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Ionic Liquids in Pharmaceutics: Biocompatibility, Physicochemical Properties, and Applications of API-ILs in Modern Drug Delivery Systems

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Abstract. **General Background**: Ionic liquids (ILs) have emerged as highly versatile solvent systems distinguished by tunable physicochemical properties, negligible vapor pressure, and broad solvation capacity, positioning them as promising alternatives to conventional organic solvents in pharmaceutical science. **Specific Background**: Increasing proportions of drug candidates exhibit poor aqueous solubility, polymorphic instability, and limited bioavailability, challenges that hinder formulation efficiency and therapeutic performance. **Knowledge Gap**: Although ILs have been widely explored as green solvents and catalysts, their potential as active pharmaceutical ingredient–ionic liquids (API-ILs) remains insufficiently characterized, particularly regarding biocompatibility, pharmacokinetics, and translational feasibility. **Aims**: This review synthesizes current advances in IL design, physicochemical behavior, and biomedical applications, with a focus on API-ILs as emerging platforms for drug delivery and solubility enhancement. **Results:** Evidence shows that ILs can significantly improve solubility, permeability, stability, and crystalline behavior of diverse APIs, while certain API-ILs exhibit dual pharmacological activity and enhanced antimicrobial or transdermal performance. **Novelty**: The work consolidates the evolution of IL generations, mechanochemical synthesis strategies, and structure–activity relationships governing their pharmaceutical utility. **Implications**: API-ILs represent a transformative approach for overcoming long-standing formulation barriers, underscoring the need for expanded in vivo studies to validate their safety, biocompatibility, and therapeutic potential in modern drug-delivery systems.

Highlights:

1. API-ILs address solubility, bioavailability, and polymorphism issues in poorly water-soluble drugs.
2. Ionic liquids offer tunable physicochemical properties that support improved drug delivery and stability.
3. Biocompatible ILs provide greener alternatives for synthesis while enhancing permeability and therapeutic performance.

Keywords: Ionic liquids (ILs), API-ILs, Dissolution, Poorly Water-Soluble Drugs, Drug Development

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Introduction

Pharmaceuticals significantly contribute to medical care, enhancing quality of life and durability, particularly in the context of chronic disorders. While active medicinal agents may be marketed in many different dosage formulations, crystalline versions are the favored choice. Nonetheless,(40%-70%) of drugs under development exhibit insufficient water solubility, potentially impacting bioavailability and therapeutic effectiveness, resulting in failures during the latter stages of research [1, 2].The inconsistent absorption of solid formulations from GIT, as well as the limited therapeutic effectiveness, potential toxicities and the polymorphic adverse effects are presents as significant challenges to address [3]. The therapeutic dose of a specific API may equate to a hazardous or potentially deadly dose if an incorrect polymorph is provided. In addition to the established disadvantages of polymorph, the APIs water solubility, the dissolution and bioavailability are contingent upon particle size and characteristics [4]. Various ways were established to improve the aqueous solubility of medicines and their bioavailability, particularly when the oral administration route is considered [1]. Nonetheless, the majority of these procedures continue to employ substantial amounts of organic diluents during these mixtures manufacturing, particularly to promote crystalline formation of distinct polymorph and particles dimensions, which presents issues related to environment and the health [5]. Additionally, solvent molecules may be integrated into the crystal lattice of the active pharmaceutical ingredient during crystallization [6]. Consequently, while evaluating the organic solvents application, they must be eliminated from the active pharmaceutical ingredient or their concentrations must be regulated to guarantee safety for human intake [5]. Despite the availability of comprehensive literature detailing innovative and environmentally friendly solvents for this purpose, the pharmaceutical sector is hesitant to adopt and execute these alternatives. liquid formulations of APIs offer appealing alternatives that avoid polymorphic variability and enhance the low aqueous solubility challenges, while reducing the organic solvents dependance. The pharmaceutical sector has therefore depend on eutectic mixes, but it is now looking into other options for commercialization [7]. Additionally, ionic liquids (ILs) demonstrate considerable promise in the pharmaceutical industry, principally due to their exceptional versatility in generating diverse chemical structures for targeted applications. Ionic liquids are fused salts composed of a significant organic cation and either an organic or inorganic anion. The considerable dimensions of their ions lead to charge dispersion, hindering the formation of a uniform crystalline structure [8]. Ionic liquids possess distinctive features, particularly their remarkable thermal and chemical stability, together with their potent solvation capacity for a diverse array of molecules, dependent upon appropriate formulation [9]. The appropriate choice of cation_anion pairings in ionic liquids enable the integration of pharmaceuticals as ionic constituents, thus converting solid pharmaceutical agents to liquify forms (API - ILs). So, this technique resolves the challenge of polymorphic diversity, improves bioavailability, and maximally optimizes therapeutic benefits [10, 11]. The unique properties of ionic liquids (ILs) have led to their extensive application in the pharmaceutical industry, extending beyond the formulation of novel liquid preparations (API-ILs) to many stages of drug discovery and delivery. Nevertheless, the majority of them concentrate on a particular use of ionic liquids in the pharmaceutical sector [12].

Ionic liquids (ILs)

Are a class of molten organic salts typically containing asymmetrical organic cations and

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inorganic or organic anions, with melting points (MPs) not higher than 100 °C. The physical and chemical features of ionic liquids can be readily modified by altering the combination of the cations and anions, together with the substitution on these ions. [13, 14]. Ionic liquids (ILs) have distinctive features that make them very appealing for various applications. Their great thermal stability and capacity to dissolve an extensive variety of metal and organic compounds as solvent media for materials synthesis provide novel preparative options. Their robust electrostatic interactions make them almost nonvolatile and hence of low flammability. Conversely, the structural diversity of their constituent molecule ions offers a wide array of solubility characteristics, unequalled by other liquid media [15]. Ionic liquids are widely used techniques in the pharmaceuticals sector, allowing the following benefits such as solubility enhancement, improved stability and drugs delivery through different routes (e.g., oral, topical, and transdermal). Eco-friendly substitutes for hazardous organic solvents, typically synthesized through neutralization, exhibit improved physio-thermal stability, enhanced solubility of poorly soluble pharmaceuticals, modification of the specific features of traditional chemical penetration enhancers (CPEs), facilitated medication delivery by breaching barriers of skin, superior antibacterial efficacy compared to parent compounds, and effective resolution of potential issues associated with solid-state APIs via conversion to the IL form [16].

The most widely investigated ILs

The predominant ionic liquids explored are imidazolium ionic liquids because to high stability under different environments, lower viscosity and ease of production [17]. However, these substances are classified as hazardous, with their toxicity dependent on the size of the alkyl substituents, hence restricting their application primarily in the pharmaceutical industry [18]. These ionic liquids have been employed as catalysts, diluents, and solubility enhancing agents. Pyridinium-containing ionic liquids are employed as solvents, in the synthesis of organic compounds, polymerization and the manufacture of medicinal compounds. Phosphonium-based ionic liquids are currently utilized as solvents and catalysts [19, 20]. They have superior thermal stability relative to imidazolium or ammonium containing salts, making them suitable for reactions at temperatures beyond 100°C. Recent work indicates that newer quaternary ammonium-based ionic liquids exhibit less toxicity. Ionic liquids (ILs) are referred to as "green" alternatives to solvents employed in the pharmaceutical sector because of their exceptionally minimal vapor pressure and good thermal stability, providing distinct advantages such as recyclability and the capacity to dissolve various organometallic and organic molecules [21].Most commonly used cations and anions are summarized in **Figure 1**.

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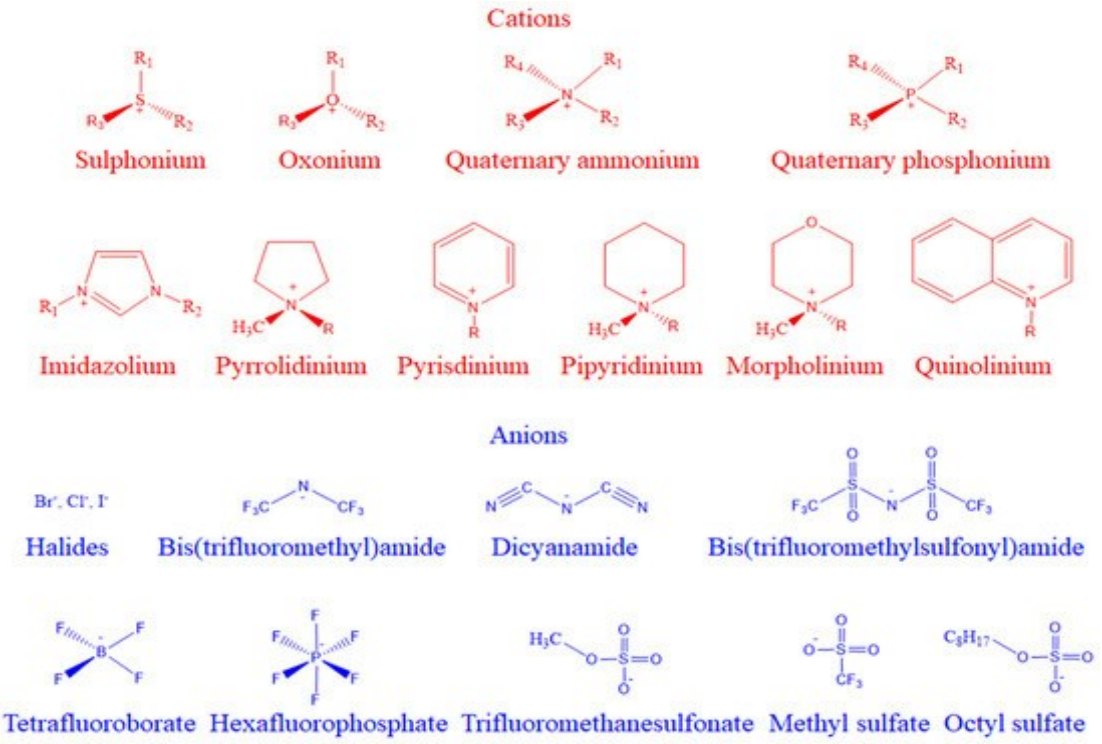

Figure 1: Most commonly used cations and anions in ionic liquids [22].

A. Generation of ILs.

Ionic liquids with varying chemical compositions and characteristics, are often classified to three categories based on their organization and date of first identification. The first generation, primarily utilized in electroplating, fundamentally combined (di-alkyl imidazolium) and alkyl pyridinium cations with anions of metal halide. Those ionic liquids, characterised by exceptional physical features like elevated thermal stability, lower melting point, and extensive fluidity, can serve as functional solvents in place of different diluents. Majority of the first category ionic liquids exhibit limited biodegradability, elevated toxicity to aquatic ecosystems, and substantial preparation expenses [23, 24]. The second generation exhibits stability in both aqueous and atmospheric environments, created from cations such as dialkylimidazolium, alkyl pyridinium, ammonium, and phosphonium, along with anions like (tetra-fluoroborate) and (hexa-fluorophosphate). These ionic liquids with distinctive chemical characteristics can be utilized to synthesize useful compounds. The alteration of anions or cations, and the substitutions, one can tailor physicochemical characteristics including melting temperature, viscosity, heat stability, hydrophilic nature, water solubility, toxicological profile and biodegradability [25, 26]. The third generation of ionic liquids utilizes certain natural resources for anions (e.g., amino acids, fatty acids) and cations (e.g., choline). Besides favorable physicochemical features, the 3rd generation of ionic liquids exhibits lower toxic effects and commendable biodegradability. The development of the 3rd generation of ionic liquids has led to a gradual increase in research about their application in biomedicine [25, 27].

The quantity of papers concerning ionic liquids is substantial and is increasing markedly;

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some indicate that ionic liquids can enhance reaction processes, increase yields, and reduce environmental contamination [28]. They are being effectively utilized in environmentally friendly diluents, delivery of medications, drug manufacturing, and other domains with significant application potential. Moreover, their significant tunability and effective solubilization present a novel approach to mitigating issues related to inadequate solubility, unstable crystalline structures, Weak biological functioning and reduced medication delivery effectiveness in the pharmaceutical sector [29, 30].

B. Structures and properties of ionic liquids

2.1 Molecular structure of ILs

The extensive utilization of ionic liquids (ILs), facilitated by the capacity to readily modify cation and anion, has led to a vast array of ILs. Although numerous classifications exist based on the type of cation—whether protonated or non-protonated, or categorized by acidic, basic or neutral characteristics—typically ionic liquids comprise 3 components: cationic part, anionic part and substituent groups. Figure 1 illustrates the chemical frameworks of common ILs. The cationic parts are predominantly organic and may be classified into (imidazole, pyridine, piperidine, amine, pyrrole, morpholine, and phosphine). Anions may be organic (such as amino acid salts and benzene sulfonates) or inorganic (including halides, tetra-fluoroborate, and hexa-fluorophosphate). The introduction of chemical groups including (cyano, hydroxyl, ether, amino, sulfonic, ester, and carboxyl, to the framework may produce functioning ionic liquids with unique characteristics [31, 32]. Generally, the selection of anionic components and substituting elements affects the acidic and basic features of ionic liquids.

2.2 Melting point of ILs

Ionic liquids often have a melting temperature less than (100 °C) and remain in a liquify state at ambient degree of temperature, rendering them advantageous for medical applications at body temperatures. The primary explanation of the reduced ionic liquids melting temperature is because ions asymmetries create a loosely structure, preventing close packing. The point of melting of ionic liquids is influenced by ionic dimension, charge dislocation, and formation of hydrogen bonds. Third-generation ionic liquids (ILs) and deep eutectic solvents (DESs) have been progressively formulated with enhanced compositions for applications in drug production and administration, owing to their liquid state at ambient temperature and favorable biocompatibility [33-35].

2.3 Solubility of ILs

Solubility is an essential feature in pharmaceuticals development, as it directly influences the in vivo bioavailability of medications. Organic and inorganic molecules have significant solubility in several ionic liquids. The principal differentiating feature between ionic liquids and conventional organic diluents is their miscibility with water. Typically, ionic liquids (ILs) possessing hydrophilic moieties, such as hydroxylic or carboxylic substituents, can establish a homogeneous mixture in aqueous solution ; conversely, ILs characterized by heavily fluorinated and charge dislocated anion, such as (Bis, tri-fluoromethanesulfonyl-imide) ([NTf2]) and [PF6], experience liquid-liquid separation

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from aqueous solution [36]. This characteristic can be related to the poor contact between ionic liquids and water [37]. Furthermore, the hydrophilic characteristics of ionic liquids decreased as the alkylic chain 'length of the cation increases [38]. The hydrophilic and hydrophobic features of ionic liquids can be modulated by varying anion, cation and substitutions. The lipophilicity of [NTf2] may be alleviated by integrating compensatory hydrophilic compounds as a cations that improve the ionic liquid's capacity to hydrogen bonds formation with water [37]. Consequently, the majority of ionic liquids have amphiphilic characteristics, acting as a conduit between water and insoluble pharmaceuticals, thereby enhancing the solubility of several active pharmacological compounds.

2.4 Polarity and solvation

Ionic liquids are primarily and successfully used as solvents in chemical reactions. Consequently, one of the most crucial characteristics in the study of solvents is polarity. Polar and nonpolar compounds may be dissolved by ionic solutions. Solvating capacity investigations reveal different interactions include interactions between solute and solvent, Coulombic, and diverse dipole interactions; hydrogen bond, van der Waals forces and electron pair donating-accepting interactions [39]. The solvent characteristics may be modified by the wise selection of cations and anions. Consequently, certain solvents may serve as substitutes or in instances requiring specialized solvation. The solvent characteristics of ionic liquids are more organized than those of molecular organic solvents [40].

2.5. Viscosity and density

Ionic liquids frequently possess greater viscosity than molecular solvents. The viscosity of ILs are often associated with the cationic dimensions, rising with the lengthening of the alkyl chain [41]. The viscosity of ionic liquids is influenced by temperature fluctuations and decreases as temperature rises [42]. The density of ionic liquids diminishes as the cationic alkyl chain 'length increases; this phenomenon is attributable to the diminished van der Waals interactions among ions, that decrease when temperature increase, hence reducing the effective packing of ions [43].

C. Toxicity and biodegradability of ionic liquids

In accordance with environmentally friendly chemical principles, toxicity and biological degradation are critical factors to assess in ionic liquids prior to their designation as ecological solvents or adjunct solvents for prospective medicinal applications [44].

3.1 toxicity

The ionic liquids toxic effects are inconsistent because of the absence of standardized assessment protocols. Certain ionic liquids have been shown to have minimal toxicity; yet, they still exhibit considerable toxicological consequences across several biological systems. Numerous research have examined the correlation between toxicity and the chemical composition of cationic and anionic parts together with the physical and chemical characteristics of ionic liquids [45].

Although a broad association has not yet been demonstrated, a number of tendencies

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have been identified. Highly water-soluble ionic liquids are deemed to have greater environmental impacts due to their simple permeation into various ecosystems. The chemical effects of ionic liquids in biological environment and their interaction with water indicate the intermediate inclusion of water in ILs may improve biological compatibility [46],[47].The body toxicity and biodegradability data that has been collected over the past several decades demonstrates that:

A) The best way to get biocompatible ionic liquids is to employ precursors that originate from biologically compatible origins.

B) The length of aliphatic side chain of the cation may influence the ionic liquid's toxic potential.

C) The toxic effect of ILs is influenced by the functional groups present in the cation.

D) The properties of anions and interposition.

E) Interactions between cation and anion—these are intermolecular forces, which also affect ionic liquids on toxicity. However, compared to the 1st and 2nd generation ILs, the 3rd generation ILs are receiving greater interest for usage in DDSs, particularly for pharmaceutical applications, because to their advantageous biocompatible and biodegradable characteristics [47].

The more frequently researched biologically compatible ionic liquids use a cholinium ion as the cation or its derivative [48]. Ionic liquids containing choline heading part act as a cation exhibit biodegradable characteristics and reduced impacts on the environment in comparison to phosphonium, imidazolium and ammonium containing ionic liquids. The biological compatibility of choline-based compounds was expected due to their naturally origin. The incorporation of choline as the cation with other active medicinal agents such as pyrazinoate, ampicillinate, nalidixic acid, phenytoin, picolinate, methotrexate, and 4-aminosalicylate, has shown the formation of biocompatible API-ionic liquids (ILs) with enhanced solubility[44].

3.2 Biodegradability/biocompatibility

Numerous ionic liquids have undergone toxicity assessments; however, investigations on biodegradation are few. Data on biodegradability are limited due to the restricted production of novel ionic liquids. Recently, researchers have concentrated on the creation of biodegradable ionic liquids. Biodegradability is in contrast with the design of biocompatible ionic liquids [49].

Short alkyl chains linked to the cation of ionic liquids exhibit minimal toxicity but are resistant to biodegradation [50]. Side chains are essential for biodegradability. Ionic liquids containing cationic groups such as imidazolium, pyridinium, phosphonium, and ammonium are biodegradable in the ecosystem and toxic to bacteria. Ionic liquids with elongated alkyl side chains (> C6) at the cationic core exhibit superior biodegradability compared to those with shorter side chains. Imidazolium-based ionic liquids are less biodegradable than those based on 1-alkyl-3-methylpyridinium due to their fundamental structure [51]. Anions, like cations, influence the biodegradability of ionic liquids. Ionic liquids with anions of elongated side chain, such as (buta-, penta-, hexa- and octanoate),

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exhibited biodegradability, but those with shorter anions, such as ethanoate and propanoate, did not. Biodegradable organic anions include acetate, sulfate, and phosphate groups. Fluorinated anions such as [PF6] and [BF4] exhibit instability and undergo hydrolysis, resulting in the release of toxic and corrosive HF into the environment [52]

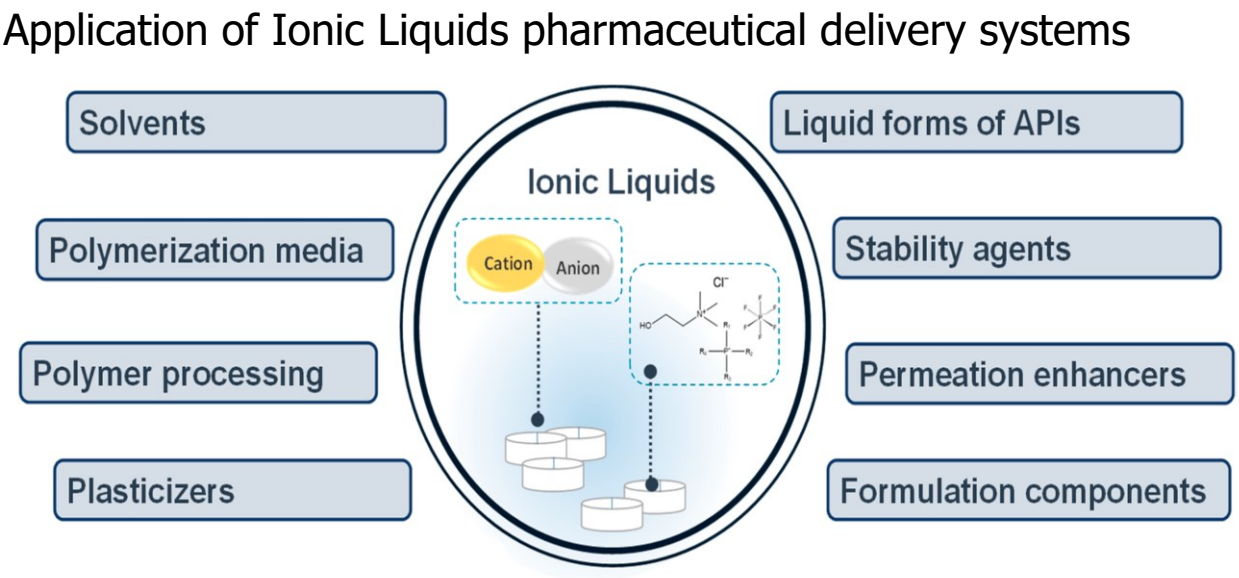

Figure 2: Applications of ILs in the pharmaceutical delivery systems design and development [53].

In recent years, the industrial application of various ionic liquids in the pharmaceutical sector has received significant global attention, targeting issues such as polymorphism, limited solubility, poor permeability, instability, and low bioavailability of crystalline drugs.

A. Solvents and Catalysts in Drug Synthesis

Green solvents primarily consist of aqueous solution, ILs, lower eutectic diluents and carbon dioxide. The widespread use of vaporized and hazardous organic diluents in pharmaceutical manufacturing is a considerable environmental impact which requires careful examination. There has been a recent increase in interest about the prospective utilization of ionic liquids as substitutes for traditional vaporized organic diluents in pharmaceutical manufacture under moderate circumstances [54, 55]. Ionic liquids (ILs) have several benefits, including remarkable stable thermally and chemically, increased solubilization, higher miscibility with water. Ions may be modified by incorporation active substituents includes hydroxylic and ether groups, to create functioning ionic liquids that exhibit minimal toxicity and facile disintegration, therefore fulfilling certain needs [56, 57].

Ionic liquids (ILs) have low vapor pressure and limited volatility compared to traditional organic solvents, making them appropriate for typical chemical interactions, purification and separation processes. Ionic liquids function as solvents in pharmaceutical manufacturing, leading to the creation of ionic liquid-organic compounds. Initially,

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volatile constituents such organic diluents in the chemical reaction, are removed utilizing distillation under vacuum, using the ionic liquids with reduced vapor pressure during purifying process. Ionic liquids (ILs) are chiefly categorized into 2 types: hydrophilic and hydrophobic ionic liquids. The utilization of organic diluents for extracting the reacted products from hydrophilic ionic liquids enhances the separating of additional components in ionic liquid and enables the reuse of the ionic liquids. Lipophilic ionic liquids are not solubilized in some organic diluents such as hexane and ether. Upon the introduction of certain organic solvents, which are immiscible with ionic liquids (ILs), two separate phases will form in the IL solution. The hydrophobic compounds, challenging to vaporize can be removed to the organic diluents, thereby enabling the separation and recovery of ionic liquids. Ionic liquids are preferred for reacted systems requiring elevated vacuum and/or extreme temperatures because of their exceptional stability, significant solubilization, recyclability, and resistance to combustion and explosion [58, 59].

The industrial synthesis of medicinal substances often employs catalysts, whose catalytic effects influence both the result of final product and organic pollutants present in it. Ionic liquids (ILs) serve not just as chemical solvents but also as specific catalysts and influences on particular processes. They extensively employed in diverse pharmaceutical production techniques, such as heterocyclic production, oxidation, alkylation and dehydration, because of their exceptional catalytic characteristics, sustainability with the environment, cost-effectiveness, rapid reaction times, recyclability, operational simplicity, and safe, mild reaction conditions [60, 61].

B. Ionic Liquids as Permeability Enhancing agents and Microemulsion Components for pharmaceutical Delivery.

API permeation enhancement agents augment the permeability of biological membranes to APIs. To enhance API skin penetration, Megwa et al. amalgamated salicylate anions with alkylammonium and quaternary ammonium cations [53]. Ionic liquids (ILs) may be developed to possess adjustable lipophilicity and hydrophilicity, enhance aqueous solubility, and augment biological membrane permeability [62]. The first surface-active ionic liquids (SAILs) surpassed conventional surfactants in their efficacy as drug transporters. Numerous investigations on IL-biological membrane interactions have sought to elucidate how ILs enhance medication distribution [63]. The rupture of the membrane depends on the hydrophobicity of the alkyl chains of IL cations and anions. Imidazolium-based hydrophobic ionic liquids destabilize membranes and facilitate active pharmaceutical ingredient transport channels via biological membranes, whereas hydrophilic ionic liquids have the opposite effect [64]. By meticulously controlling the ions, content, and therapeutic target of the IL, APIs may be delivered transdermally without compromising membrane integrity. Micelles developed by SAIL have undergone testing via intravenous, topical, and transdermal administration. ILs generated microemulsions in the preceding delivery pathway. Colloidal water-oil microemulsions stabilized by surfactants exhibit thermodynamic stability [65].ILs shown promise as viable substitutes for these components, capable of replacing oil, water, and surfactant phases, as seen in (Figure 3), hence enhancing the transport of APIs across biological membranes.

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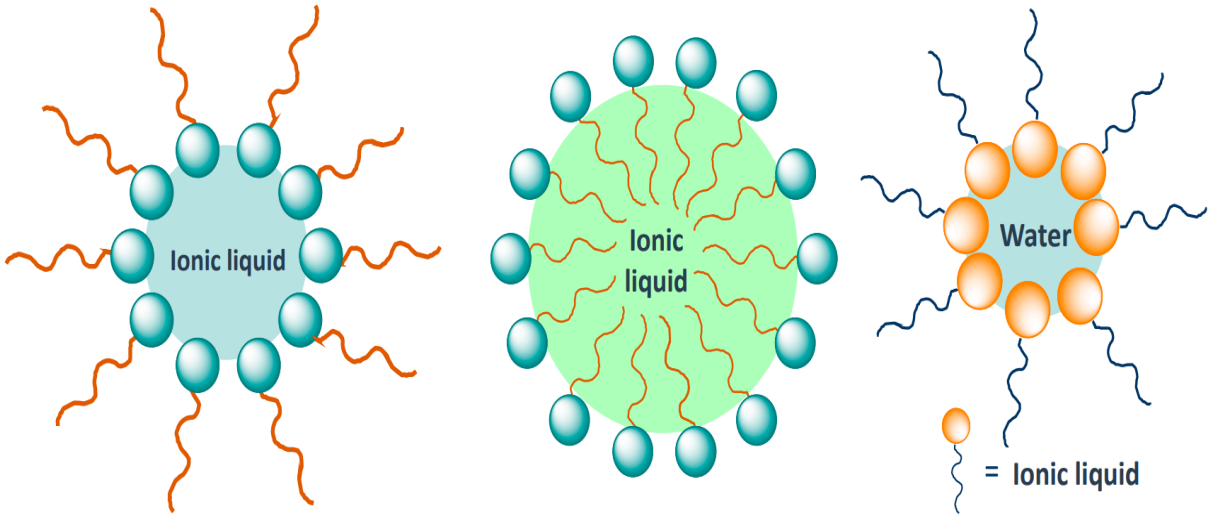

Figure 3: Schematic representation of the incorporation of ionic liquids as constituents in aqueous, oily, and surfactant phases (from left to right) inside the microemulsions [53].

C. Ionic liquids as innovative Solvents for (Bio)Polymers

The distinctive characteristics of ILs and their broad spectrum of intermolecular interactions render them appropriate for biopolymer breakdown, serving as alternatives to organic solvents. Imidazolium-based ionic liquids mostly dissolve proteins and polysaccharides such as cellulose, chitosan, and chitin. Notwithstanding promising results, biopolymers often disintegrate at rather high temperatures. To prevent degradation or incomplete dissolution, the dissolution parameters must be meticulously assessed and the ionic liquid accurately formulated [66].

The solvation processes of biopolymers differ based on their structure and ionic liquid. Intense hydrogen bonding between the hydroxyl protons of the biopolymer's carbohydrates and the chloride ions of the ionic liquid resulted in significant cellulose dissolution with 1-butyl-3-methylimidazolium chloride ([C4C1im]Cl) [67]. The extent of acetylation, crystallinity, molecular weight, and the kind of IL anion influence chitin solubility in ILs. Chitin rapidly dissolves when characterized by low acetylation, crystallinity, and molecular weight [68]. subsequent studies with chitosan revealed that the hydrogen bond-accepting capacity of ionic liquids roughly linearly enhanced the solubility of the biopolymer. Chitosan readily dissolves in the presence of imidazolium-based anions, perhaps due to their disruption of its inherent hydrogen bonds. The elevated solubility of polymers in ionic liquids is attributed to favorable molecular interactions, such as hydrogen bonding, n-π interactions, π-π interactions, electrostatic forces, and dispersive forces [69].

D. API-ILs as Liquid Forms of APIs

The development of innovative liquid formulations of active pharmaceutical ingredients

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(APIs) combined with ions in ionic liquids (API-ILs) is a promising strategy to tackle challenges related to solubility, bioavailability, and polymorphism. Their ionic and liquid state enables the surmounting of the melting enthalpy barrier, hence improving solubility and bioavailability. The extensive variety of ionic liquid cation-anion pairings promotes the creation of innovative medicines as active medicinal ingredients in ionic liquids, possessing unique physicochemical and biological properties, and possibly demonstrating dual pharmacological effects. Ionic liquids may also be manufactured using oligomeric ions or by the prodrug technique applied to one of the ions of an active medicinal component ionic liquid [70].

The API-ILs were first identified by Rogers and colleagues in 2007, including the formation of ranitidine docusate ([Ran][Doc]), which persists in a liquid state at ambient temperature. Ranitidine, a histamine H2-receptor antagonist, is recognized for its polymorphic metamorphosis that influences its pharmacological efficacy. Upon dissolution, the combination of active pharmaceutical ingredients with simple and inert counterions or other active compounds will dissociate in physiological fluids, with the cationic and anionic components following their respective pharmacokinetic and metabolic pathways [71].

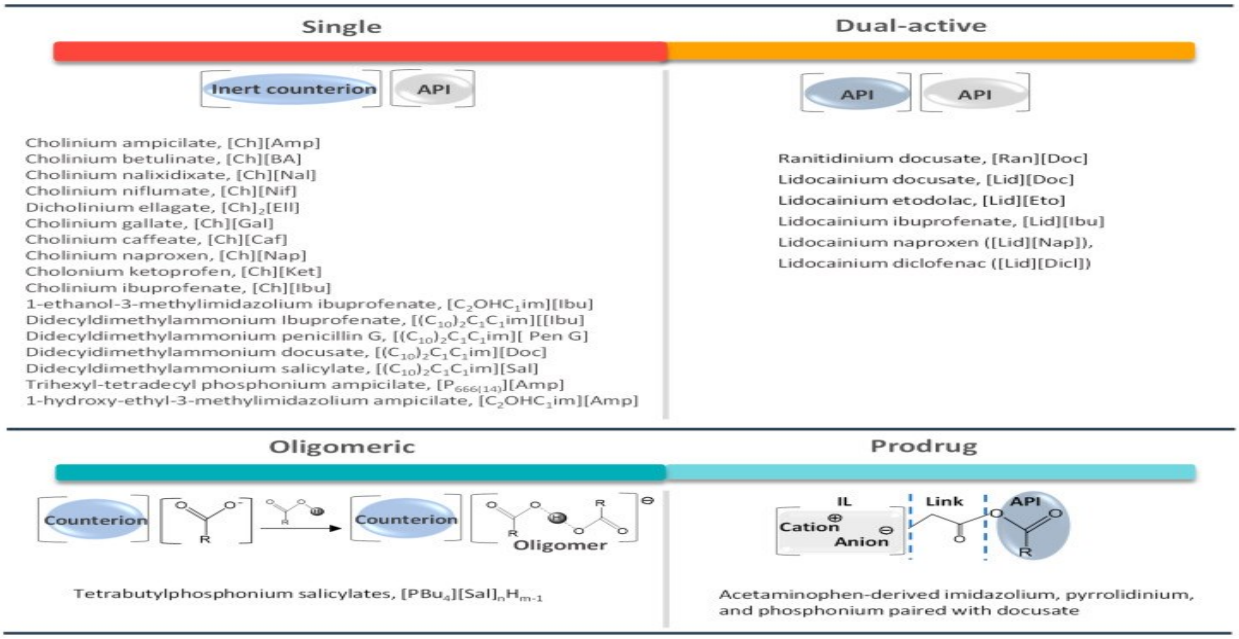

Figure 4: Graphical examples of API-ILs pharmacological formulations [70].

4.1 API-ILs with Single-Activity

A combination of crystalline active pharmaceutical ingredients with a suitable ionic liquid-generating counterion represents a viable method for transforming traditional medications into ionic liquid salts. These salts typically liquefy at temperatures below their normal range and consist of one pharmacologically active pharmaceutical ingredient (API) and an ionic liquid-generating counterion. Selecting an appropriate IL-forming counterion facilitates alterations in the biological and physicochemical characteristics of the associated parent API, such as solubility, dissolution, permeability, and

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bioavailability. API- ionic liquids may alleviate the challenges of polymorphism and crystallinity associated with poor water solubility, limited therapeutic efficacy, and thermal instability of pharmaceuticals. Number of API-ionic liquids exhibiting diverse pharmacological properties has been documented, wherein solid APIs such as lidocaine, sulfasalazine, indomethacin, procaine, ibuprofen, sulfacetamide, aspirin, salicylic acid, methotrexate, piperacillin, and penicillin are transformed into the IL form through the integration with IL-forming cations, including cholinium, amino acid esters, ammonium, or phosphonium [14, 16].

4.2 API-ILs with Dual-Activity

The dual-active API-IL technique is significant for the enhancement of efficient drug delivery systems because to its dual-functional properties and potential synergistic effects that surpass those of the original APIs. Any combination of two or more APIs can be done if both medicines generate stable ions. Dual-active API-ILs include an active cation and an active anion, both demonstrating unique pharmacological characteristics. Counterions affect the crystallinity of drug molecules and preserve their own biomedical activity, leading to multiple functional capacities or imparting new therapeutic qualities unattainable with separate active pharmaceutical components or traditional salt forms. Multiple notable examples of dual-active API-ILs have been recorded to enhance their physicochemical and biological properties. A dual-functional API-IL was synthesized by amalgamating acetylsalicylate with its principal metabolite, salicylic acid, resulting in enhanced solubility of acetylsalicylate while reducing gastrointestinal discomfort [72].

4.3 Oligomeric API- ionic liquids

The non-stoichiometric method for transforming crystalline medicines into liquid forms entails the synthesis of oligomeric active pharmaceutical ingredient ionic liquids (API-ILs). In addition to neutral, non-ionized medicinal molecules, oligomeric API- ionic liquids often include hydrogen-bonded cations and anions. These molecules interchange delocalized protons between the protonated cation and the deprotonated anion, avoiding crystal formation. The API- ionic liquids may be adjusted by altering the stoichiometric proportion and/or the level complexity of the ions by the addition of free acids or bases that correspond to the conjugate bases or acids in the salt formulations. The term 'ionic liquid' for this liquid salt formulation is challenging until non-covalently bonded entities function as a singular ion, since all components in API- ionic liquids are partly to completely ionized liquids. In 2010, Rogers' teams first introduced the concept by synthesizing 'oligomeric' tetrabutylphosphonium salicylates. Lidocainium salicylate, a viscous liquid, serves as an example of an oligomeric API-IL, produced by the incorporation of an excess of salicylic acid or lidocaine into lidocainium salicylate [73].

4.4 Prodrug API-ILs

The prodrug strategy is an effective method for augmenting the therapeutic effectiveness of active pharmacological components and enabling their absorption via various modes of administration. A prodrug is an inert pharmacological substance that is transformed into an active agent by chemically and/or enzymatically process inside

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the human body [70]. Prodrugs are often used to improve solubility, target specificity, diminish rapid drug metabolism and cellular toxicity, and provide regulated drug delivery. Prodrugs may exist in different polymorphism forms, experiencing identical polymorphic challenges as any solid active pharmaceutical ingredient (API). Integrating the benefits of API-IL with a prodrug strategy may improve drug efficacy while reducing the adverse effects linked to solid formulations. In order to manufacture prodrug API- ionic liquids, neutral APIs are modified to include hydrolysable functional groups, which are susceptible to biochemical cleavage. These functional groups are then combined with ionic liquid-generating counterions to produce new ILs. The choice of an appropriate IL-producing counterion would provide a prodrug API-IL with the required physicochemical and biological characteristics. A compilation of API-IL prodrugs, created by amalgamating acetaminophen with imidazolium, phosphonium, pyridinium, and pyrrolidinium prodrugs with docusate, demonstrated the absence of a melting point, decreased water solubility, and sustained release characteristics in biological fluids [74].

Synthesis and Characterization of API-ILs

A. Synthesis of API- ionic liquids

The transformation of active pharmaceutical ingredients into liquid forms is a potential technique for enhancing their effectiveness and delivery. This may be optimized by choosing physiologically active ions and suitable IL-forming counterions characterized by significant asymmetry and diffuse charge, together with a small number of possible hydrogen bonds among the molecules [75]. The transformation of active pharmaceutical ingredients into liquid forms is a potential technique for enhancing their effectiveness and delivery. This may be optimized by choosing physiologically active ions and suitable IL-forming counterions characterized by significant asymmetry and diffuse charge, together with a small number of possible hydrogen bonds among the molecules [16]. Generally, the accessible salt forms of cations and anions are agitated at ambient or designated temperatures to provide the desired ionic liquids by eliminating inorganic salts. Alternative metathesis methodologies have been employed to synthesize ionic liquids; for example, cationic salts were converted into hydroxide forms in methanol through ion exchange, subsequently neutralizing the basic solution by incorporating acidic API solutions. The use of significant amounts of organic solvents in the production of ionic liquids led to the formation of unwanted pollutants, potentially detrimental to human health and the environment. Mechanochemical processing, a sustainable option for synthesizing API- ionic liquids, has gained considerable interest because to its dependence on a grinding approach and little use of organic solvents, or the complete absence of solvents[76]. Figure (5) below illustrates the schematic schematics of the standard approach and the mechanochemical process.

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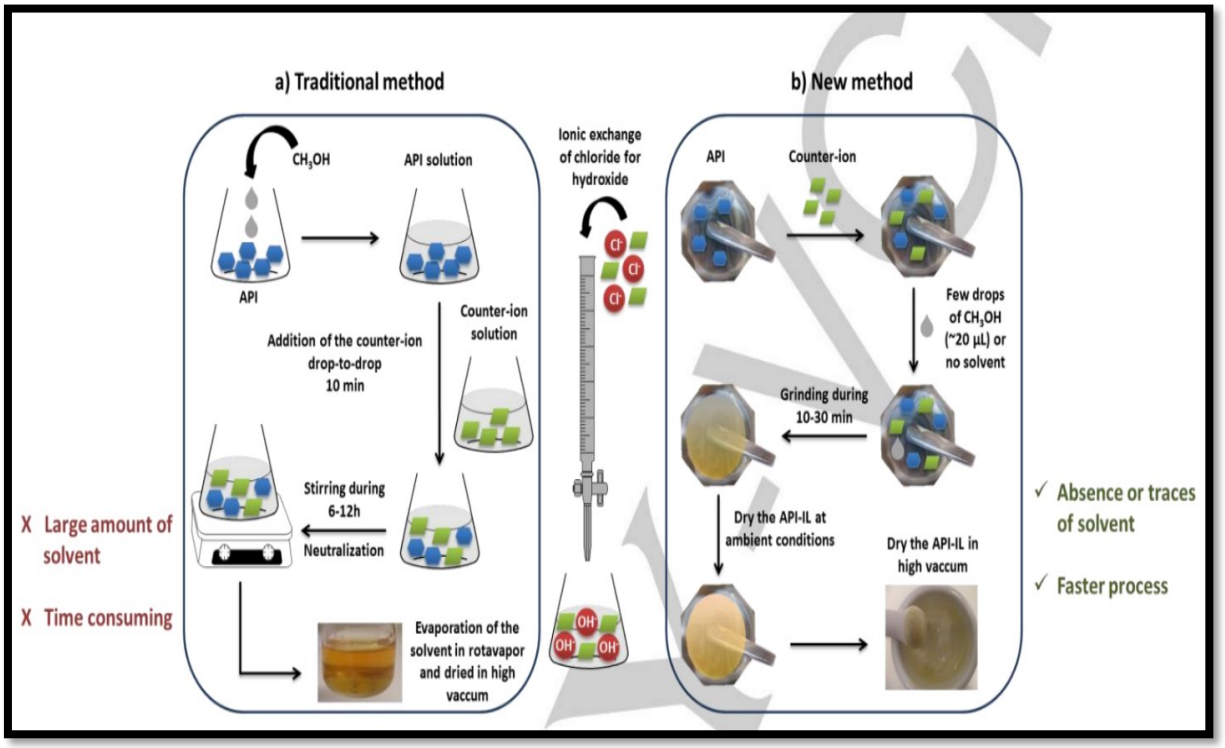

Figure 5: Schematic representations of a) the conventional approach and b) the mechanochemical process for the synthesis of API-IL [46].

B. Characterization of API-ionic liquids

Designing API- ionic liquids for pharmaceutical applications requires comprehensive evaluation to guarantee suitable physio-thermal characteristics and improved therapeutic efficacy, while minimizing adverse effects. The formation of API- ionic liquids is typically confirmed by NMR spectroscopy via qualitative assessment of proton transfer, wherein the chemical shifts of 1H, 13C, and 15N are carefully investigated to determine the extent of proton transfer from an acidic API to a basic IL-forming counterion, signifying ionization or the formation of hydrogen-bonded complexes[77].Infrared spectroscopy is used to qualitatively evaluate proton transfer, total ionization, and contaminants in API-ionic liquid entities. X-ray diffraction of single crystals or powders is used to evaluate the crystallinity of API- ionic liquids and the uniform distribution of APIs inside the ionic matrix of the IL. Halide analyses identify inorganic contaminants by metathesis processes. Thermoanalytical techniques, such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), and derivative thermal gravimetric analysis, are employed to evaluate decomposition temperatures, melting points, and phase transitions, including glass transition temperature and solid–solid transitions [78, 79].

C. Physico-Thermal and Solubility Characteristics of API-ILs

The transformation of neutral APIs into IL forms may effectively address the deficiencies in physico-thermal characteristics and solubility issues of APIs. The physicochemical and biological characteristics of API-ionic liquids primarily rely on the careful selection of IL-forming cations. Utilizing APIs in an IL format is recommended to improve their physicochemical and biological characteristics. A wide range of significant investigations

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have been undertaken to illustrate the influence of counterions on several pharmacological characteristics of API-ionic liquids, including solubility, physicochemical properties, stability, biological activity, and bioavailability [80].

3.1 Physico-Thermal Properties

The thermal characteristics, including the glass transition temperature (Tg) and melting point (Tm), of crystalline solid active pharmaceutical ingredients (APIs) are markedly reduced when transformed into API-ionic liquids (API-ILs) compared to their parent compounds. Ibuprofen, ketoprofen, and naproxen containing cholinium are in a liquid state at ambient temperature (Tg between −90 and −70°C) [81]. Ampicillin- and penicillin-derived ionic liquids with cholinium, ammonium, pyridinium, phosphonium, and imidazolium cations and active pharmaceutical ingredients as anions, exhibited markedly reduced melting temperatures compared to their respective precursor active pharmaceutical ingredients or traditional API salts [82].

3.2 Improved Solubility

The principal anticipated advantage of the API-IL method is the improvement in water solubility and bioavailability compared to the pure APIs, dependent on the characteristics of the IL-generating counterions. For example, the poorly soluble pharmaceuticals acyclovir (ACV) and methotrexate (MTX) have been converted into ionic liquid (IL) forms using various IL-forming counterions. In comparison to neutral MTX, MTX including cholinium and ammonium exhibited a solubility in water and physiological fluid models that was at least 5000 times greater [83]. The combination of acyclovir with IL-forming counterions such as ammonium, phosphonium, cholinium, and docusate yielded comparable variations in solubility in water and simulated physiological fluids(up to 400 times the solubility of the parent medication) [84]. API-ILs including cholinium with nalidixic acid, 4-amino-salicylic acid, picolinic acid, pyrazinoic acid, naproxen, ketoprofen, ibuprofen, and betulinic acid have markedly enhanced water solubility relative to the neutral APIs and their sodium analogs [85].

Biomedical Activity

Despite extensive documentation of the synthesis and physicochemical characteristics of API-ionic liquids, their biological efficacy has so far been evaluated mainly via in vitro models. Numerous API-ionic liquids demonstrated enhanced water solubility relative to the parent medicines, suggesting the potential for increased in vivo bioavailability. Moreover, API-ILs resolved the polymorphism issues associated with several traditional solid APIs, while their amorphous form provided enhanced solubility and decreased polymorphism. The effect of transforming the APIs into ILs on biological activity remains unclear. An optimal API-IL must possess liquidity and significant physicochemical features to prevent polymorph formation while maintaining the biological activity of the parent API [70].

A. Increased Biological Activity

A number of studies have been performed to examine the biological activity of the various synthesized API-ionic liquids. The biological action of API-ILs is dependent upon

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the ion structure. The antibacterial efficacy of the API-ILs was significantly affected by the IL-forming cations when combined with antibacterial agents (benzalkonium or 3-hydroxy-1-octyloxymethylpyridinium) and an artificial sweetener (acesulfame or saccharinate), thereby notably influencing the antibacterial activity of the API-ionic liquids. Comparing dual-active API-ILs of ibuprofenate-based ranitidinium and diphenhydraminium to their precursors, they demonstrated comparable solubility and enhanced antibacterial efficacy against Candida [86, 87].

B. Increased Permeability

Numerous topical medications have been identified as incapable of penetrating the dermal barrier and crystallizing before application [88]. The bioavailability and therapeutic effectiveness of topical and transdermal applications are intricately connected to the drug's permeation into the skin. As a result, significant research is now focused on increasing drug delivery across the skin obstacle via a permeation enhancer. The skin-enhancing properties of API-ILs provide them an appropriate medium for transdermal distribution, while salt forms of pharmaceuticals encounter challenges in permeating the skin. Numerous researches have been undertaken to assess the involvement of ILs in permeation. API-ILs' in vitro permeability was often assessed utilizing synthetic model membranes or animal dermis. The Rogers group created a series of API-ILs to investigate the permeability of a model membrane to various combinations of acidic and basic APIs, demonstrating their enhanced penetration compared to that of the free APIs. PEGylated salicylate ionic liquids demonstrated a 2.5-fold increase in transdermal transport relative to PEG-free cations, whereas AAE-containing salicylate ionic liquids improved skin permeability compared to the parent medication [89, 90]

Conclusion

The present review highlights the significance and benefits of ILs as solvents and/or agents in pharmaceuticals. The significant solubility of several weakly water-soluble medications in ionic liquids allows innovative delivery methods unattainable with traditional solvents, highlighting the significance and benefits of API-ionic liquids as viable substitutes for solid crystalline APIs in the pharmaceutical industry. API-ionic liquids have successfully resolved the solubility and crystalline polymorphism issues associated with solid APIs, which were the main obstacles to the creation of viable drug delivery systems. The ability to systematically design API-ionic liquids also makes it possible to modify novel drug forms with the appropriate biological and physicochemical characteristics. Progress in this field has shown that API-ILs can enhance medication solubility in aqueous solutions and simulated biological fluids, in addition to facilitating drug absorption over physiological skin barriers. The published findings are very promising, characterized by specific or dual pharmacological activity, as well as improved bioavailability and effectiveness, which are the defining features of the IL-strategy. The presented results are very promising, distinguished by specific or dual pharmacological action, with enhanced bioavailability and efficacy, which are the hallmark attributes of the IL-strategy. The lack of research on the in vivo bioavailability of API-ILs, however,

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emphasizes the need of pharmacokinetic and pharmacodynamic studies to elucidate the mechanisms controlling their distribution, metabolism, excretion, and absorption. Moreover, experimental and foundational methodologies are crucial for the synthesis of new API-ILs and for a more profound understanding of the physicochemical and biological characteristics of these systems. The current understanding of ILs provides an essential basis for forthcoming research and the creation of API-ILs for pharmaceutical applications.

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