IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# Unlocking The Potential Of Ionic Liquids In Advanced Drug Delivery Systems

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***Abstract:*** Controlled and targeted delivery of active pharmaceutical ingredients (APIs) has emerged as a promising therapeutic strategy. However, challenges such as low water solubility of most APIs and the need for efficient drug delivery systems persist. Traditional organic solvents used in drug formulation pose health and environmental concerns. Ionic liquids (ILs) have garnered attention as potential alternatives due to their unique properties. This review paper explores the diverse applications of ILs in drug delivery, ranging from solubilizing APIs and enhancing their bioavailability to serving as novel components in biopolymer-based delivery systems.We discuss the potential of ILs as solvents and co-solvents for low water-soluble APIs, showcasing significant improvements in solubility and stability. Furthermore, ILs enable the conversion of solid APIs into liquid forms (API-ILs), addressing challenges related to polymorphism and bioavailability. Their role as effective permeation enhancers and microemulsion components for drug delivery is also highlighted, along with their ability to dissolve biopolymers like cellulose and chitosan. ILs open avenues for customized drug delivery systems, allowing for controlled release profiles and responsive behaviors based on environmental stimuli.Through an in-depth analysis of recent research and advancements, this paper underscores the vast potential of ILs in revolutionizing drug delivery systems, offering safer, more efficient, and sustainable alternatives to traditional approaches.

***Index Terms*** - Controlled drug delivery, Ionic liquids (ILs), Liquid forms of APIs (API-ILs), Active pharmaceutical ingredients (APIs), Biopolymers

## I. INTRODUCTION

Controlled or targeted distribution of active pharmaceutical ingredients (APIs) is an interesting therapeutic strategy [1]. Developing drug delivery systems might be challenging due to the low water solubility of most APIs in the market and development that can provide high efficiency and bioavailability is a difficult task [2]. Drug delivery systems are formulations or devices that introduce an API into the body, enhancing efficacy and safety by managing the rate, time, and location of release [3]. Drug administration technologies have evolved continuously since the 1950s [4]. Recent research on nanoparticles, including micelles, liposomes, dendrimers, nanocapsules, and nanospheres, has provided opportunities for developing effective medicines and reducing side effects.The FDA has approved several successful nanoparticle-based systems, including Doxil (liposomal doxorubicin) and AmBisome (liposomal amphotericin B) [5]. Volatile organic solvents are commonly used in medication formulation and administration to enhance the solubility of APIs and investigate their effects on biological targets. However, using huge volumes of organic solvents raises significant health and environmental problems [6]. Choosing the appropriate solvents or co-solvents for the planned route of administration is crucial [7]. Water is the ideal choice, while excipients, such as Surfactants, lipids, and

polymers may enhance the solubility and stability of target APIs. Excipients are inert medicinal substances that are included in product formulations. Excipients, such as pH adjusters, preservatives, or carriers, have specific applications that affect the dosage form's efficacy. The final dosage form's qualities are mostly determined by the excipients used, their concentration, and the interaction with the API. Selecting a solvent/mixture that serves as a vehicle and improves medication solubility, permeability, stability, and bioavailability while being biocompatible is an intriguing option[8].

Despite substantial research on "greener" solvents for drug solubilization and delivery, their approval and implementation remain inconsistent [9]. In 1914, Paul Walden suggested the possibility of liquid salts at room temperature, which are now known as ionic liquids (ILs). ILs are molten salts made up of a large organic cation and an organic/inorganic anion that show promise as alternate solvents for medication solubilization and delivery. The enormous size of their ions cause charge dispersion, making it difficult to construct a regular crystalline structure [10]. If properly built, ILs exhibit a number of distinguishing characteristics, including excellent thermal and chemical stability and strong solvation capacity for a wide range of chemicals, among which APIs and (bio)polymers can be identified [11]. This adaptability also reveals significant potential in a variety of medication delivery applications. The proper selection of anions and cations enables the synthesis of ILs with improved solvation ability for APIs or of ILs with specialized biological activity [12]. In the first approach, ILs were utilized as API solvents and co-solvents, resulting in paclitaxel increases of up to 11 106-fold . On the other hand, ILs have been shown to exhibit promising antioxidant,anti-tumoral [12], and antibacterial properties [13]. Furthermore, the presence of APIs as cations and/or anions in the IL composition allows for the conversion of a solid API into a liquid form (API-ILs). This method addresses polymorphism problems, increases solubility, and, presumably, improves therapeutic efficacy [14].API-ILs' design flexibility allows for improved penetration into biological membranes [15]. This applies not only to the combination of APIs and permeation enhancers, but also to the usage of ILs with surfactant activity as novel excipients in formulations [16]. Given this possibility, ILs have been investigated as distinct formulation components of microemulsions in order to find more effective delivery mechanisms. To improve medication delivery, innovative systems containing polymers and biopolymers have been developed by employing ILs as mediums for polymerization operations, polymer processing, and in situ functionalization [17]. Because of the diversity of IL applications, it is possible to create IL and polymer-based nanosystems [18], as well as stimuli-responsive API delivery [19].
Because of their favorable qualities, ILs have been widely researched as various components in drug delivery systems, as seen in Figure 1, in an attempt to uncover novel and more effective alternatives[20].

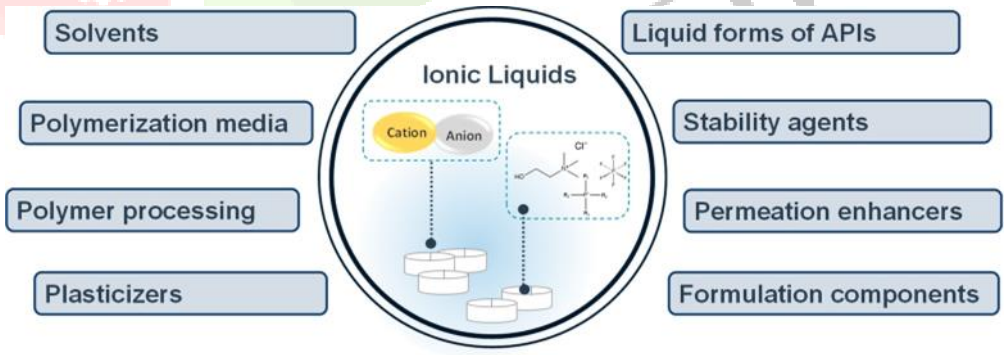


**Figure 1** shows the use of ionic liquids (ILs) in medication delivery system design and development.

## II. IONIC LIQUIDS' USE IN DRUG DELIVERY

### 2.1.ILs as Novel Solvents of APIs

APIs with low water solubility are routinely solubilized in pharmaceutical formulations by using organic solvents as solvents or co-solvents (for example, ethanol or dimethyl sulfoxide) [34]. In this regard, in addition to their usage as surfactants, which may improve API solubilization, ILs have been studied as prospective solvents, co-solvents, and hydrotropes for increasing API aqueous solubility [21]. Jaitely et al. were the first to introduce ILs as an alternate solvent for this application. [22], in 2008, when utilizing imidazolium-based ILs to solubilize potassium penicillin V, dexamethasone, dehydroepiandrosterone, and progesterone. Following this, other investigations found that employing ILs increased the solubility of antifungal [23], analgesic , non-

steroidal anti-inflammatory [24], and anti-cancer [25] medications by several orders of magnitude when compared to their water solubility. The right selection of IL anions and cations has been shown to influence the solubilization process of low water-soluble APIs as well as the IL solvation mechanism/ability. An suitable hydrophilic-lipophilic balance between IL cations and anions allows for the development of both drug delivery systems and solubilization agents to improve the aqueous solubility of APIs from various pharmacological classes [26]. These APIs are solubilized by cosolvency, hydrotropy, and micellization mechanisms, which allow for solubility increases. ILs can increase the solubility of medications such amphotericin B, itraconazole, paclitaxel, or etodolac, which are weakly soluble in water, by up to 5.6 x 106-fold (see Table 1). While imidazolium-based ILs have been extensively studied for this purpose, the use of cholinium-based ILs highlights the need for safer alternatives. In addition to their application to improve solubility, the stability of these APIs in IL media, as well as their bioavailability in IL-based formulations, require more investigation[27].

**2.2. Liquid Forms of APIs**

Low water-soluble APIs raise bioavailability problems, which have a negative impact on final therapeutic efficacy; as a result, these APIs typically fail in the later phases of development or have side effects associated with their deposition [28]. Solid forms of APIs, on the other hand, can have varied bioavailability profiles due to the presence of distinct polymorphs, which may be problematic if the inappropriate polymorph, i.e., more hazardous, is administered [29]. As a result, developing liquid APIs can be a useful method for avoiding such difficulties. Furthermore, unlike solid APIs, liquids can overcome the energy barrier associated with the enthalpy of fusion, resulting in increased solubility in water and a greater therapeutic response [30]. ILs have demonstrated encouraging results in improving physical stability while boosting medication solubility and penetration. The appropriate selection of IL components also enables the use of APIs as anions or cations, resulting in liquid medication forms (API-ILs). API-ILs were initially introduced in 2007 by Rogers et al. [31], who synthesized ranitidinium docusate ([Ran][Doc]), a liquid at room temperature that improves API absorption. This discovery enabled the development of new liquid forms of APIs with specialized physicochemical and biological features, as well as liquids with dual pharmacological action [32]. These novel ILs can also be obtained by applying the prodrug strategy to one of the API-IL ions, i.e., a biologically inert compound that undergoes enzymatic conversion into the active species of the API-IL, or by using oligomeric ions by simply changing the stoichiometry or introducing the free acid/base of the conjugate base/acid within the salt formulation [33].

API-ILs from several pharmacological classes have been shown to exhibit anesthetic , anti-inflammatory [34], analgesic [50,54], and antibacterial properties [35]. When examining API-ILs with twofold therapeutic action, the two APIs have different melting temperatures, solubilities, bioavailability profiles, and stabilities than the predecessors. Table 21summarizes some of the dual API-ILs reported so far, along with their distinct pharmacological actions[36].

| API-IL | Cation Activity | Anion Activity | Application |
|---|---|---|---|
| Ranitidinium docusate | Decreases acid stomach production | Prevents drug ,Laxative | polymorphism |
| Procainium salicylate | Local anesthetic | Antimicrobial | Enhanced solubility |
| Tramadolium salicylate | Analgesic | Antimicrobial | Enhanced solubility |
| Lidocainium etodolac | Anesthetic | Anti-inflammatory | Enhanced skin permeation (invitro testing ) |
| Lidocainium ibuprofenate | Anesthetic | Anti-inflammatory | Supported ILs Fast release profile in GI environment |
| Bromohexinium ibuprofenate | Mucolytic | Anti-inflammatory | Enhanced membrane permeasion |

Table no.1

The combination of lidocaine and etodolac, both very low-water soluble medicines, and their conversion into the form of lidocainium etodolac leads in better water solubility when compared to the individualistic APIs, with an increase of more than 90-fold for etodolac and 2-fold for lidocaine [37]. Such behavior led to the creation of the Etoreat patch by IL Pharma Inc. (MEDRx, Kagawa, Japan) for the treatment of ankle sprains and low back pain . This is one of the few API-IL systems to have entered clinical testing. However, further development of the patch has been halted due to a lack of statistically meaningful outcomes between Etoreat and placebo treatment[38].

**2.3. ILs are effective permeation enhancers and microemulsion components for drug delivery.**

Given the versatility of the API-IL approach's design, it is possible to improve API penetration through biological membranes by combining APIs with permeation enhancers [39]. Megwa et al. [40] were the first to examine this technique, which involved combining the salicylate anion with alkylammonium and quaternary ammonium cations to increase API skin permeability. Following this pioneering work, other investigations attempted to improve salicylate penetration across membranes, resulting in novel salicylate-based ILs and ILs including poly(ethylene glycol) derivatives [41]. For this goal, more biocompatible cations, such as amino acids, were examined [42].

In addition to API-IL formulations, ILs can be engineered to have variable lipophilicity/hydrophilicity characteristics, increasing solubility in aqueous media while also improving penetration through biological membranes . These ILs (also known as surface-active ionic liquids (SAILs)) have been examined as novel drug transporters, and their performance has been compared to traditional surfactants, with the former demonstrating greater capabilities [43]. Several research on the interaction of IL and biological membranes have been undertaken in an attempt to explain the processes by which these ILs permit improved drug transport . Using neutron scattering, it was demonstrated that ILs can cause a decrease in bilayer thickness, whilst the buildup of ILs' cations between the polar heads and hydrocarbon tails of lipids happens concurrently with changes in lipidic bilayer composition [44]. Later, fluorescence imaging, light and X-ray scattering techniques were used to demonstrate the insertion of amphiphilic ILs into the lipid bilayer [45]. The hydrophobicity of the IL cation and anion's alkyl chain determines the possibility of membrane breakdown. Following these discoveries, ILs have been studied for their ability to fluidize cell membranes; imidazolium-based ILs with hydrophobic characteristics destabilize membranes and create channels through biological membranes for API transportation, whereas hydrophilic ILs behave in the opposite manner [46].

As a result, by carefully adjusting the IL's ions, composition, and therapeutic target, it is possible to improve the transdermal distribution of various APIs while maintaining membrane integrity (in accordance with the IL's hydrophobic/hydrophilic balance) [47]. Overall, the use of SAILs to form micelles has been studied for intravenous, topical, and transdermal administration [48]. In the previous distribution route, ILs were primarily used to develop microemulsions. Microemulsions are thermodynamically stable colloidal mixes of two immiscible liquids (water and oil) stabilized with surfactant molecules[49].
. ILs have proven to be potential replacements to these components, replacing oil, water, and surfactant phases (Figure 2) and boosting API distribution across biological membranes [50].

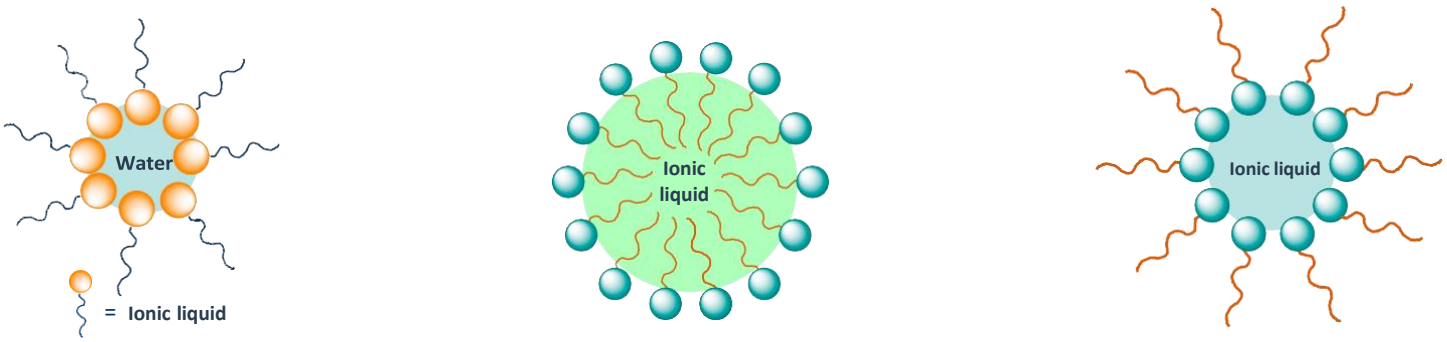


Figure 2 . depicts the utilization of ILs as components in the water, oil, and surfactant phases of microemulsions (left to right).

### 2.4. ILs: A New Solvent for Biopolymers

Because of their unique characteristics and the vast range of intermolecular interactions they provide, ILs have proven to be suitable solvents for biopolymer dissolution, allowing them to replace organic solvents in this field. In this context, the dissolving of proteins [51], and more extensively polysaccharides (e.g., cellulose , chitosan , chitin , or guar gum [52]), has been reported utilizing mainly imidazolium-based ILs. Despite the positive findings obtained, biopolymer dissolving is often carried out at moderately high temperatures; hence, to avoid biopolymer disintegration or partial dissolution, the dissolution conditions should be carefully examined and the IL adequately constructed for this purpose. The solvation process for biopolymers discussed varies depending on the structure of the biopolymer and the IL. Using 1-butyl-3-methylimidazolium chloride ([C4C1im]Cl), the remarkable cellulose dissolving ability was due to strong hydrogen bonding between the biopolymer's carbohydrate hydroxyl protons and the IL chloride ions [53]. On the other hand, chitin dissolving in ILs appears to be regulated by the degree of acetylation, crystallinity, and molecular weight of chitin, as well as the type of the IL anion [54]. Chitin is easily dissolved when it has low levels of acetylation, crystallinity, and molecular weight. The usage of ILs also has a significant advantage in that it allows for the dissolution and extraction of the desired biopolymer from raw biomass without the need for further purification. The extraction of chitin from crab shells is an excellent illustration of this possibility [55]. One particular IL, 1-ethyl-3-methyl-imidazolium acetate ([C2C1im][CH3CO2]), has been used to completely dissolve fresh shrimp shells. The use of this alternate solvent results in the recovery of high purity (>80%) and high molecular weight chitin powder [56]. Using this method, chitin-based systems, such as fibers, can be spun directly from the extract solution. The favorable results of this technique led to the establishment of the first facility (Mari Signum) that uses an IL-based approach for chitin extraction on a large scale, with the goal of producing sufficient supplies of high-quality chitin and becoming a competitive alternative in this market [57].

Further chitosan investigations revealed an essentially linear rise in biopolymer solubility as the IL's hydrogen bond-accepting capacity increased . Imidazolium-based anions appear to have a significant role in the dissolving of chitosan, presumably due to the breakdown of native hydrogen bonds. Overall, the accumulated fundamental knowledge has permitted the use of ILs in the simultaneous dissolution of many biopolymers and polymers, resulting in new approaches for materials and delivery systems. One example is the ability to prepare micro and nanoparticles through suspension polymerization reactions, where the average particle size can be tuned by adjusting the concentration and alkyl chain length of ILs [58], or to obtain homogeneous biopolymer blends in a faster and easier process . In addition to solubilizing biopolymers, ILs can also be utilized as solvents to solubilize synthetic polymers used in medication delivery. However, phase separation between ILs and some polymers, gel formation, and slow dissolution kinetics have largely hampered IL utilization in the polymer solubilization process. In fact, various investigations have been conducted on liquid-liquid phase diagrams (phase separation) for polymer-IL binary mixtures [59]. Noda et al. discuss the insoluble nature of poly(methyl methacrylate) (PMMA), polyacrylonitrile (PAN), and poly(ethylene glycol) (PEG) in 1-butylpyridinium chloride ([C4py]Cl). However, several ILs have demonstrated the ability to solubilize polyether, polystyrene, and polyvinyl-based polymers under various circumstances. Despite the fact that there are multiple IL cation-anion combinations, research on the solubility of these polymers has focused primarily on imidazolium-based IL. Imidazolium-based cations, such as [C2-8C1im]+ and [CH=C2C1im]+, have been studied in combination with various anions, namely chloride, acetate, and several fluoride-based anions, such as tetrafluoroborate, hexafluorophosphate, bis(trifluoromethanesulfonyl)imide, and trifluoromethanesulfonate [60]. In general, it appears that ILs have a stronger propensity to solubilize hydrophilic polymers than hydrophobic ones. Polymer hydrophilic domains have a stronger affinity for IL polar groups, facilitating solubilization, as demonstrated by Chen et al. [61] for polyvinyl alcohol (PVA). In contrast, hydrophobic polymers are more likely to engage with the non-polar domains of ILs (alkyl chains), causing the polymer to aggregate [62].

The investigation of ILs on biopolymer dissolution and processing revealed a link between cellulose solubility and ILs' ability to accept hydrogen bonds [63]. ILs' anions with a better ability to take protons, such as chloride and acetate,based systems allow for greater cellulose solubility. Following this idea, Ueno et al. [64] investigated IL-solvent factors such as Lewis basicity, solubility, and hydrophobicity to determine the best IL for synthetic polymer solubilization, such as poly(methyl methacrylate) (PMMA). The authors confirmed that in order to increase the solubility of polymers such as PMMA, the non-polar nature of both the IL cation and anion must be considered[65].In instance, a relationship has been discovered between PMMA solubility and the hydrophobicity of the anion of imidazolium-based ILs, rather than the alkyl chain length of the cationic structure [66].

Some polymers' high solubility in ILs is due to advantageous interactions between the two compounds, such as hydrogen bonding, n-π, π-π, electrostatic, and dispersive interactions . To properly select ILs for polymer processing, it's important to completely grasp the solubilization process at the molecular level, as they are more complex than ordinary solvents[67].

## III. ILs PLAY A ROLE IN DEVELOPING DRUG DELIVERY SYSTEMS USING BIOPOLYMERS.

Because of the infinite design options, customized (bio)polymer drug delivery systems may be created. This is because ILs can be made to have polymerizable character in addition to their ability to dissolve biopolymers. For instance, ILs have been used as reaction media in the direct and homogenous esterification of acid chlorides, namely hexanoyl, acryloyl, and 2-chloropropyonyl chlorides, to create custom-made guar gum derivatives [68]. The degree of guar gum substitution can be adjusted (0.12–2.70) by modifying the experimental parameters, including reaction time, according to the results. An enticing workaround for the issue of low and uncontrolled substitution reactions for this biopolymer is to employ these imidazolium-based media. Finally, guar chains with adjustable emulsifying qualities were produced through esterification with hexanoyl chloride. Conversely, the acryloyl inclusion provided a means to create reactive precursors that, upon radical cross-linking, could facilitate the creation of pH-sensitive drug delivery vehicles [69]. As their use in drug delivery systems expands, ILs further enable new administration routes to be explored since they increase the solubility of both low-water soluble APIs and biopolymers. To date, successful reports of drug polymeric delivery systems containing ILs and API-ILs have been made for topical, intravenous, oral, and, more widely, transdermal administration [70]. Within this framework, ILs have been studied for the production of polymerizable systems, fibers, ionogels, patches and membranes, microemulsions, and nanoparticles. One straightforward and efficient way to create delivery systems is by dissolving biopolymers in IL media since certain steps, such as coating, can be completed in a single pot or step. When cellulose is dissolved in [C2C1im][CH3CO2], an example similar to this has been confirmed for cellulose coating onto chitosan hydrogel beads [71]. The model medicine for hypertension, verapamil hydrochloride, was impregnated into the chitosan beads coated with cellulose. The resulting beads demonstrated drug release patterns that were sustained in both the stomach and intestinal environments, with maximal release times of 60 and 300 minutes, respectively. In addition, new grafting polymerization and chemical modification [72] media have been made possible by the use of ILs in the development of polymer-based drug delivery systems. Furthermore, ILs have made it possible to build biopolymer-based systems using solvent casting, eletrospinning [73], and straightforward insertion of an API-IL into a biopolymer matrix, like bacterial cellulose . In the context of topical distribution, promising cellulose-based delivery methods have been reported for the inclusion of cholinium-based ILs, which include vitamins , antioxidants , and anti-inflammatory medicines [74]. Because of the increased drug solubility made possible by the API-IL formulation, these systems offer a quick or regulated release of the API.ILs can be used as parts of delivery systems that enable the tunable release profile of systems that respond to stimuli. This field has investigated cholinium-based ILs to provide a better regulated release of ionic medications, like sodium phosphate derived from chitosan-based polymers is dexamethasone (DXA) [75].

Films that are obtained can be used to deliver DXA and loaded with ionic liquid (cholinium dihydrogen phosphate) as pH-responsive drug delivery devices. Regardless of the release medium's pH, the amount of DXA released from films loaded with IL was found to be less than that of films without IL, demonstrating the ability to regulate the release of the API. When compared to the release at pH 7 and pH 10, the chitosan-based films permit smaller total released levels of DXA at pH 4. The construction of biocompatible and biodegradable iontophoretic devices may also be made possible by the inclusion of ILs into chitosan-based films, given their shown features like conductivity. ILs have an interesting pharmacological profile, can be employed as substitute gelling agents in therapeutic formulations, and have the ability to directly affect cell membranes [78]. Responsive ionogels with enhanced sustained release profiles of pharmaceuticals could be produced by combining ILs exhibiting surface-active activity with an API. For instance, at a crucial gelation concentration, cetylpyridinium salicylate creates a temperature-responsive ionogel that can encapsulate the chemotherapy medication imatinib mesylate in its matrix. Depending on the pH and temperature of the medium, this ionogel enables the extraction of distinct release profiles for the API; the release is faster at body temperature and at pH = 5, which corresponds to the tumoral environment [79]. By including responsive polymer and biopolymer motifs in the planned formulations, it is also possible to construct "smart" systems that can react to their surroundings . These systems can be made to react in a certain way to changes in temperature, redox, pH, or the presence of particular enzymes. In order to develop these systems, ILs can be applied in three different ways: (i) by changing the (bio)polymers in IL media, where sensitive polymer units are incorporated; (ii) by

designing ILs to give the system particular properties; and (iii) by designing polymerizable forms of ILs that make it possible to synthesize so-called polymeric ionic liquids (PILs)[80].

## IV. CONCLUSION

In conclusion, the review paper highlights the immense potential of ionic liquids (ILs) in revolutionizing drug delivery systems. Traditional challenges in drug formulation, such as low water solubility of active pharmaceutical ingredients (APIs), have hindered effective drug delivery. However, ILs offer a promising solution by serving as novel solvents, co-solvents, and hydrotropes that significantly enhance the aqueous solubility of APIs across various pharmacological classes. Notably, the judicious selection of IL anions and cations influences the solubilization process and ILs' solvation capacity, leading to remarkable improvements in API solubility by several orders of magnitude. Furthermore, ILs facilitate the creation of liquid forms of APIs (API-ILs) that address issues related to polymorphism, increase solubility, and potentially improve therapeutic efficacy. The flexibility in designing API-ILs allows for enhanced penetration into biological membranes, paving the way for novel drug delivery mechanisms. ILs also demonstrate effectiveness as permeation enhancers and microemulsion components, enabling improved API transport across biological barriers. Their role in dissolving and processing biopolymers opens avenues for customized drug delivery systems with tailored release profiles and improved bioavailability .Moreover, ILs contribute to the development of responsive drug delivery systems that can adapt to environmental stimuli, such as changes in pH or temperature. This capability, combined with ILs' biocompatibility and biodegradability, makes them ideal candidates for creating "smart" drug delivery systems that can respond dynamically to therapeutic needs. Overall, the comprehensive exploration of ILs in drug delivery systems signifies a paradigm shift towards more effective, targeted, and patient-friendly medication administration, promising significant advancements in the pharmaceutical industry.

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