AAPS PharmSciTech (2022) 23:161
https://doi.org/10.1208/s12249-022-02313-w

REVIEW ARTICLE

Ionic Liquids Assisted Topical Drug Delivery for Permeation Enhancement: Formulation Strategies, Biomedical Applications, and Toxicological Perspective

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Received: 4 February 2022 / Accepted: 20 May 2022

Abstract
Topical drug delivery provides several benefits over other conventional routes by providing localizing therapeutic effects and also avoids the gastrointestinal tract circumventing the first-pass metabolism and enzymatic drug degradation. Being painless, the topical route also prevents the difficulties linked with the parenteral route. However, there are limitations to the current topical systems which necessitate the need for further research to find functional excipients to overcome these limitations. This review deals in depth with the ionic liquids concerning their physicochemical properties and applicability as well as their role in the arena of topical drug delivery in permeation enhancement, bioavailability enhancement of the drugs by solvation, and drug moiety modification. The review gives a detailed insight into the recent literature on ionic liquid–based topical formulations like ionic liquid–based emulsions, active pharmaceutical ingredient-ionic liquids, ionic liquid–based bacterial cellulose membranes, topical small interfering RNA (siRNA) delivery, and ionogels as a possible solutions for overcoming the challenges associated with the topical route. This review also takes into account the toxicological aspects and biomedical applications of ionic liquids.

KEY WORDS ionic liquids · skin · topical delivery · permeation · biomedical applications · toxicological aspects

INTRODUCTION

In recent times, different modes of drug administration are well identified and tried. The selection of a particular administration route is determined by the aspects like the drug, drug pharmacokinetic profile, and the anticipated target site. Usually, non-invasiveness is the criteria for selecting the administration route. Though the oral route is mostly utilized but owing to the disadvantages associated with the oral route and other routes like the parenteral route, alternative safer and non-invasive administration routes have been explored by the pharmaceutical industries for effective drug delivery thereby improving patient compliance. Skin acts as a potential site for the application of drugs for providing local and systemic effects. Drug delivery via the skin is an accepted alternative route among the patients since it is non-invasive and also avoids gastrointestinal tract and other problems (1, 2).

Skin is composed of both hydrophilic and hydrophobic realms, and the drug utilized should possess the capability to penetrate both realms but the lower solubility of many drugs in water presents a hurdle. Reduced stability of the formulations owing to the lower solubility of many drugs is another problem faced by the pharma industries (1). In drug development, it has been observed that approximately 40% of the commercialized drugs and 90% of the under-investigation drugs possess insufficient pharmaceutical properties affecting the therapeutic outcome. There is a need for exploring the strategies for improving the drug delivery for such drugs (3). The efficient delivery of the drugs through the skin presents certain challenges and hence several techniques for disrupting the tough stratum corneum layer have been explored which are physical or chemical. Physical methods

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Published online: 08 June 2022

include sonophoresis, iontophoresis, and laser-based treatments. These require special types of equipment and are laborious and have also been reported to cause irreversible damage to the skin (4). Hence, various functional excipients have been explored to solve these problems. Recent literature has revealed the significance of ionic liquids (ILs) for improving drug loading/solubility and permeation through the skin (1). Nowadays, ILs have been explored widely in pharmaceutical sciences owing to their flexible physical and chemical properties like polarity and viscosity, their function as a catalyst in active pharmaceutical ingredient (API) synthesis, and solubilization potential for hydrophilic and hydrophobic drug molecules (5). ILs have been reported to bypass barrier characteristics of the tough outermost stratum corneum (SC) layer of the skin, thereby improving the transcellular and paracellular transport through the skin by using different mechanisms like fluidization, disruption of the cell integrity, and creation of diffusional pathways for extracting the lipid portions in SC. Also, the capacity to modify room temperature ionic liquids (RT-ILs) for diverse reasons makes them useful in many contexts like solubilizing agents, or as permeation enhancers that interact with the biological membranes improving the permeability and clinical efficacy (2–4). Some ILs are reported to exhibit antimicrobial activity resulting in their use as preservatives or as APIs (6). Thus, ILs possess various applications as excipients in the area of dermal formulations.

This review delivers an insight into the recent advances of ILs in topical drug delivery and their role as an excipient in the fabrication of efficient formulations with improved drug penetration and as therapeutic moieties for improving the disease outcomes based on the mechanistic and structure-activity evidence studies.

What Are Ionic Liquids?

ILs are the liquids existing in the ionic form (7). Because of their ionic nature, most ILs possess advantages over other solvents like non-volatility under ambient conditions, and high chemical and thermal stability (8). Other properties of ILs include less viscosity and lower vapor pressure (7). ILs refer to the organic salts, synthesized from a combination of cation and anion with melting points below 100 °C or at room temperature. ILs existing as liquids at room temperature are called room-temperature ionic liquids. This remarkable solvent class shows fascinating properties concerning polarity, chemical and electrochemical stability, and hydrophobicity (1). These characteristics and activity originate as a result of the combination of their constitutive ions. The counter-ion can be chosen to improve the beneficial effects or to neutralize the side effects of the active constituent. Pharmacologically, they could be selected to act independently or to enhance the pharmacokinetic properties as illustrated in Fig. 1 (9, 10). ILs have established themselves for use in the industry, academics, and laboratory as solvents, which could be reflected by the increasing number of publications in these fields (7). It is feasible to enhance the API permeation through biological membranes due to the flexibility in the design of ILs. This is possible by employing ILs having surfactant activity as novel ingredients in the formulations. Presently, ILs are being studied as formulation excipients, especially in the case of microemulsions for creating effective delivery systems (8). Interest has been shown in using ILs in topical delivery to the skin owing to the reported application of ILs as chemical permeation enhancers. ILs have been utilized to increase solvation of the drugs with poor solubility by co-solvency, micellization, and hydrotropy or as permeation enhancers in topical systems. This efficient solvation potential of ILs leads to the use of ILs not only in oral but also in topical formulations. Improved therapeutic results have been reported when the approaches like developing APIs as the ILs (API-IL) displaying a thermodynamically stable system, preventing difficulties like polymorphic conversion of the APIs and improving therapeutic properties or using ILs with pharmacological activity including but not limited to antibacterial, antiviral, antifungal, and cytotoxic activity as well as biofilm-disrupting agents (8, 11).

Most Commonly Studied ILs

Mostly studied ILs include imidazolium ILs owing to their stability in oxidative and reductive conditions with very low viscosity and easy synthesis (12). But these are reported to be toxic with the toxicity based upon the alkyl chain size limiting their use typically in the pharma field (13, 14). These ILs have been utilized as catalysts,

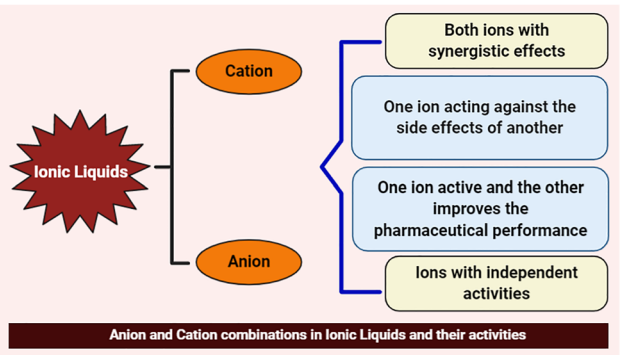


Fig. 1 Anion and cation combinations in ILs and their activities

solvents, and solubility enhancers (1). Pyridinium-based ILs are utilized as solvents (1), in organic compound synthesis, biocatalysis, polymerization (15), and pharmaceutical compound synthesis (1). Recently, phosphonium-based ILs are used as solvents, and as catalysts (1, 16). They possess high thermal stability compared to ammonium-based or imidazolium salts and are thus appropriate for reactions at temperatures exceeding 100°C. In the literature, the newer quaternary ammonium-based ILs are mentioned to be having lesser toxicity. ILs are termed as "green" substitutes to the solvents utilized in the pharmaceutical industry due to their extremely low vapor pressure and higher thermal stability offering unique benefits like recycling ability, and the ability to dissolve several organometallic and organic compounds (17).

Table I summarizes the commonly used ILs as well as the newly emerging cationic and anionic precursors (11, 20, 21).

Properties of ILs

The first IL was reported as ethyl ammonium nitrate by Paul Walden in the year 1914 (12, 22) with a melting point of 12 °C. This was later followed by the 2nd and 3rd generations of ILs over succeeding years together with the development of new green ILs. IL is made of two separate constituents—an anion and a cation of which cation is organic and bulky and an anion is inorganic and small. This leads to the reduction in the system crystallinity which allows ILs to exist as liquids at low temperatures and offer the advantageous properties stated above (11). The IL structure denotes *n* number of permutations that can be possible provided that the cation and anion species with inadequate packing are present. This resulted in the new species being discovered including the cholinium and guanidium cations, conferring the benefit of biodegradability and are hence referred to as bioinspired ILs (BILs) (11, 23). Conventional base cations are quaternary ammonium, pyrrolidinium, imidazolium, phosphonium, and pyridinium cations. Few recent novel ones like cations containing metal do not fall into the conventional framework of ILs wherein the organic cation is united with inorganic anion. These newer metal ILs are synthesized utilizing metal cations and different anions permitting the development of salts that are IL-like. The additional category of metal-ILs includes ILs having magnetic properties (11, 24). These newer species and the abovementioned cations enhance the scope of these ILs in biomedical research, typically the BILs. The development of biodegradable tetramethylguanidium cation–based surface fatty acid protic ionic liquids for cutaneous delivery in skin cancer is one such example (25). Choline-based ILs are also gaining importance in drug delivery due to their biodegradability, biocompatibility, and lesser toxicity (26). Recently, two cholinium-amino acid ILs, cholinium analinate [Ch][Ala], and cholinium glycinate [Ch][Gly] were found to enhance the solubility and topical permeation of ibuprofen (27).

Physicochemical Properties of ILs

ILs possess excellent physicochemical characteristics owing to which ILs are gaining much importance as solvents. The IL properties include the following.

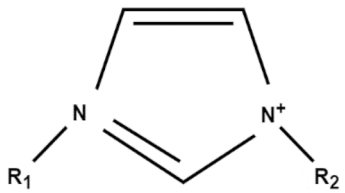
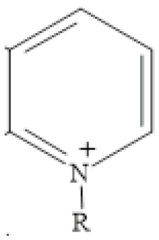
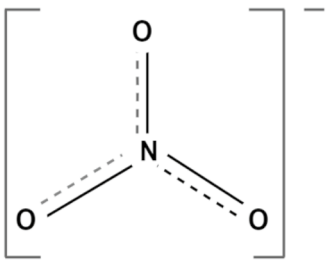
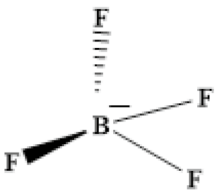
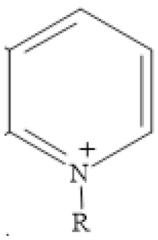
Density, Viscosity, and Melting Point IL density varies from 0.9 to 1.7 g/cm^3 at 20–25 °C rendering ILs denser than the conventional organic solvents (11). The alkyl chain length present on the cation and the anion affects IL density. Also, as the cation bulkiness increases, the density decreases. Density gets affected when the anion structure is varied (28). Viscosity factor is of prime importance in affecting the application of ILs for skin delivery (11). Usually, both van der Waals forces and hydrogen bonds determine IL viscosity. Alkyl chain length or fluorine substitution in cation enhances the IL viscosity because of stronger van der Waals interactions. Owing to the hydrogen bonding suppression, the inherent lower melting point of ILs is the main reason ILs have become more popular. Though ILs possess melting points less than 100 °C, the majority of them are liquids at room temperature. RTILs bear melting points at or lesser than room temperature (11).

Polarity and Vapor Pressure The factors affecting IL polarity include variation in chain length wherein long and branching chains are hydrophobic (11, 29). ILs do not lead to the emission of the significant vapor pressure making ILs a subset of green chemistry. Hence, ILs are recognized as a solution to the regular volatile organic compounds used as industrial solvents. ILs are stable thermally. The length of heteroatom-hydrogen and heteroatom-carbon bonds restrict IL stability (28).

Miscibility ILs are well-known ideal solvents for many organic and inorganic as well as polymeric substances (28). IL solubility in organic solvents and water could be changed by altering the cation and anion structure. Cation structure influences solubility by the similarity in polarity between IL as well as the other solvent and free space generated among the molecules by larger side chains (28).

Anderson *et al.* suggested that ILs can dissolve substances by several forces like dipole-dipole forces, Π-Π interactions, and H bonds (30). Visser *et al*. showed that neutral

Table I Most Commonly Explored Anions and Cations Along with their IL Generations and the Newly Emerging Cations and Anions (11, 18, 19)

First-generation ILs	
Anions	**Cations**
Tetrachloroaluminate **$AlCl_4^-$**	Imidazolium 
Dialuminium heptachloride **$Al_2Cl_7^-$**	Pyridinium 
Nitrate 	
Second-generation ILs	
Tetrafluoroborate 	Pyridinium 

substances possess better solubility in ILs whereas ionized substances dissolve better in water rather than in ILs (31). The solvation mechanism in ILs is not clear yet (29). ILs are found to form a homogenous solution with organic solvents and are completely miscible if the dielectric constant of the ILs exceeds a particular point, and this limit is influenced by the cation-anion pair combination (32). Many ILs form a homogenous system with polar organic solvents like ethanol and acetone, whereas if hydrophobic ILs are mixed with water, a biphasic system is formed (33).

Table I (continued)

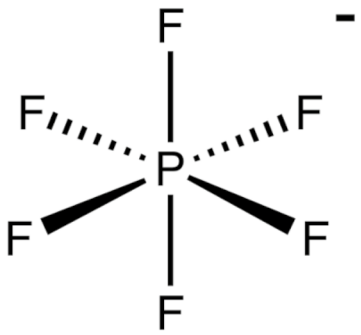
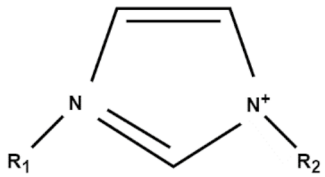
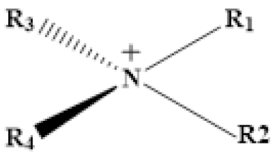
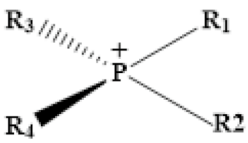
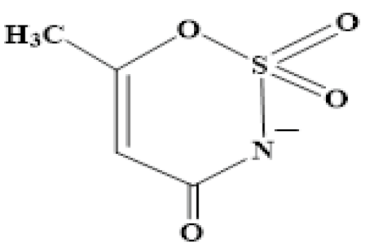
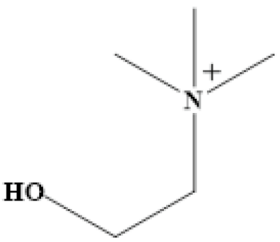
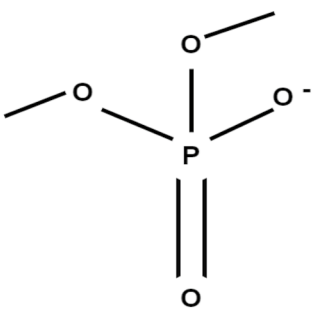
<table>
<tr><td>Hexafluorophosphate
  </td><td>Imidazolium
  </td></tr>
<tr><td rowspan="2"></td><td>Quarternary ammonium
  </td></tr>
<tr><td>Halides
Cl⁻, Br⁻, I⁻</td><td>Quarternary phosphonium
  </td></tr>
<tr><td colspan="2">Third-generation ILs</td></tr>
<tr><td>Acesulfame
  </td><td rowspan="2">Choline
  </td></tr>
<tr><td>Dimethylphosphate
  </td></tr>
</table>

Table I (continued)

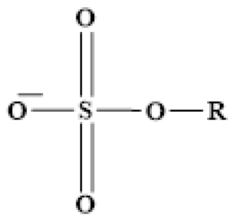
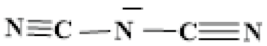
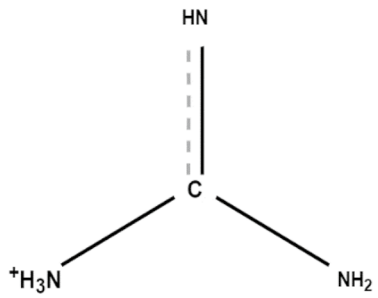
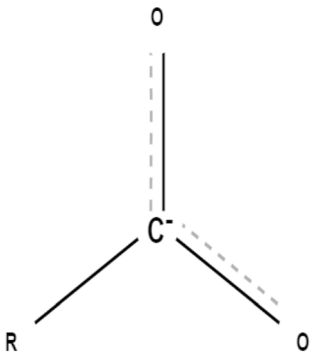
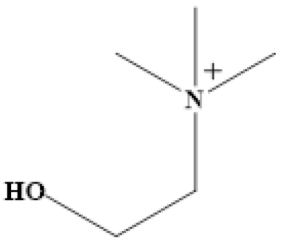
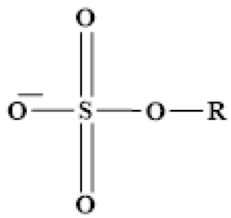
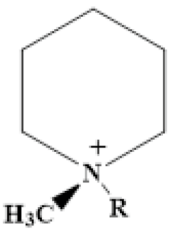
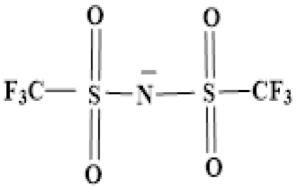
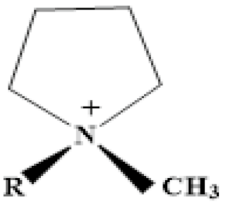
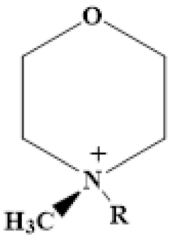
Alkyl sulfate 	
Amino acids **NH_2-CH_2-COO^-**	
Newer emerging anionic precursors	**Newer emerging cationic precursors**
Dicyanamide 	Guanidinium 
Carboxylate 	Cholinium 
Alkyl sulfate 	Piperidinium 
Bistriflimide	Pyrrolidinium

Table I (continued)





Morpholinium



Chemical Properties of ILs

The investigation of the chemical effects is very difficult owing to the numerous possible permutations of the components that make up the ILs (11). Recently, Hayes *et al.* showed that ILs are made of micro/nano hierarchical structures and the ions are self-assembled into the subdomains developing into the amphiphilic nanostructures (34). These structural features of ILs are similar to nano-heterogeneous substances which are a special property and are not seen in other dissolution media and solvents. Spatial studies are very difficult and hence these domains are modeled using discrete Fourier transform molecular dynamics. Spectral studies have proved the work to be an established one accounting for the challenges when the characterization of definite ILs is done by nuclear magnetic resonance spectroscopy and hence involves external forces that disrupt ultrastructures (34). The main generators in the structural association within ILs include hydrogen bonding and ionic forces. The key distinction between the ILs and inorganic salts is the ion size involved. Inorganic salts are made of circular species with compact orderly packing

Table II Effect of Chain Length Modification on Physicochemical Properties

Modification in chain length	Change in physicochemical properties	Reference
1. Increase in the chain length	A decline in water solubility	(35)
	Increase in the melting point	(36)
	Increased viscosity	(37, 38)
	Increased enthalpy of vaporization	(38)
	Increased surfactant activity	(38)
	Increased cytotoxicity in bacterial and marine life	(39, 40)
	Decreased density	(41)
	Increased aggregation	(37, 38, 42)
2. The decrease in the chain length	Increased conductivity	(43, 44)
	Increased polarity	(11)
	Increase in interaction energy and electrostatic forces	(45)
	Increased catalytic activity	(46)
	Ordered aggregation	(11, 38, 42)
3. Chain lengths analogous to biological membranes	A rise in bioaccumulation (possible risk of toxicity)	(11)

unlike larger cation of ILs with its charge spread over a large region which affects the IL structure locally, and very minor variations may cause major changes in the activity proved easily by the choice of the cation. The cation influences properties like polarity, aggregation, surfactant properties, and toxicity (11). The chain length can influence the physicochemical properties of ILs drastically as illustrated in Table II.

CLASSIFICATION OF ILs

Based on the structure, properties, and applications, ILs are categorized into three different generations. First-generation ILs are categorized by specific and customizable physical properties like low or no volatility, thermal stability, and larger liquid range. This category consists of alkyl pyridinium and dialkyl imidazolium cations along with metal halide anions. Second-generation ILs are generally designed by alkyl pyridinium, dialkyl imidazolium, phosphonium, ammonium cations, and tetrafluoroborate, hexafluorophosphate anions. The third-generation ILs consist of the natural and biodegradable ions or the ions having recognized biological activities as the primary IL activity and choline-based ILs with amino acids are commonly used in this category. The generations of ILs are depicted in Fig. 2. This last generation finds applications in ecology, biology, and pharmaceutics. Another classification of ILs includes a grouping of ILs into 4 categories by cation, like N-alkyl-pyridinium, dialkyl imidazolium, alkylammonium, or phosphonium cation (1, 21, 47).

IL INTERACTIONS WITH BIO-MOLECULES AND BIOMEMBRANES

Previous experimental results have shown that the ILs possess specific mechanisms for binding to the cell membrane, insertion, and membrane disruption. These activities can be correlated with the biological activities of ILs. The results showed that the IL head groups and the side chain composition influence the membrane activity and cell toxicity of ILs (48).

Several ILs possess the ability to diffuse into the biomembranes and disrupt them, stabilization, and storage of biomolecules like proteins and enzymes as well as DNA, supporting, or preventing protein aggregation in amyloids, extraction, purification, or preservation of DNAs (11, 21, 49–52). ILs also bear the ability to re-functionalize the malfunctioning amyloid fibers, dissolving the complex polysaccharides, and creating holes in the biomembranes (11, 21, 53). This leads to certain advantages like specific bacterial killing, and toxicity to selective cancer cells without harming the healthy cells (11) emphasizing the usefulness of ILs in topical delivery in skin diseases.

Initially, the biomembrane will interact with the ILs and this reaction occurs at the bio-membrane-IL interface. The widely accepted model used for studying these interactions is the phospholipid bilayer. A group of researchers investigated the IL-bio-membrane interactions using biophysical techniques on the model biomembrane, phosphatidylcholine membrane. From the results, it was evident that the ILs permeate the cell membrane and disturb the structural, dynamic, and membrane phase behavior. IL fusion distorts the membrane, shifting the phase transition to a low temperature and broadening it. Reflectometry studies in line with the molecular dynamics simulation results show that

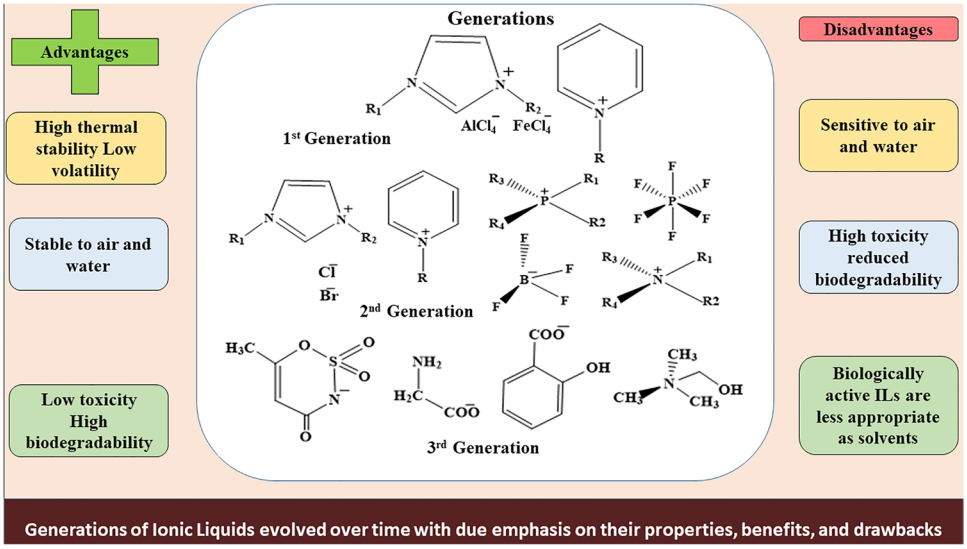


Fig. 2 Generations of ILs, evolved over time with due emphasis on their properties, benefits, and drawbacks

IL addition leads to the shrinkage of the bilayer. Elastic intensity scan and QENS measurement results show that IL acts as a plasticizer influencing the internal as well as lateral motions of the biomembrane. IL interactions with the biomembrane depend on the length of the alkyl chain of the IL, and an upsurge is seen with the growing chain length. Higher IL concentration contributes to further integration of ILs into the biomembrane, and IL's effect on the cell membrane's biophysical properties becomes greater (54). Yoo and coworkers studied the interaction of 1-n-alkyl-3-methylimidazolium-based ILs with a phosphatidylcholine lipid membrane. Bulk atomistic molecular dynamics simulation studies depicted rapid cation insertion in the lipid bilayer irrespective of alkyl chain length and a favored orientation preferred after the insertion of a cation. If introduced with a non-favored positioning, the cations possess the property to flip inside the bilayer so that the alkyl chain gets incorporated in the lipophilic bilayer portions. Flipping time is generally higher for the cations with longer alkyl chain lengths. Cation insertion enhances the bilayer surface roughening with increasing concentrations resulting in greater surface roughness. This roughening was suggested to be a probable cause for bilayer disruption (55).

Wang *et al*. (56) synthesized salts having two alkyl chains in the imidazolium framework resembling the bilayered lipid structure. The alkyl chain length was reported to be of importance for antibiofilm activities of the lipid-mimicking components. Similar literature is available on the interaction of imidazolium-based ILs with biomembranes (54). Benedetto *et al.* (57) designed ILs with choline-based cations and various amino acid anion pairs and assessed them for the biological system as the preliminary ingredients. There were resemblances seen between the intrinsic groups and the artificial substrates. IL compatibility and safety are not guaranteed by the biomimicry among the IL and endogenous phospholipid. This was seen in the work of Evans *et al.* wherein slight modifications in the cation chain while utilizing 1-butyl-3-methylimidazolium chloride harmed the biomembranes used in the investigation (11, 58, 59).

The penetration of this particular IL was further explored by Benedetto and coworkers (60). The concentration of choline chloride ILs within the biomembranes was determined by neutron scattering. It was seen that up to the IL concentration of 0.5M, the phospholipid bilayers retained their 2D configurations. The insight into the changes in the bilayered membrane such as shrinkage of the thickness, build-up of IL cations at the conjunction among the polar head and a non-polar tail, the composition of lipid bilayer affecting the accumulation which occurs, and also the penetration degree but not the accumulation location. Jing *et al.* (58) confirmed the IL bioaccumulation by utilizing amphiphilic 3-methylimidazolium-based ILs thereby leading to the cation insertion in the bilayer resulting in swelling of lipid bilayers at a concentration higher than the lower critical concentration and showed that the IL concentration was of prime importance and could disrupt the bilayer completely. In conclusion, the IL effect on the biomembrane and the cytotoxicity depend upon factors like IL concentration wherein higher concentration causes bilayer shrinkage and increased elasticity and on the chain length present on cation resulting in phospholipid bilayer disruption. Short-chain ILs are easily inserted into the biomembrane but the ones with long chain get assembled into micelles and are absorbed (11).

IL-BASED TOPICAL DRUG DELIVERY ENHANCEMENT APPROACHES AND IL-BASED FORMULATIONS

ILs belonging to second- and third-generation have generally been used in topical drug delivery. Numerous reported IL-based formulations for topical delivery include IL-based emulsions, microemulsions, nanoemulsions, IL-based gel, active pharmaceutical ingredient-ILs, IL-based bacterial cellulose membranes, IL-based siRNA delivery, and ionogels. ILs help in improving the topical delivery of the drugs by promoting the drug permeation via the skin, and by enhancing the API bioavailability in different ways discussed below.

Permeation Enhancement Approach

The use of ILs has been reported to improve the drug permeation through the skin (11, 56, 61). Ionic liquids are of prime importance while designing the topical or transdermal delivery system. According to a study conducted by a group of researchers in 2017 (13), the highest permeation flux was seen with more hydrophobic ionic liquid. Another study suggested the neutral behavior of these paired compounds thereby acting as neutral species cross the membrane more fast compared to the more ionic drugs (62). A study by Monti and coworkers showed that the structure of ILs affects the degree of permeation (63). It is reported that all the ILs with permeation enhancement are either hydrophilic or lipophilic. Hydrophilic ILs open the tight junctions in the SC and by following the paracellular transport promotes the fluidization in the protein and lipid expanses while lipophilic ILs enhance partitioning in the epithelium by offering channels encouraging transcellular transport in the lipid regions. The recently reported work is of the 1-octyl-3-methylimidazolium-based ILs acting by disruption of structural integrity by insertion inside the membrane (64). ILs bear the capacity to fluidize the cell membranes especially the hydrophilic imidazolium-based ILs and also the lipid extraction in SC (65). IL-based formulation strategies

that have been tried for permeation enhancement through skin include the utilization of ILs in emulsions, microemulsions, nano-emulsions, and siRNA delivery using ILs for the treatment of skin infections.

Ionic Liquid–Based Emulsions, Microemulsions, and Nano-emulsions

The major distinguishing feature between the emulsions and microemulsions is their droplet size and thermodynamic stability. The microemulsion droplet size is <100 nm and microemulsions are more stable thermodynamically (66). The droplet size of the nano-emulsion also lies in the nanometer range. However, the surfactant used imparts stability to the system. The uniform and small droplet size lie in the range of 20–200 nm (67). ILs when used as dispersed/continuous phases in an emulsion or microemulsion make the formulation attractive because of their unusual solvent properties. ILs could be utilized either as polar or as nonpolar phase solvents to create a stable formulation depending upon their cation and anion properties (68).

Ionic Liquid–Based Topical Small Interfering RNA Delivery

Different skin diseases like cancer, lupus, and psoriasis could be efficiently treated by the suppression of allele-specific genes utilizing siRNA. As the siRNA injections into the skin cover small areas and are painful, they are unsuitable for long-term treatment. Hence, topical siRNA delivery is a suitable alternative possessing numerous advantages including easy contact with the diseased site, ease of examination of the success of the therapy, ease of monitoring and site excision of an adverse reaction, controlled/sustained drug delivery, and potential potent knockdown of causal proteins. But skin acts as a barrier preventing effective siRNA permeation (69).

Zakrewsky and Mitragotri *et al.* synthesized robed-siRNA with IL moieties. Robing imparted tunability required for skin delivery like partitioning, transport into the skin, and cell internalization. Robed-siRNA were prepared by a two-step procedure wherein the first step was cation and anion exchange resulting in basic IL moieties and acidic siRNA, and the second step involved acid-base neutralization resulting in aqueous siRNA robed with IL moieties (70). Another study involved effective siRNA delivery in the skin using two strategies. The first strategy involved robing of siRNA using benzyldimethyloctylammonium by acid-base neutralization and the second strategy involved the enhancement of dermal permeation utilizing the choline-geranic acid ionic liquid (CAGE) IL (69).

Bioavailability Enhancement of API

IL modification could be done to obtain several desired properties and could be also employed in API synthesis as a catalyst and as transformative media. ILs can also assist by modification of drug delivery systems for efficient delivery of API by acting as solvents, dispersants, nanocarriers, and substrate activation (11).

Ionogels

Ionogels constitute a newer class of drug delivery systems and are among the techniques used to improve API bioavailability (9). Herein, the unique properties of ILs are combined with another constituent which could be low molecular weight organic gelator or inorganic components like carbon nanotubes and silica, or hybrid organic and inorganic components like polymer and inorganic fillers (71).

Modification of Drug Moiety by the ILs

IL modification could be done to obtain several desired properties and could be also employed in API synthesis as a catalyst and as transformative media. ILs can also assist by modification of drug delivery systems for efficient delivery of API by acting as solvents, dispersants, nanocarriers, and substrate activation (11). Also, APIs can be utilized as cations or anions and could be united with a suitable counterion to form an IL thereby leading to beneficial outcomes (9)

Active Pharmaceutical Ingredient-Ionic Liquids Approach

Challenges associated with the API like the polymorphism owing to its crystallinity, solubility, and bioavailability could be taken care of using ILs. The use of API-ILs has not only been reported to overcome the challenges associated with manufacture but also has a positive outcome on permeation enhancement and improved bioavailability. API used could be either anion, cation, or both. Commonly employed cations include lidocaine, ranitidine, and didecyldimethylammonium whereas the anions include the ones approved by the FDA for pharmaceutical use.

The etodolac-lidocaine IL is reported to have enhanced lipophilicity/hydrophilicity of etodolac and etodolac skin penetration by 9.3 times (72). Various API ILs reported include lidocaine docusate (72), lidocaine ibuprofenate (73, 74), lidocaine salicylate (74), and ranitidine docusate (75). API-IL use has not only helped in overcoming the manufacturing challenges but has also impacted the resultant outcomes by enhancing API bioavailability and permeation and by providing positive synergistic interactions. Lidocaine ibuprofenate and lidocaine salicylate ILs were reported and

were found to be more stable thermally compared to the individual compounds (74).

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Solvation/Solubilizing Efficiency Enhancement Approach

API solvation is an important step of drug absorption and a crucial aspect to be considered for any effective drug delivery system. The solubility of the API in the solvent for medical and biomedical applications should be higher than 1 mg/mL. Zhang *et al.* showed that 5% 1-butyl-3-methylimidazolium chloride enhanced solubility as well as the skin penetration of ginsenoside Rh1 (76).

McCrary along with a group of researchers developed an IL excipient that acted by maximizing the interactions required to increase the water solubility and inhibited the de-aggregation of a drug in water. Higher solubility was achieved in water, simulated gastric fluid, phosphate buffer, and simulated intestinal fluid for both the drugs by imparting suitable hydrophilic-lipophilic balance in either one or both the ions of IL (77). Wu and coworkers developed different ILs to increase the solubilization capacity of ketoconazole. IL formed by choline and geranic acid was the optimum IL and improved the solubility of the drug 100 times**.** The *in vitro* studies showed that the IL possessed synergistic action along with the drug. Also, there was no irritation seen for the IL on the skin (78). Another work aimed at producing NSAID-based ILs for enhancing the water solubility of these drugs and incorporating them in the BC membranes for cutaneous delivery (79).

Ionic Liquid–Based Bacterial Cellulose (BC) Membranes

Recently, the ILs have been incorporated into the homogenous, thermally stable, transparent bacterial nanocellulose membranes to form efficient dermal drug delivery systems having appropriate mechanical properties for topical application (80). The detailed literature reported on the ionic liquid–based topical formulations is mentioned in Table III

Synergism Between ILs and Other Chemical Permeation Enhancers

Synergy implies that the combined action of the two agents is greater than the sum of the efficacy of the individual agent (93). Synergy could be assessed from the results of *ex vivo* permeation studies showing superior permeation of the therapeutic agent in the skin and by the improved therapeutic activity of the formulation (94). Chemical permeation enhancers (CPEs) incorporated with ILs can be beneficial in several ways and can lead to the improvement of drug penetration. The use of ILs with permeation enhancers based on alcohol can help in incorporating a broad range of APIs by co-solvency aiding in drug solubility. The challenge of drug incorporation could be overcome by IL combination with other CPEs like terpenes (11). By the synergistic combination of terpenes and ILs, specific targeting of receptors can be done with improved drug delivery. According to a study reported by Ali and coworkers, surface-active IL at 20% surfactant concentration, i.e., (SAIL)-based IL/O ME showed 4.7-5 fold high loading for the drugs celecoxib and acyclovir in contrast to Tween–80 based IL/O ME. This improvement in solubility could be due to hydrogen bond formation and electrostatic interactions within the SAIL surfactant head groups, IL anions, and polar drug molecules (95). Incorporating dimethylsulfoxide (DMSO) into ILs could overcome certain disadvantages like less DMSO concentration for permeation and reduced side effects. The presence of DMSO decreases the discrete IL profile and hence must be considered in the sealed systems (11) (Fig. 3).

BIOMEDICAL APPLICATIONS OF TOPICAL IONIC LIQUIDS

Various biomedical applications of ILs include applications in topical cancer therapy and the treatment of skin diseases like psoriasis and lupus. ILs are also utilized in topical delivery for the treatment of pain, delivery of antibiotics, and other cosmetic applications like acne treatment, skin moisturizing, and anti-aging properties. The abovementioned biomedical applications are discussed in detail in the below sections.

In Cancer Therapy, in the Treatment of Skin Diseases, and for the Delivery of Immunomodulators

Currently, ILs are designed for use in cancer therapy as anticancer agents and for other applications (96, 97). Studies have shown the application of ILs as antitumor agents (98, 99). In the cancer field, the main concern is selective drug targeting to a particular organ/tissue and hence the pharmaceutical industry is searching for effective strategies for drug targeting. The cancer therapy should be such that it should only affect the cancerous cells avoiding harm to the healthy cells. The disadvantages associated with anticancer agents are their larger body distribution, poor absorption, and poor diffusion from the tumor mass leading to not only the loss of efficiency and off-target effects but also raising

Table III IL-based Formulations Utilized in Topical Delivery

IL-based topical formulation	ILs used	*In vitro* cell-lines/*in vivo* animal model used	Outcome	Reference
Ionic liquid–based topical emulsions	Hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM] [PF6]) and hydrophilic 1-hexyl-3-methylimidazolium chloride ([HMIM] [Cl]).	Human epidermal keratinocyte cell line (HaCaT)	O/W and W/O emulsions containing hydrophobic and hydrophilic ILs showed higher permeation in the presence of ILs.	(81)
Ionic liquid–based dermal gels	Choline dihydrogen phosphate [CDHP], hexylpyridinium chloride [HPyr][Cl], and 1-ethyl-3-methylimidazolium ethyl sulfate [EMIM][EtSO4]	Human reconstructed epidermis model (EpiDerm™), MTT assay	Skin penetration enhancement of hydrophilic caffeine was observed in the presence of [HPyr][Cl].	(6)
Ionic liquid–based topical micro-emulsions	Imidazole-based IL 1-butyl-3-methylimidazolium bromide (BMIMBr)	Dimethylbenz(a)anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA) in female Swiss albino Laca mice.	IL/O ME demonstrated a 4-times surge in 5-fluorouracil (5-FU) penetration.	(82)
	1-Hydroxyethyl-3-methylimidazolium chloride ([HOEIM]Cl and 1-butyl-3-methylimidazolium dodecanesulfate ([C4mim]$C_{12}SO_3$)	HaCaT cell line	IL/W ME enhanced the Denchicine permeation rate 10 times.	(83)
	BMIMPF6 (1-butyl-3-methylimidazolium hexafluorophosphate)	CaCo-2 cell lines and MCF-7 cell lines.	IL/W ME showed 99.03% of Etodolac permeation and showed enhanced anti-inflammatory, and anti-arthritic properties.	(84)
	[C_1mim][$(MeO)_2PO_2$], i.e., dimethyl imidazolium dimethyl phosphate	---	IL/O ME showed high acyclovir solubility, better stability, and good permeability.	(85)
	1-Butyl-3-methyl imidazolium hexafluorophosphate [BMIM][PF_6] and 1-octyl-3-methyl imidazolium hexafluorophosphate [OMIM][PF_6]	---	Celecoxib percent release and permeation from IL/W microemulsions was superior to O/W formulation in both microemulsion and microemulgel	(86)
Ionic liquid–based topical nano-emulsions	Hydrophilic 1-hexyl-3-methylimidazolium chloride [Hmim][Cl] and hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate [Bmim][PF6]	---	Piroxicam permeation was higher in the IL/O NE with the surfactant ratio 2:1 and the IL [Hmim][Cl] used showing 93% drug release.	(87)
Ionic liquid–based topical siRNA delivery	Benzyl-dimethyl tetradecyl ammonium (BDTA), benzyl-dimethyl stearyl (BDSA), and Benzyl-dimethyl octyl (BDOA)	HaCaT cell line	The robed-siRNA, benzyl dimethyl octyl ammonium (BDOA)-siRNA showed enhanced skin internalization, and better biocompatibility compared to naked siRNA.	(88)
	Benzyl-dimethyl octyl (BDOA) and choline and geranic acid (CAGE)	SKH-1E hairless mice for assessing	Binary IL CAGE-BDOA-siRNA synergistically demonstrated reduction in the expression of the target gene GAPDH and reduced target protein expression by 44%.	(69)

Table III (continued)

IL-based topical formulation	ILs used	*In vitro* cell-lines/*in vivo* animal model used	Outcome	Reference
	CAGE, choline and dimethyl acrylic acid (CADA), choline and isovaleric acid (CAVA), choline and phenylpropanoic acid (CAPA), and choline and biphenyl-3-carboxylic acid (CABA).	Imiquimod-induced psoriasis model in SKH-1 elite hairless mice	CAPA-CAGE combination showed the highest permeation of siRNA. IL-NFK-BIZ siRNA was effectively delivered topically, leading to the silencing of NFKBIZ locally.	(89)
Ionogels	1-Methyl-3-butylimidazolium chloride and sodium ibuprofenate	---	The release kinetics for ibuprofen ionogel was slower compared to the crystalline ibuprofen acting as a reservoir for controlled drug delivery	(90)
API-ILs	Lidocaine and ibuprofen	Hot plate method and Von Frey hair test to assess the local anesthesia in CD male rats.	Lidocaine-ibuprofen IL caused local anesthesia within 10–20 min, which was faster than the commercial product with an onset time of 60 min.	(73)
	N-Methyl-2-pyrrolidonium and ibuprofen	Mammalian cell lines (HepG2, L929, and NIH3T3 cells)	NMP-based API-IL exhibited good thermal stability, better skin permeation, and drug retention 2.6-fold greater compared to IL [Cho][Ibu].	(91)
	Etodolac and lidocaine	--	The IL enhanced the hydrophilicity/lipophilicity of both the APIs. The skin penetration of etodolac was enhanced by 9.3 times.	(72)
Ionic liquid–based bacterial cellulose (BC) membranes	Cholinium ibuprofenate, cholinium naproxenate, and cholinium ketoprofenate	---	Choline-based ILs, i.e., [Ch][NSAID], led to a 2-fold enhancement in drug solubility.	(79)
	Cholinium nicotinate [Ch][B3], cholinium pantothenate [Ch][B5], and cholinium pyridoxylate [Ch][B6]	HaCaT cell line	The solubility was found to be enhanced 30.6 times specifically for vitamin B3 after transforming into IL.	(92)

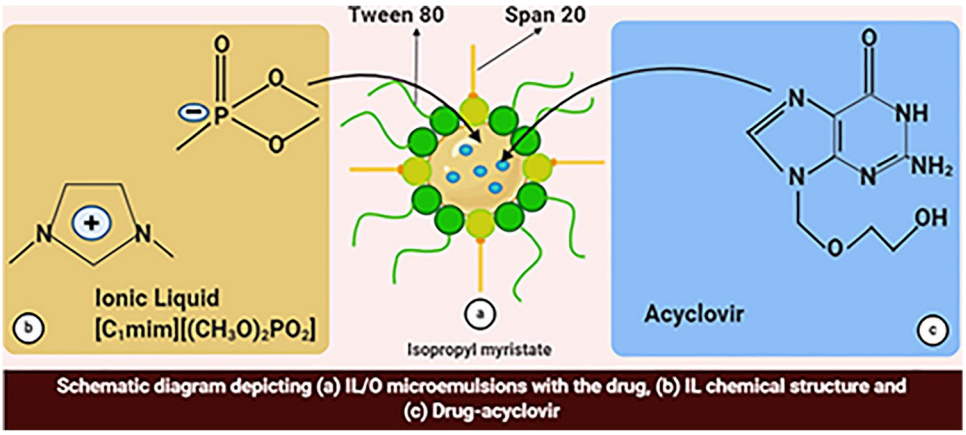

Fig. 3 Schematic diagram depicting **a** IL/O microemulsions with the drug, **b** IL chemical structure, and **c** drug-acyclovir

safety concerns and hampering the utilization of larger doses for compensating unfavorable pharmacokinetics (96).

These issues are also applicable to topical anticancer drugs like 5-fluorouracil (5-FU) used for treating melanoma. 5-FU is a water-soluble drug with low skin permeability. The available commercial formulation is a cream with a 5% drug. The formulation causes irritancy, redness, and pain. Different strategies have been tried for efficient topical 5-FU delivery like niosomes, microsponges, and patented colloid formulations, for enhancing the permeation, selective cytotoxicity, increased efficiency, and low risk of irritancy (96, 97). As discussed earlier, Goindi and coworkers prepared IL/O ME using ILs for efficiently solubilizing 5-FU (5). The use of IL-based technologies provides an exciting window of opportunity in the topical delivery arena for cancer treatment. Recently, other strategies like topical siRNA delivery in the skin utilizing ILs have also been explored for the treatment of cancer and skin diseases like psoriasis and lupus as discussed earlier (69, 89).

Tampucci and coworkers synthesized novel fatty acid protic ILs (FA-PILs) based on tetramethylguanidinium cation (HTMG) and various hydrophobic natural fatty acid carboxylates to act like surfactants and form micelles having a size range in nanometers. The drug used in the study was imiquimod (IMQ), an immunostimulant drug. The main aim of the study was to develop a pH-sensitive nano-drug delivery system for topical skin cancer therapy to selectively release the drug in the acidic microenvironment of tumor cells. Also, vitamin E TPGS and FA-PILs mixture in water was investigated for micelle formation to study the formation of potential novel micelles. FA-PILs-TPGS mixed micelles were found to be pH sensitive suggesting the release of IMQ by a pH-triggered mechanism. The micelle-based formulation was found to produce efficacious drug amounts in the skin after topical application as revealed by *in vitro* cutaneous permeation studies indicating a potential topical delivery system for skin cancer therapy (25).

Recently, a team of researchers reported an IL-based strategy for delivering immunomodulators to the skin. The model drugs used were IMQ and triamcinolone acetonide (TCA). The IL used in the study was CAGE. The IL was found to enhance the solubility of the immunomodulators and also the penetration into the deep layers of the skin compared to the commercial topical products. The IMQIL-based gel formulation showed 10 times better efficiency compared to the commercial 5% IMQ cream (100).

For the Topical Treatment of Pain

Many studies have shown the use of ILs for topical pain relief. As already discussed earlier, Mahamat Nor and coworkers reported piroxicam ionic liquid in oil nanoemulsions (IL/O) NEs using ILs (67). Park *et al.* prepared lidocaine-based IL utilizing ibuprofen as the counterion (73). Miwa and coworkers formulated an API-IL combining anionic etodolac and cationic counterion lidocaine (1:1 mol/mol) (72) and Moshikur *et al*. synthesized a novel API-IL using a biocompatible cation, *N*-methyl-2-pyrrolidonium, to form an API-IL with NSAID drug ibuprofen by using a neutral *N*-methyl-2-pyrrolidone (NMP) solvent (91).

As an Antibiotic and in Biofilm Control

There are reports available on the utilization of ILs in biofilm control and as an antibiotic for topical delivery. Pyridinium-based ILs and bialkylpyridinium derivatives were used as a topical treatment for the control of biofilm infections (101, 102). Literature highlights the use of choline-based ILs for the control of pathogenic biofilms. Particularly, choline geranate has shown effects against *Salmonella enterica* and *Pseudomonas aeruginosa* biofilms and has led to a more than 16-fold increase in the cefadroxil delivery to the deep skin layers. Further, the efficacy of the IL was ensured in a *P. aeruginosa* biofilm–infected wound model validating the IL use in enhancing topical delivery and antibiotic action (88).

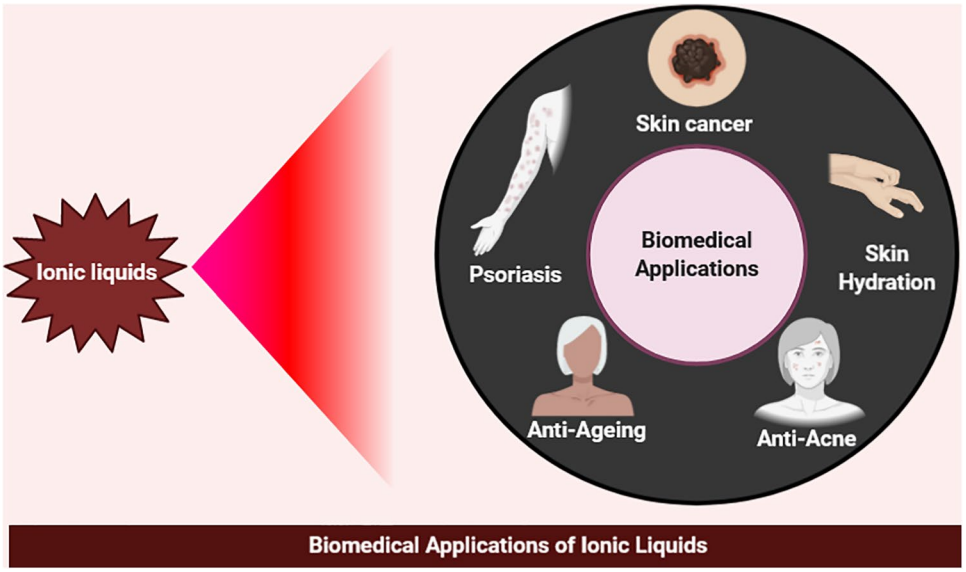

Fig. 4 Biomedical applications of ionic liquids

Applications in Cosmetics

Ionic liquids offer various uses in the field of cosmetics. These include antimicrobial applications in the treatment of acne, in treating skin dehydration by promoting skin moisture retention, and anti-aging applications. The biomedical applications are summarized in Fig. 4.

In Acne Treatment

A recent study reported inherently antimicrobial poly(ionic liquid)-based microneedle patches loaded with salicylic acid. These patches were formulated by photocrosslinking of 3 heptyl-1-vinylimidazoliumbromide with cross-linking agents like hydroxyethylmethacrylate and poly(ethyleneglycol) diacrylate. The patches showed better antimicrobial properties against *E coli*, *S. aureus*, and *P. acnes* and higher mechanical strength. The higher mechanical property of PIL-MN allowed for the maintenance of drug delivery for 7 days. This study presents a way for the treatment of acne and provides a way for the design of newer effective topical treatments (103).

For Skin Hydration

In a recent study, choline-based ILs were prepared and evaluated for their skin permeation enhancement efficiency and toxicity by *in vivo* and *in vitro* experiments. Findings revealed that the ILs were successful in boosting the skin permeation ability of hyaluronic acid, a natural skin moisturizing factor. Typically, choline citrate IL [Ch][Cit] showed enhancement in the *in vivo* and *in vitro* results. The ILs were not to be found to cause any irritation to the mouse skin. The inclusion of ILs in the formulation further improves the ability of ILs. The decreasing skin dehydration was evaluated by the trans-epidermal water loss (TEWL). As anticipated, the choline and malic acid IL [Ch][Mala] and [Ch][Cit] enhanced skin moisture and reduced the TEWL by enhancing the HA permeation in the skin. Hence, it was seen that ILs depicted a favorable vehicle for the topical application of hydrophilic macromolecules (104).

Anti-aging

Skin aging is a dynamic biological mechanism mediated by different exogenous and endogenous factors ultimately resulting not only in the alterations to the skin layers but also changes in the skin appearance affecting an individual's image and may lead to skin diseases like dermatitis or skin cancer. Research on aging is conducted for years. A study was conducted recently wherein a W/O emulsion was formulated using alpha-lipoic acid (ALA) using an ionic liquid strategy to enhance ALA solubility in the inner water phase. The emulsion showed good antiaging efficiency. Also, the ionic liquid strategy helped in achieving higher ALA solubilization. Diverse ILs showed varying skin retention controlled by the skin layers compared to the drug release among which ALA-triethanolamine showed an optimum affinity with SC as well as the epidermis and the dermis, whereas ALA-N-(2-Hydroxyethyl)piperidine and ALA-(2-Hydroxyethyl)pyrrolidine had an affinity towards either SC or VED respectively. This study is a favorable start for the strategies of ideal skin retention important in the topical formulation development, especially for hydrophilic drugs (105).

TOXICOLOGY ASPECTS AND ENVIRONMENTAL FATE OF ILs

Toxicity is an important factor when considering ILs. Older IL generations were unsuitable for medical applications (11). Studies on environmental toxicity and the fate of ILs have reported that the ILs utilized nowadays are toxic and the toxicity varies according to the organism and tropic levels. To get over this limitation, bioinspired ILs were developed and showed desired biodegradation and reduced toxicity profiles. Bioinspired ILs based on choline form the most studied ILs (11). Very few studies were reported supporting the IL toxicity in humans including enzymatic assays and cytotoxicity studies against cancer cell lines (breast, colonic, and cervical) and even on human bronchial epithelial lines (61). Extended chain lengths are reported to be further toxic. The impact of the anionic component is not so strong as the alkyl chain length except for the IL [(CF3SO2)2N], indicating the potential for ecotoxicological hazard. Other fluorinated anions are also reported as dangerous owing to their hydrolytically unstable nature.

The presence of a polar functional group in the alkyl chain is found to decrease the IL toxicity and also biodegradation efficiency. This indicated the chance of IL modification by combining specific functional groups to IL structure leading to an environment-friendly product. This emphasizes the need to minimize toxicity and maximize biodegradability (106). Luckily, in the last few years, nontoxic ILs are made by choosing biocompatible organic cations and inorganic anions. Also, by modifying the side chains in the IL cations, biocompatible ILs could be formed. In the recent literature, the addition of ether groups in the ester side chain in the IL cation was found to decrease the toxicity in comparison to the alkyl derivatives (9). With the increasing alkyl chain length or lipophilicity, the degradation rate, as well as the toxicity, was enhanced. Also among the cations, pyridinium cation is reported to be more environmentally friendly than the imidazolium from both toxicology and microbial degradation perspectives (106).

Skin is made of keratinocytes and fibroblasts. Hwang *et al*. used human keratinocytes and fibroblast cell lines as a model system to assess skin toxicity. Results showed that the keratinocyte cell line was more vulnerable compared to the fibroblast cell line. This was similar to the results seen with the 3D human skin model, Keraskin-FTTM. In conclusion, it was seen that the ionic liquids can cause skin toxicity to which lipophilicity could be a significant contributor. The toxicity of ILs to the skin is manifested as cell necrosis and the primary target of IL used in the study was keratinocytes and the epidermal layer (107). The IL permeation is high with very little cytotoxicity, meeting the criteria of ideal permeation enhancers (11). Numerous excipients like dimethylsulfoxide and nonionic surfactants such as polysorbate 80 show toxicity identical to ILs. Therefore IL toxicity does not impede their use as solvents (9).

FUTURE PROSPECTS

ILs bear a wide number of options in their design and ILs are a developing field in topical drug delivery systems and in pharmaceuticals as described in this review. ILs display underexplored and promising candidates with immense opportunities.

Many APIs in the developed pharmaceuticals fail in phase III clinical trials owing to the problems associated with the solid form, lower bioavailability, and poor water solubility of the API. Many strategies are explored to increase the FDA's passing rate for solubilizing poorly water-soluble APIs and to increase the drug efficacy. API-ILs can be the main interest. FDA has approved numerous pharmaceuticals and has led to drug approvals in the last 2 years. API ILs are very similar to the already approved products. This strategy could be beneficial for the API owing to the enhanced solubility and bioavailability and can also result in the fast track protocol for the API IL entry into the market because of the resemblance with the already existing drugs. The newer API ILs would help to ensure the drug permeation through the skin barrier as well as better water solubility and increased stability. The clinical utilization of IL technology remains limited. The only clinical study which was conducted was on the ionic liquid analgesic patch from MEDRx Co. Ltd., a Japanese pharmaceutical company, and IL Pharma Inc., on a patch called Etodolac with lidocaine for the treatment of back pain and has completed phase III clinical trials. The results have displayed the safety and efficacy of the ILs incorporated in the patch (108). There is still a need to develop techniques to prove the purity of ILs. ILs can be recycled and are emerging safe and greener alternatives that could be used in the solvation of a variety of drugs.

CONCLUSION

The topical route for drug delivery holds numerous advantages but the effective permeation of the drugs is still uncertain due to the barrier function of the stratum corneum (109). This review describes the beneficial utility of ILs in improving topical drug delivery. ILs act as a potential green alternative to the organic liquids employed in the formulation. Several studies have been reported on the ability of ILs in the improvement of topical drug delivery. ILs help in overcoming issues like lower drug solubility and decreased stability of several topical delivery systems. Also, ILs can be

synergistically combined with the already-existing chemical permeation enhancers without any risk of toxicity owing to their versatility (11). The only limiting feature while considering ILs is their toxicity. Combining ILs with other formulation strategies, the topical permeation is seen to be potentially enhanced (110).

Acknowledgements The authors are thankful to (i) All India Council for Technical Education (AICTE), Government of India, for providing National Doctoral Fellowship to Prerana D. Navti and Bharath Singh Padya, and (ii) Manipal Academy of Higher Education (MAHE), Manipal, for providing Dr. T.M.A Pai Doctoral Fellowship to Ajinkya N. Nikam and Postdoctoral Research Fellowship to Dr. Abhijeet Pandey. The authors thank biorender.com for providing a platform for creating images. The authors acknowledge Manipal College of Pharmaceutical Sciences, MAHE, Manipal, for providing the necessary facilities.

Author Contribution Prerana D. Navti: acquisition and interpretation of previous data, drafting of the article, and revision of the article.

Abhijeet Pandey: conception or design of the work.

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Bharath Singh Padya: acquisition and interpretation of previous data.

Guruprasad Kalthur: critical revision of the article.

Kunnatur B. Koteshwara: conception or design of the work, revision of the article.

Srinivas Mutalik: conception or design of the work, drafting and revision of the article.

Funding Open access funding provided by Manipal Academy of Higher Education, Manipal Prerana D Navti and Bharath Singh Padya received National Doctoral Fellowship from All India Council for Technical Education (AICTE), Government of India. Ajinkya N. Nikam and Dr. Abhijeet Pandey received Dr. T.M.A Pai Doctoral Fellowship to and Postdoctoral Research Fellowship, respectively, from Manipal Academy of Higher Education (MAHE), Manipal.

Declarations

Conflict of Interest The authors declare no competing interests.

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