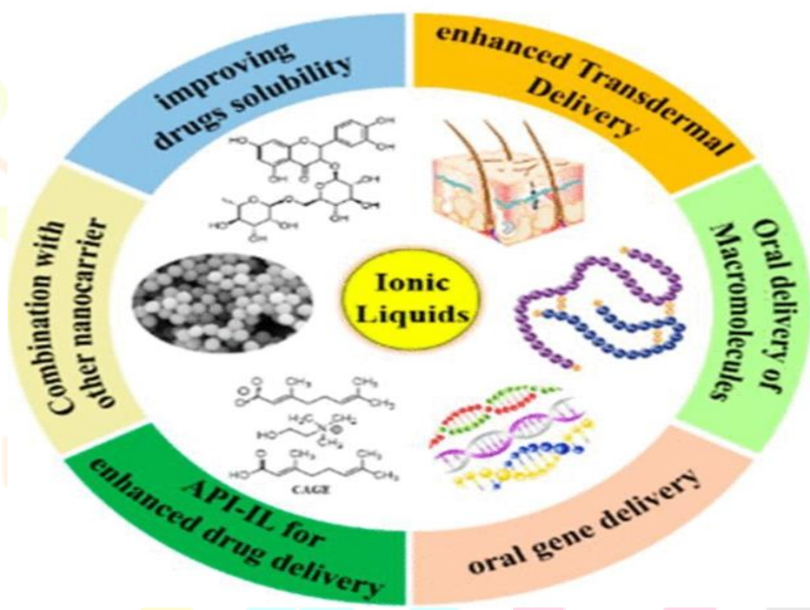

Fig 6: Ionic Liquid

MECHANISMS OF SOLUBILITY ENHANCEMENT

1. Solubilization:

ILs can solubilize hydrophobic drugs by forming strong interactions with drug molecules, thereby increasing their apparent solubility.

2. Hydrotropic Action:

Some ILs act as hydrotropism, enhancing the solubility of poorly soluble compounds by altering the solvent properties.

3. Complexation:

ILs can form complexes with drug molecules, stabilizing them in solution and enhancing solubility.

4. Modification of Polarity:

By tuning the composition of ILs, the polarity can be adjusted to better match that of the drug, improving solubility[65]

CASE STUDIES

- **Curcumin:**

Problem: Curcumin has low solubility in water.
Solution: Various ILs have been tested, showing significant increases in curcumin solubility. For example, the use of 1-ethyl-3-methylimidazolium acetate led to improved solubility and bioavailability.

- **Anti-cancer Agents:**

Problem: Many anti-cancer drugs, such as paclitaxel, face solubility issues.

Solution: ILs like chlorine chloride-based systems have been utilized to enhance the solubility of these compounds, facilitating better drug formulation.

- **Non-steroidal Anti-inflammatory Drugs (NSAIDs):**

Example: Salicylic acid and ibuprofen have shown improved solubility when formulated with specific ILs, which aids in quicker absorption and better therapeutic outcomes[6].

ADVANTAGES OF USING IONIC LIQUIDS

- **Versatility:**

The wide range of available ILs allows for tailoring solubility properties to specific drugs.

- **Low Volatility:**

ILs do not evaporate easily, making them suitable for long-term storage of drug formulations.

- **Environmental Friendliness:**

Many ILs are less toxic and more environmentally benign than traditional organic solvents[66].

CHALLENGES AND CONSIDERATIONS

- **Toxicity:**

Some ILs may exhibit toxicity, necessitating careful selection and evaluation [67].

- **Regulatory Approval:**

The unique nature of ILs may complicate their regulatory assessment, requiring thorough safety and efficacy studies [68].

- **Cost and Scalability:**

The production of ILs can be more expensive than conventional, which could affect commercial viability.

CHEMICAL APPLICATIONS OF IONIC LIQUIDS IN PHARMACY

Ionic liquids (ILs) have gained significant attention in pharmaceutical applications due to their unique physicochemical properties, such as low volatility, high thermal stability, and tunable solubility. Here's an overview of their key chemical applications in pharmacy [69]:

1. Solubilization of Active Pharmaceutical Ingredients (APIs)

Challenge: Many APIs exhibit poor solubility, limiting their bioavailability.

Application: ILs can enhance the solubility of hydrophobic drugs through solubilization and complications. For example, ILs have been successfully used to improve the solubility of curcumin and various anti-cancer drugs[6].

2. Synthesis of Active Pharmaceutical Ingredients

Role as Solvents: ILs serve as green solvents in chemical synthesis, offering a more environmentally friendly alternative to traditional organic solvents. They facilitate various reactions, including:

Catalysis: ILs can act as solvents for catalytic reactions, improving reaction rates and yields.

Re-crystallization: They can assist in the recrystallization of APIs, controlling polymorphism and enhancing purity[70].

3. Drug Delivery Systems

Nanoparticle Formulations: ILs are used to prepare nanoparticles that encapsulate drugs, providing controlled release and improving solubility.

Hydrogels: Incorporating ILs into hydrogels enhances their properties, making them suitable for localized drug delivery.

Microneedles: ILs can improve the performance of microneedles for transdermal drug delivery by enhancing drug solubility and stability.

4. Stabilization of Biologics

Biologics Formulation: ILs can stabilize sensitive biologics (proteins, peptides, and nucleic acids) during formulation and storage, preventing degradation and denaturation.

5. Pharmaceutical Extraction Processes

Extraction of Natural Compounds: ILs serve as solvents for the extraction of bioactive compounds from natural sources, such as plant extracts. They facilitate the extraction of antioxidants and other phytochemicals while minimizing environmental impact[71].

6. Enhanced Formulation of Vaccines

Vaccine Adjuvant: ILs can be used as adjutants in vaccine formulations, enhancing immune responses and stabilizing antigens.

7. Chemical Analysis and Separation Techniques:

Chromatography: ILs can be used as mobile phases in chromatographic techniques, improving the separation and analysis of pharmaceutical compounds [72].

Electrochemistry: ILs can serve as electrolytes in electrochemical sensors for detecting drug levels and quality control.

8. Stability and Storage of Pharmaceuticals

Improved Shelf Life: ILs can enhance the stability of pharmaceuticals during storage, reducing degradation and improving overall shelf life.

9. Environmentally Friendly Processes

Green Chemistry: ILs contribute to green chemistry by reducing waste and energy consumption in pharmaceutical processes, aligning with sustainability goals in drug development [73].

Ionic liquids hold substantial potential for various chemical applications in pharmacy, from drug formulation to synthesis and extraction processes. Their unique properties offer innovative solutions to longstanding challenges in the pharmaceutical industry, promoting more efficient, stable, and environmentally friendly practices. As research advances, the integration of ILs into pharmaceutical applications is expected to expand, paving the way for novel therapeutic strategies and improved drug delivery systems[72,73].

IONIC LIQUIDS AS PHARMACEUTICALS:

Ionic liquids (ILs) are salts that exist in a liquid state at or near room temperature, characterized by their unique properties such as low volatility, high thermal stability, and tunable solubility. While traditionally used as solvents and reagents in various chemical processes, there is growing interest in the direct use of ionic liquids as pharmaceuticals. This involves exploring their therapeutic potential, safety, and application in drug formulations[4].

Therapeutic Applications

1. Antimicrobial Agents: Certain ILs exhibit significant antimicrobial properties, making them candidates for developing new antibacterial and antifungal agents. For example, some imidazolium-based ILs have shown efficacy against a range of pathogens, potentially addressing antibiotic resistance.

2. Antiviral Activity: Research indicates that specific ILs may possess antiviral properties, which can be harnessed for developing treatments against viral infections.

3. Anti-inflammatory Agents: Some ILs have demonstrated anti-inflammatory effects, providing opportunities for the development of new anti-inflammatory drugs.

DRUG FORMULATION AND DELIVERY

1. Enhancers in Drug Formulation: ILs can enhance the solubility and stability of poorly soluble drugs. They can be integrated into formulations to improve bioavailability and therapeutic efficacy. For instance, ILs are being studied as solubilizers for various APIs, such as curcumin and other natural compounds [74].

2. Controlled Release Systems: ILs can be utilized in drug delivery systems (e.g., nanoparticles, hydrogels) that provide controlled or sustained release of therapeutic agents. This enhances treatment adherence and efficacy[74].

3. Transdermal Delivery: ILs can facilitate the penetration of drugs through the skin, making them suitable for transdermal drug delivery systems.[74]

STABILIZATION OF BIOLOGICS

ILs can stabilize sensitive biological compounds (proteins, peptides) during formulation and storage, reducing denaturation and improving shelf life. This is particularly valuable for therapeutic proteins and vaccines[75].

CHEMICAL ANALYSIS AND DIAGNOSTICS

ILs can be employed in analytical chemistry and diagnostics to improve the detection and quantification of pharmaceuticals. Their use in electrochemical sensors and chromatographic methods enhances sensitivity and selectivity.

SAFETY AND TOXICITY CONSIDERATIONS

While ILs shows promise, their safety and toxicity must be thoroughly evaluated. The biocompatibility of ILs varies, and some may exhibit cytotoxicity. It is crucial to assess their long-term effects on human health and the environment[76].

REGULATORY AND COMMERCIAL CHALLENGES

The use of ILs as pharmaceuticals faces regulatory challenges due to their novel nature. Comprehensive safety studies and adherence to regulatory standards are necessary before they can be approved for widespread use in therapeutic applications[77].

Ionic liquids present a novel class of compounds with significant potential in pharmaceuticals, both as therapeutic agents and as enhancers in drug formulation and delivery. Their unique properties can address some of the critical challenges in modern medicine, particularly in improving the solubility and stability of drugs. Ongoing research is essential to explore their full potential, evaluate safety profiles, and navigate regulatory pathways for their incorporation into therapeutic applications.

IONIC LIQUIDS IMPACT ON OLD AND NEW ENERGY TECHNOLOGY

Ionic liquids (ILs) are a fascinating class of solvents characterized by their low volatility and unique properties, which make them highly suitable for a variety of applications in both old and new energy technologies. Following is an overview of their impacts[1,78]:

1. Energy Storage:

Batteries:

- Lithium-ion Batteries: ILs can improve the performance of electrolytes, enhancing conductivity and thermal stability, leading to safer and more efficient batteries.
- Supercapacitors: They enable higher energy density and faster charge/discharge rates.
- Super capacitors: The use of ILs can enhance the charge storage capacity and cycle life, making super capacitors more effective for energy storage.

2. Fuel Cells: ILs can serve as electrolytes in fuel cells, offering high ionic conductivity and stability over a wide temperature range. They reduce fuel crossover and improve efficiency, particularly in polymer electrolyte membrane fuel cells (PEMFCs) [79].

3. Carbon Capture and Storage (CCS): ILs have shown promise in capturing CO2 due to their tunable properties and ability to selectively absorb gases. This is vital for reducing emissions from traditional fossil fuel energy sources.

4. Biofuels Production: ILs can be used in the extraction and processing of biofuels, helping to break down biomass more efficiently. They can dissolve lignocellulose materials, facilitating the conversion of biomass into fermentable sugars.

5. Solar Energy: In solar energy applications, ILs can be used in dye-sensitized solar cells (DSSCs) to improve the stability and efficiency of the electrolyte, enhancing overall performance.

6. Thermal Energy Storage: ILs has high heat capacities and thermal stability, making them suitable for use in thermal energy storage systems. They can store and release energy effectively, aiding in the management of renewable energy sources.

7. Electrochemical Processes: In electrochemical applications, such as electroplating and electrosynthesis, ILs can facilitate more efficient processes by providing better conductivity and stability than traditional solvents.

8. Safety and Environmental Impact: The low volatility of ILs means they pose reduced risks of air pollution and hazards associated with flammable solvents. Their design can also be tailored to minimize toxicity and enhance biodegradability, supporting sustainable practices.

9. Challenges: Despite their benefits, challenges remain, including the cost of IL production and potential issues with scalability. Research is ongoing to address these limitations and optimize their use across various technologies.

Ionic liquids represent a transformative approach to energy technologies, blending well with both traditional systems and innovative solutions [80]. Their unique properties can lead to significant advancements in efficiency, safety, and sustainability, making them an exciting area of research and application in the ongoing energy transition.

CLASSIFICATION OF GELS BY INTERACTIONS

Gels can be classified based on various criteria, including their nature. Here are some common classifications of gels based on their nature:[81]

1. **Based on the composition**

i. Organic Gels: Made from organic compounds, such as polymers or surfactants. Common examples include silicone gels and polymer gels.

ii. Inorganic Gels: Composed of inorganic materials, such as silica gels or metal oxide gels.

iii. Biopolymer Gels**:** Derived from natural sources, such as alginate, gelatin, or pectin. These gels often have biocompatibility and are used in food and pharmaceutical applications[81].

2. **Based on Structure:**

i. Physical Gels: Formed through weak interactions (like Vander Waals forces or hydrogen bonds) and can be easily reversed. Examples include gelatin gels and agar gels.

ii. Chemical Gels: Formed through covalent bonds, resulting in a more permanent structure. These gels are usually more stable and less reversible.

3. Based on Water Content:

i. Hydrogels: Gels that have a highwater content, usually more than 90%. They are often used in biomedical applications, such as drug delivery and tissue engineering[82].

ii. Aerogels: Extremely low-density gels where the liquid component has been replaced with gas. They are often used for thermal insulation and as absorbents.

4. Based on Temperature Sensitivity:

i. Thermo reversible Gels: Gels that can transition between sol and gel states with temperature changes. An example is gelatin, which melts upon heating and gels upon cooling.

ii. Thermosetting Gels: Gels that, once set, cannot be reverted to a liquid state by heating. They maintain their structure at elevated temperatures.

5. Based on Ionic Nature:

i. Cationic Gels: Gels that contain positively charged ions. They often exhibit different properties compared to anionic or non-ionic gels.

ii. Anionic Gels: Gels containing negatively charged ions, which can interact differently with other charged substances.[81,82]

iii. Non-ionic Gels: Gels that do not carry a net charge, often leading to distinct interactions and behaviors.

6. Based on Response to External Stimuli:

1. Smart Gels:

Gels that respond to external stimuli, such as pH, temperature, or light. They can undergo significant changes in properties upon stimulation.

Gels can be classified based on the types of interactions that lead to their formation. Here are the main classifications:

2. Physical Gels:

Weak Interactions: Formed through non-covalent interactions, such as hydrogen bonds, Vander Waals forces, and hydrophobic interactions.

Examples: Gelatin, agarose, and certain polymer gels. These gels can often be reversed, meaning they can transition back to a liquid state upon heating or agitation.

3. Chemical Gels:

Covalent Bonds: Formed through strong covalent bonds, resulting in a more stable and permanent structure.
Examples: Polyacrylamide gels and certain epoxy-based gels. These gels do not revert easily to a liquid state and maintain their structure under various conditions.[81]

4. Associative Gels:

Micelle or Network Formation: Formed by the self-assembly of amphiphilic molecules or polymers that create a three-dimensional network through hydrophobic interactions and hydrogen bonding[83].

Examples: Certain surfactant-based gels and polymer gels that utilize block copolymers.

5. Gelation via Ionic Interactions:

Ionic Cross-Linking: Formed when charged groups on polymers interact with counter ions or other charged species, creating a network.

Examples: Alginate gels, which are formed by the ionic cross-linking of alginate with calcium ions.

6. Interpenetrating Network Gels (IPNs):

Multiple Networks: Composed of two or more interpenetrating polymer networks that are not chemically bonded to each other but work together to form a gel.

Examples: Hydrogels that combine natural and synthetic polymers to achieve desirable properties.

7. Solvent-Responsive Gels:

Solvent Interactions: Gels that change their structure or properties in response to solvent conditions (e.g., polarity, ionic strength) [84].

Examples: Some hydrogels that swell or shrink based on the concentration of salts in the solution.

Ionic liquids (ILs) have garnered significant attention in the pharmaceutical industry due to their unique properties, including low volatility, high thermal stability, and tunable solubility. Recent advances have highlighted their potential as antimicrobial agents. Here’s an overview of their antimicrobial mechanisms and applications [84].

ANTIMICROBIAL MECHANISMS OF IONIC LIQUIDS

1. Disruption of Membrane Integrity:

ILs can interact with microbial cell membranes, leading to increased permeability and eventual lysis. This disruption is often due to the amphiphilic nature of ILs, which can insert into lipid bilayers [85].

2. Cationic Nature:

Many ILs are cationic and possess a positive charge, allowing them to electrostatically attract negatively charged bacterial membranes. This interaction can destabilize the membrane and enhance antimicrobial activity.

3. Formation of Reactive Oxygen Species (ROS):

Certain ILs can promote the generation of ROS within microbial cells, leading to oxidative stress and damage to cellular components such as DNA, proteins, and lipids.

4. Interference with Metabolic Pathways:

ILs can inhibit specific metabolic pathways within microorganisms, disrupting their growth and reproduction. For instance, some ILs affect enzymatic activity essential for cellular function.

5. Biofilm Disruption:

ILs have shown the potential to disrupt biofilms, which are communities of microorganisms encased in a protective matrix. This property is crucial for preventing infections and enhancing the effectiveness of other antimicrobial agents [86].

RECENT ADVANCES IN APPLICATIONS [87]:

1. Antimicrobial Formulations:

ILs are being incorporated into formulations for topical antimicrobial agents, coatings, and disinfectants. Their ability to remain effective at lower concentrations makes them appealing for reducing toxicity and side effects.

2. Drug Delivery Systems:

ILs can enhance the solubility and stability of poorly soluble drugs, improving their bioavailability. They can be used in controlled-release systems to provide sustained antimicrobial activity[87].

3. Pharmaceutical Manufacturing:

ILs are being explored as solvents and reaction media in pharmaceutical synthesis, particularly for green chemistry applications. They can facilitate reactions while minimizing waste and environmental impact.

4. Preservation of Pharmaceutical Products:

Due to their antimicrobial properties, ILs can be used as preservatives in pharmaceutical formulations, extending shelf life and maintaining product efficacy.

5. Antimicrobial Coatings:

ILs can be applied to surfaces to create antimicrobial coatings for medical devices, packaging materials, and other applications, reducing the risk of infections.

6. Enhanced Extraction Processes:

ILs can be utilized in the extraction of bioactive compounds from natural sources, enhancing the production of natural antimicrobial agents for pharmaceuticals[87].

CHALLENGES AND FUTURE DIRECTIONS

Toxicity and Biocompatibility: While many ILs show promise, assessing their toxicity and ensuring biocompatibility for pharmaceutical applications is essential.

- Regulatory Approval: The path to regulatory approval for IL-based formulations may be complex, requiring comprehensive studies on safety and efficacy.
- Optimization of Formulations: Continued research is needed to optimize IL structures for specific antimicrobial applications, balancing efficacy with safety and environmental impact.

Ionic liquids offer exciting opportunities in the pharmaceutical industry, particularly as antimicrobial agents [88]. Their unique properties and mechanisms of action position them as valuable tools for addressing challenges in infection control and drug delivery, paving the way for innovative applications in healthcare. Ongoing research will likely uncover even more potential uses and refine existing formulations for optimal performance.

The classification of gels by interaction types provides insight into their formation mechanisms, properties, and potential applications. Understanding these interactions is crucial for developing gels tailored to specific uses in fields like pharmaceuticals, food science, and materials engineering[88].

CYTOTOXICITY

Cytotoxicity in ionic liquids (ILs) is a significant concern, particularly in biomedical and pharmaceutical applications[89]. While ILs possess unique properties that make them attractive for various uses, their potential toxic effects on living cells must be thoroughly evaluated. Here's an overview of the factors influencing cytotoxicity in ILs, mechanisms of toxicity, and implications for their use:

Factors Influencing Cytotoxicity

1. Chemical Structure: The cation and anion components of ILs significantly influence their cytotoxicity. Different combinations can lead to varying degrees of toxicity. Common cations (e.g., imidazolium, pyridinium) and anions (e.g., chloride, acetate) exhibit different interactions with cell membranes and metabolic pathways.

2. Concentration: Higher concentrations of ILs typically correlate with increased cytotoxic effects.

Determining safe exposure levels is crucial for any application.

3. Duration of Exposure: Prolonged exposure to ILs can lead to more severe cytotoxic effects compared to shorter exposure times.

4. Cell Type: Different cell lines (e.g., epithelial, fibroblast, cancer) exhibit varying sensitivities to ILs, necessitating a comprehensive evaluation of cytotoxicity across multiple cell types.

5. PH and Ionic Strength: The physicochemical environment can influence the behavior of ILs, potentially affecting their interaction with cells [90]

Mechanisms of Cytotoxicity

1. Membrane Disruption: ILs can interact with and disrupt cell membranes, leading to increased permeability and cell lysis.

2. Oxidative Stress: ILs may induce the production of reactive oxygen species (ROS), causing oxidative damage to cellular components like lipids, proteins, and DNA.

3. Alteration of Cellular Metabolism: ILs can interfere with cellular metabolic processes, leading to dysfunction and apoptosis (programmed cell death).

4. Inflammatory Response: Certain ILs may trigger inflammatory pathways, leading to cytotoxic effects mediated by immune responses[89,90].

Assessment of Cytotoxicity

1. In Vitro Studies: Various assays (e.g., MTT, Alamar Blue, LDH leakage) are used to assess cell viability and cytotoxic effects in different cell lines.

2. Mechanistic Studies: Understanding how specific ILs interact with cellular components helps elucidate their mechanisms of cytotoxicity.

3. Comparative Studies: Comparing ILs with traditional solvents or antimicrobials can provide insight into their relative safety and effectiveness[90].

Implications For Use

1. Biomedical Applications: While some ILs show potential as drug delivery vehicles or antimicrobial agents, their cytotoxicity must be balanced against therapeutic benefits.

2. Toxicity Mitigation: Designing ILs with reduced cytotoxicity through structural modifications or selecting less toxic components can enhance their safety profiles.

3. Regulatory Considerations: Comprehensive toxicological assessments are essential for the regulatory approval of IL-based products, especially in pharmaceuticals and medical devices.

The choice of cation and anion in ionic liquids (ILs) plays a crucial role in determining their properties and applications. Here's an overview of how these components affect the characteristics of ILs:

EFFECT OF CATIONS AND ANIONS:

1. Cation Effects

a. Structure and Size:

Alkyl Chain Length: Cations with longer alkyl chains (e.g., alkyl imidazolium) often result in ILs with lower melting points and increased hydrophobicity. This can enhance solubility for organic compounds but may also lead to higher viscosity.

Cation Type: Different cations (e.g., imidazolium, pyridinium, and ammonium) influence thermal stability, viscosity, and conductivity. For example, imidazolium-based ILs tend to have good thermal stability and ionic conductivity [91].

b. Charge Distribution:

The distribution of charge within the cation affects solvation properties and the ability to form hydrogen bonds. Cations with delocalized charges (e.g., pyridinium) can exhibit different solubility characteristics compared to those with localized charges[91].

c. Polarity:

The polarity of the cation influences the solubility of various compounds in the IL. More polar cations can enhance the solubility of polar solutes, making ILs versatile solvents for chemical reactions.

2. Anion Effects

a. Size and Shape:

Anion Size: Larger anions (e.g., hexafluorophosphate) often lead to lower viscosity and melting points, while smaller anions (e.g., chloride) can enhance ionic interactions and conductivity.

Anion Geometry: The geometry (e.g., planar, spherical) affects how the anion interacts with cations and solutes, influencing overall solubility and stability [91].

b. Acidity and Basicity:

Anions with varying acidity/basicity can impact reactivity in chemical processes. For example, more basic anions (e.g., acetate) can engage in nucleophilic reactions, while acidic anions may act as Lewis acids.

3. Hydrophobicity:

The hydrophobic or hydrophilic nature of the anion influences the IL's solubility in water and organic solvents. Hydrophobic anions can lead to ILs with enhanced solubility for organic compounds [91].

Combined Effects of Cations and Anions

- **Thermodynamic Properties**: The interaction between the cation and anion affects melting point, thermal stability, and phase behavior. ILs can be designed to remain liquid at room temperature or even exhibit low viscosity.

Ionic Conductivity: The choice of cation and anion can significantly impact ionic conductivity, which is critical for applications in batteries and electrochemical devices. Generally, smaller, more mobile ions lead to higher conductivity.

- **Toxicity and Biocompatibility**: The combination of cation and anion influences the cytotoxicity of ILs. For instance, some cations may be less toxic, while specific anions may enhance or mitigate overall toxicity[90].

Applications Based on Cation and Anion Selection

- Solvents for Chemical Reactions: The choice of cation and anion can tailor ILs for specific reactions, enhancing the solubility and reactivity of reactants.

- Electrolytes in Batteries and Fuel Cells: The conductivity and thermal stability of ILs, influenced by their ionic components, make them suitable for use in energy storage applications.
- Pharmaceutical Applications: Selecting appropriate cations and anions can improve the solubility and stability of drug compounds in IL formulations.
- The effects of cations and anions in ionic liquids are multifaceted and critically essential for tailoring their properties for specific applications. By systematically varying these components, researchers can design ILs with desired characteristics, enhancing their utility in fields like chemistry, materials science, and biomedicine.

BIOMEDICAL APPLICATIONS OF IONIC LIQUIDS:

Ionic liquids (ILs) have gained considerable attention in the biomedical field due to their unique properties, such as low volatility, high thermal stability, and tunable solubility. Here are some notable biomedical applications of ionic liquids:[92]

1. Drug Delivery Systems: Enhanced Solubility and Stability: ILs can improve the solubility and stability of poorly soluble drugs, facilitating their bioavailability. **Controlled Release**: ILs can be used to develop drug delivery systems that provide controlled and sustained release of therapeutics, improving treatment efficacy.

2. Antimicrobial Agents:

Infection Control: Certain ILs exhibit significant antimicrobial activity against a wide range of bacteria and fungi, making them suitable for use in antimicrobial formulations and coatings.

Biofilm Disruption: ILs can help disrupt biofilms, enhancing the effectiveness of other antimicrobial agents in preventing and treating infections.

3. Tissue Engineering:

Scaffolds: ILs can be incorporated into polymeric scaffolds used in tissue engineering to improve mechanical properties and biocompatibility.

Cell Encapsulation: ILs can facilitate the encapsulation of cells and growth factors, promoting tissue regeneration and repair[92].

4. Cryopreservation:

Cryoprotectants: ILs can serve as alternative cryoprotectants for preserving biological samples, such as cells and tissues, at low temperatures. Their unique properties can help maintain cell viability during freezing and thawing processes.

5. Diagnostic Applications:

Biosensors: ILs can enhance the sensitivity and selectivity of biosensors by providing an optimal medium for enzyme activity and promoting electron transfer processes.

Sample Preparation: ILs can be used in sample preparation techniques, improving the extraction of biomolecules for analytical assays.

6. Gene Delivery:

Gene Therapy: ILs can facilitate the delivery of nucleic acids, such as DNA and RNA, into cells, enhancing gene therapy approaches. Their ability to form complexes with nucleic acids can also improve transfection efficiency.

7. Nanoparticle Synthesis:

Drug-Loaded Nanoparticles: ILs can be used as solvents or stabilizers in the synthesis of nanoparticles for targeted drug delivery, improving therapeutic outcomes.

Magnetic Nanoparticles: ILs can assist in functionalizing magnetic nanoparticles for applications in targeted therapy and diagnostics.

8. Anticancer Applications:

Selective Cytotoxicity: Some ILs have shown selective cytotoxic effects against cancer cells, offering potential as therapeutic agents in cancer treatment.

Combination Therapies: ILs can be used to enhance the efficacy of existing chemotherapeutic agents by improving solubility and reducing side effects.

9. Biosafety and Environmental Impact:

Biocompatible Solvents: ILs can replace traditional organic solvents in biomedical applications, reducing toxicity and environmental impact.

Green Chemistry: Their use in pharmaceutical synthesis contributes to more sustainable practices, minimizing waste and hazardous byproducts.

RECENT ADVANCES IN IONIC LIQUIDS

The versatility of ionic liquids makes them promising candidates for a wide range of biomedical applications. As research continues to uncover their potential, ILs may play an increasingly important role in drug delivery, tissue engineering, diagnostics, and therapeutic development, contributing to advancements in healthcare and medicine. However, ongoing studies are necessary to fully understand their biocompatibility, safety, and regulatory implications[1,93].

The use of ionic liquids (ILs) in the pharmaceutical industry has gained significant attention due to their unique properties, such as low volatility, high thermal stability, and tunable solubility. Here's a look at the recent advances and prospects of ionic liquids in this field:

1. Drug Solubility Enhancement:

ILs can improve the solubility of poorly water-soluble drugs, enabling better bioavailability. Recent formulations have shown significant improvements in the dissolution rates of various active pharmaceutical ingredients (APIs).

2. Green Solvents:

ILs are increasingly recognized as green solvents due to their negligible vapor pressure and recyclability. This makes them suitable for environmentally friendly extraction and purification processes.

3. Formulation Development:

Advances in drug formulations using ILs have led to the development of novel delivery systems, including nanoformulations and solid dispersions, enhancing the therapeutic efficacy of drugs.

4. Stability Improvement:

ILs can stabilize certain APIs against degradation, extending their shelf life and efficacy. This is particularly useful for sensitive molecules prone to hydrolysis or oxidation.

5. Targeted Drug Delivery:

The tunable nature of ILs allows for the design of targeted delivery systems that can enhance the accumulation of drugs in specific tissues, potentially reducing side effects and improving treatment outcomes.

FUTURE PROSPECTIVE:

1. Personalized Medicine:

As the pharmaceutical industry shifts towards personalized medicine, ILs may play a key role in developing tailored drug formulations that meet individual patient needs based on their unique metabolic profiles[94].

2. Regulatory Acceptance:

Ongoing research and successful case studies will likely lead to increased regulatory acceptance of ILs in pharmaceutical applications, paving the way for broader adoption in drug development.

3. Biocompatibility and Safety Studies:

Future research will need to focus on the biocompatibility and long-term safety of ILs in pharmaceutical formulations, addressing any potential toxicity concerns.

4. Integration with Advanced Technologies:

The combination of ILs with emerging technologies, such as nanotechnology and 3D printing, could lead to innovative drug delivery systems and personalized dosage forms.

5. Sustainable Pharmaceutical Processes:

The push for sustainable practices in pharmaceuticals may drive further exploration of ILs in manufacturing processes, potentially replacing traditional solvents and reducing waste.

6. Broadening Applications:

Expanding the use of ILs beyond drug formulation to include their role in drug synthesis, separation processes, and catalysts in pharmaceutical reactions will enhance their relevance in the industry.

Ionic liquids hold great promise for transforming various aspects of the pharmaceutical industry, from drug development and formulation to manufacturing processes. As research continues and more applications are explored, ILs are likely to play an integral role in the future of pharmaceuticals, aligning with trends toward sustainability and personalized medicine.[94]

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