HHS Public Access

Author manuscript

Adv Drug Deliv Rev. Author manuscript; available in PMC 2024 January 13.

Published in final edited form as:

Adv Drug Deliv Rev. 2024 January ; 204: 115157. doi:10.1016/j.addr.2023.115157.

Potentials of ionic liquids to overcome physical and biological barriers

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Abstract

Over the last decades, ionic liquids (IL) have shown great potential in non-invasive delivery starting from synthetic small molecules to biological large molecules. ILs are emerging as a particular class of drug delivery systems due to their unique physiochemical properties, simple surface modification, and functionalization. These features of IL help achieve specific design principles that are essential for a non-invasive drug delivery system. In this review, we have discussed IL and their applications in non-invasive drug delivery systems. We evaluated state-of-the-art development and advances of IL aiming to mitigate the biological and physical barriers to improve transdermal and oral delivery, summarized in this review. We also provided an overview of the various factors determining the systemic transportation of IL-based formulation. Additionally, we have emphasized how the ILs facilitate the transportation of therapeutic molecules by overcoming biological barriers.

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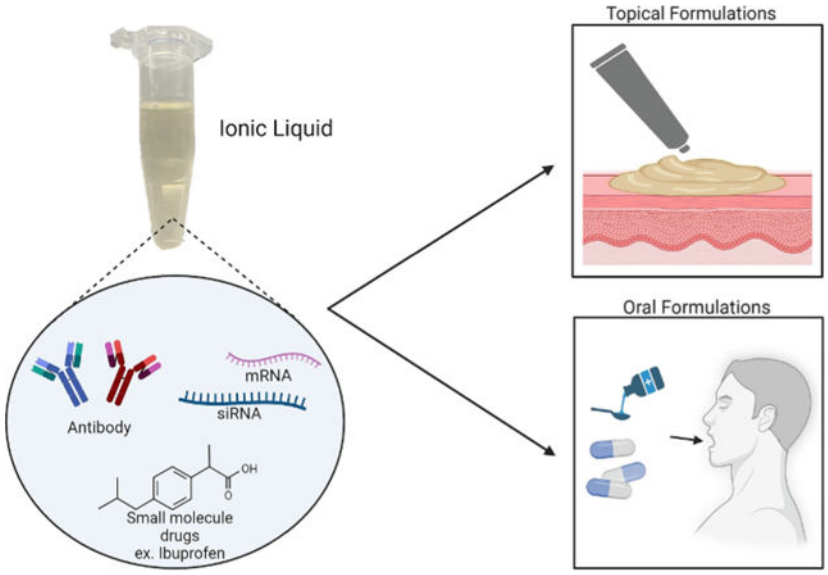
Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

GRAPHICAL ABSTRACT



Keywords

Ionic liquid; Biological barrier; Noninvasive delivery; Systemic delivery; Local delivery

1. Introduction

Non-invasive drug delivery is methods of administering treatments without causing pain while also maintaining therapeutic efficiency [1]. Typically, this refers to drug delivery systems that do not require injections or the use of invasive needles to deliver treatments. Non-invasive delivery methods include transdermal or topical applications and oral administration which are the most studied but also include nasal and ocular routes as alternatives to intravenous injections. Non-invasive drug delivery is advantageous since it increases patient compliance thus enabling increased therapeutic effect for many local diseases besides increasing acceptance for many patients.

Oral and topical delivery are two of the most common noninvasive delivery methods that are highly preferred by patients. However, physical and biological barriers of these two routes of administration limit their effectiveness as these routes typically suffer from low bioavailability, specificity, and circulation half-life. [2,3]. The gastrointestinal tract poses the greatest risk to treatments delivered orally due to the low pH of the stomach acid, severely limiting drug absorption. Similarly, the lipid bilayer makeup of the skin hinders drug absorption. Not only this, oral and transdermal routes lack specificity and targetability which can lead to toxicity in the body due to their usual preparation methods. Numerous conventional formulation methodologies require the utilization of organic solvents, which can also pose toxicity risks to patients [4,5]. As a result, the innovation of targeted drug delivery systems tailored to treat these diseases presents a formidable challenge to the pharmaceutical sector. Several innovative formulations and drug delivery systems have been

devised to overcome this challenge without compromising the safety and efficacy of the therapeutic modalities.

Developing drug delivery systems capable of enhancing both drug efficacy and bioavailability remains challenging in the pursuit of optimizing therapeutic outcomes [6]. Various formulation strategies using nanocarriers such as lipid nanoparticles [7], polymeric nanoparticles [8], metal nanoparticles [9], graphene-based nanomaterials [10,11], microemulsion [12,13], and nanocrystals [14], are continuously being explored to facilitate the targeted delivery of inadequately water-soluble therapeutic agents, but are also limited by use of organic solvents such as dichloromethane, dimethyl sulfoxide, acetonitrile, acetone, ethanol, hexane, and ethyl acetate during development which can pose safety risks. Ionic liquids (IL) are emerging as an excellent tool to mitigate some of these issues due to their unique physiochemical properties [15]. In recent years, ILs have been the subject of many reviews for biomedical application extensively discussing the history of the various generations of IL and the benefits of their uses, however, a focus on the recent studies demonstrating those successes is useful in continuing the advancement of IL research.

Due to the current limitations of conventional formulation methods, ILs are emerging as effective alternatives to enhance drug solubility, increase bioavailability, and perform as penetration enhancers by overcoming tissue barriers [15]. Multiple great reviews have extensively discussed the history, development, 1st, 2nd, and 3rd generations, and mechanisms of IL [16–18]. Briefly, ILs are chemical compounds composed of various combinations of cations and anions whose salt structure impacts their physiochemical properties [19]. The appeal of ILs stems from their non-volatile nature, high thermal and chemical stability, solubility of a wide range of insoluble compounds, and good water miscibility [19–21]. Deep eutectic solvents (DES) are a subclass of ILs that have gained attention due to their biodegradability and nontoxicity. DES differs from IL in multiple ways which are greatly explained by Plotka-Wasylka et al [22]. The tunable physiochemical properties make ILs a versatile compound allowing formulation synthesis and optimization to fit the specific design requirements. Throughout this review, we highlight various works using IL that take advantage of the unique qualities of ILs and their various compositions and discuss their potential application in topical and oral non-invasive delivery methods. Over the next sections, we analyze commonly studied ILs such as CAGE and more recently developed ILs using amino acid esters, phenolic acids, and drug based IL.

2. Ionic liquid mediated topical delivery

2.1. Barriers of the skin

Topical drug delivery (TDD) refers administering therapeutic treatments directly onto the skin [23]. TDD offers many advantages, particularly as a non-invasive alternative to injectables. The skin also has a large surface area thus allowing for multiple places of application and eliminates the first-pass effect of clearance through the liver thereby increasing drug accumulation and bioavailability [24]. However, the skin acts as a protective barrier for the body; particularly the stratum corneum (SC) which is densely packed with keratinocytes. The skin consists of three main layers: the epidermis, the dermis, and the subcutaneous tissue as shown in Fig. 3. The outermost layer of the epidermis, the stratum

corneum, is the main barrier to drug permeation through the skin [25]. The SC is composed of keratinized cells embedded in a lipid matrix, forming a brick-and-mortar structure [26]. The thickness, hydration, lipid composition, and integrity of the SC vary depending on the skin site, and pathological conditions of the skin [27,28]. These variations affect the drug diffusion and partitioning through the SC. Drug, formulation, application, and anatomical related factors affecting systemic transdermal transportation are important to consider during the development and optimization of transdermal drug delivery systems. These factors can influence the efficacy, safety, and patient compliance of transdermal therapy.

The physiochemical properties and pharmacokinetics of the drug determine how the drug interacts with its surrounding environment to penetrate and reach the targeted area. These properties include molecular weight, lipophilicity, polarity, charge, solubility, melting point, and stability [29]. Generally, drugs with low molecular weight (<500 Da), high lipophilicity (log P > 1.5), moderate polarity, and low melting point are suitable for transdermal delivery as these factors increase permeation and penetration [30,31]. The pharmacokinetics of a drug including dose, potency, clearance, half-life, bioavailability, and therapeutic window, determine the amount and duration of drug delivery required to achieve therapeutic effects [32]. Studies show that IL can overcome these existing barriers, for instance.

The composition of the IL formulation such as chemical structure, examples shown in Fig. 1, impact how it will interact with the surrounding tissue. The type of formulation can be classified into passive or active topical delivery systems. Passive systems rely on diffusion and partitioning of the drug across the SC, while active systems use external energy sources such as electric current (iontophoresis), ultrasound (sonophoresis), or microneedles to enhance drug permeation [33–35]. The composition and structure of the formulation affect the solubility, stability, release, and permeation of the drug. These factors include vehicle type (e.g., gel, emulsion, patch) [36], excipients (e.g., solvents, preservatives, penetration enhancers) [37,38], and physical characteristics (e.g., size, shape, thickness) [39]. In Fig. 1, we have shown some of the key analogs that have been considered for preparing ILs and investigated their feasibility for topical delivery.

As mentioned above, the stratum corneum is attributed as the toughest barrier to penetration and this is due to its composition of lipids, mainly ceramides, fatty acids, and cholesterol making up a complex bilayer membrane. Not only this, the SC and stratum granulosum can adapt to outside stimuli to prevent penetration making it difficult to pass through these layers [40]. The multilayered epidermis functions between corneocyte organization and the complex lipid matrix organization along with various other biological aspects. Corneocytes are clustered together with various groupings of lipids connected in between [41]. The lipids, most of which are non-polar and hydrophobic, are still slightly hydrophilic due to the lipid tail can form hydrogen bonds [42]. The structural organization of the SC with corneocytes interlinked with these lipids is the first and main barrier for transdermal delivery methods including free, drug loaded, and nanoparticles. Lipid organization is integral to TDD as most permeation happens through the lipid domain. The lipids of the SC can be classified as intercellular lipids since the organization is found both extracellularly and intracellularly, uncommon for lipid structures throughout the rest of the body but adding to the resistance of penetration [43].

While the SC is considered hydrophobic, the chemical makeup of the layer includes proteins, a small percentage of which are water-soluble [44]. Also, the deeper layers closer to the stratum granulosum contain cells of higher water content contributing to hydrophilicity [45]. This balance between hydrophobic on the outermost surface and less so towards the deeper layers can be considered an added defense against hydrophobic particles penetrating the skin. Considering the varying compositions from the stratum corneum to the stratum granulosum, pH is also variable, another consideration that needs to be kept in mind when developing new topical formulations. The pH of SC can range between 4.5 and 5.5 while layers closer to the granulosum can range from 6.8 to 7 leading any formulation passing through the skin to encounter different pH gradients [46]. pH also regulates multiple enzymes for example acid lipases, and phospholipases, responsible for degrading hydrophobic molecules. Activated keratinocytes are also responsible for the production of acid hydrolase into the extracellular matrix which helps protect the skin from invaders [47].

2.2. Using IL to enhance permeation

Penetration through the skin is the greatest challenge to delivering treatments topically. ILs can change the structure of the skin to physically interact with the lipids increasing penetration through the epidermis and into the dermis. In an effort to develop a topical insulin delivery method, Tanner et. al. analyzed various ratios of choline bicarbonate to geranic acid (CAGE) to understand the importance that proper ratio of anion to cation has on the penetration potential of ILs. Not only did they find that CAGE in a 1:2 ratio (one choline molecule to two gernate molecules) has the greatest penetration ability, but it was also able to lower blood sugar levels consistently over 12 h, as compared to subcutaneous injection lowering blood sugar for only 4 h. In Fig. 2 the images demonstrate that CAGE with a 1:2 ratio had the greatest penetration into the SC through to the dermal layer, Fig. 2a. In Fig. 2 a, d, and e 2:1 CAGE, 1:1 CAGE, and PBS respectively, had almost ability to penetrate the dermal layers of the skin. Geranic acid alone was not able to penetrate even the SC while choline bicarbonate alone showed very little ability to permeate the skin [48]. A recent study also demonstrates that a CAGE IL can transdermally deliver nanosensors to the blood vessel enabling thrombosis detection noninvasively [49]. Similarly, the same group has demonstrated that CAGE IL can facilitate self-emulsification and subcutaneously deliver apomorphine therapeutic for Parkinson’s disease therapy more efficiently [50]. The ability of CAGE 1:2 to have the greatest penetration ability is due to higher geranic acid content. This allows the IL to extract more lipids from the membrane allowing the IL to penetrate the areas of lipid extraction. The ratios with higher choline content increased the viscosity of the IL which hinders penetration into the skin barrier. CAGE IL has the ability restructure the SC and penetrate through the epidermis absorption of phospholipids composing the membrane through interactions with CH_3 and CH_2 groups [51].

Hattori et. al. suggested that CAGE is a biocompatible and effective transdermal delivery system for nobiletin (NOB) and other flavonoids with similar properties. They explored the use of ILs as transdermal delivery vehicles for NOB, a flavonoid with various physiological effects but poor water solubility and oral bioavailability. The authors used choline and geranic acid (CAGE) as the IL, which can form multipoint hydrogen bonds with NOB

and enhance its solubility 450 times higher compared to water. The authors performed in vitro and in vivo experiments to evaluate the transdermal delivery of NOB using CAGE. They found that CAGE increased the permeation of NOB in rat skin compared to other penetration enhancers and improved the bioavailability significantly greater than the drug in oral form [52].

Similarly, amino acid ester-based ILs (AAE-ILs) are novel chemical penetration enhancers studied for enhancing topical delivery through lipid extraction like the CAGE mechanism. Zheng et. al. reported on the development of novel ILs based on amino acid esters as skin permeation enhancers for transdermal drug delivery. They screened 15 methyl amino acid ester hydrochlorides and determined three, [GlyC1]Cl, [L-ProC1]Cl, and [L-LeuC1]Cl would be used for further modification with 8 and 12-length carbon chains. Penetration of 5-Fluorouracil (5-Fu) and Hydrocortisone (HC) was increased by the amino acid-based IL, through rat skin. They investigated the permeation mechanisms by various analytical methods and found that the IL extracts the lipids from the intracellular barrier, which were dependent on the dosage and time [53]. In Fig. 3 we can see the effects that dosage and incubation time had on the skin. From the 1% dosing at 4 h, thickening of the skin is observed in Fig. 3b and 3f. When the dose is increased to 5% for only one hour the epidermal layers begin to loosen Fig. 3c and 3 g, however, increasing incubation time to 4 h lipid extraction is observed Fig. 3d and 3 h.

Besides choline and gerante IL, phenolic acids are anions that can be combined with cationic choline to create ILs with higher water solubility, antioxidant, and anti-inflammatory properties. Phenolic acids have been investigated for their potential use in bacterial nanocellulose membranes for topical treatments. Morais et al investigated three phenolic acids such as ellagate, gallate, and caffeate in combination with cholinium to investigate their use with bacterial nanocellulose structures. The researchers constructed bacterial cellulose membranes and dissolved them in the three IL combinations (BC-IL). The swelling rates of each membrane was measured as this is directly related to their solubility. They found that the membrane swelling of the IL loaded membranes were higher than the membrane alone due to the hydrophilic nature of the IL and aided in preventing collapse of 3D structure during dehydration. Antioxidant activity of the BC-ILs were also studied and found that choline-gallate and choline-caffeate IL maintained an 80% antioxidant activity in both wet and dry states which allowed for sustained dissolution of the IL. The skin permeation tests revealed choline-galleate and choline caffeate results in slow and sustained drug release with burst effect in the first hour and sustained for 5 h from the bacterial membranes. They have also showed that phenolic acids possess the ability for use in biological membranes and have the potential for use in topic treatments due to their water solubility, sustained release, and prolonged permeation [55].

More recently, phenolic acids ILs have demonstrated the ability for their use in treating skin diseases. One example by Xiao et al, choline and ferulic acid IL (CF-IL) loaded with finasteride has shown potential of treating androgenetic alopecia. Finasteride inhibits the conversion of testosterone to DHT and is prescribed orally, however, it produces multiple systemic adverse effects therefore topical treatments are expected to reduce these side effects. The authors demonstrated that the addition of ferulic acid greatly increased the

solubility of finasteride. The enhanced solubility also increased the retention time of the drug in the skin while also increasing the permeation by disrupting the stratum corneum barrier compared to suspensions. In this case specifically, CF-IL promotes transdermal delivery due to their ability of lipids and keratin in the skin disruption. It was demonstrated that CF-IL is suggested to change the alpha helix of keratin to a coil which increases the intracellular space due to corneocyte shrinkage. The increased solubility and permeability lead to higher retention of finasteride within the hair follicle thus establishing CF-IL had the best rate of hair regrowth compared to suspensions of ferulic acid and finasteride alone [56].

2.3. Using IL as solubilizers

It has been shown that ILs can effectively dissolve pharmaceutical agents that are insoluble in water but soluble in organic solvents [57–60]. According to McCrary and co-workers, drug solubility is influenced by the ratio of cation to anion due to its ability to break hydrogen bonding [61]. The cation portion does not have a significant impact on the drug dissolution since the anion is responsible for creating the hydrogen bonding. Interestingly, this study found that ILs that were hydrophilic were able to dissolve hydrophobic drugs however, when the anion content of hydrophobic IL was not in optimal ratio, the IL were not able to dissolve hydrophobic drugs. [60–64].

Azevedo *et. al.* [190] analyzed 3,4-methylenedioxy benzoyl-2-thienylhydrazone (LASSBio-294) a drug with cardioactive properties and low water solubility. They found that the good solubility of the drug was attributed to CH_3COO anion in the imidazolium IL. However, the combination of the C4mim anion with two different anions resulted in low dissolution which they determined was due to the complex structure of the drug being incompatible with the bulky nature of the of the anion. [59]. These results indicate the importance not only of the ratio of cation to anion but the necessity of compatible ILs with the drug being used. The formation of hydrogen bonding of IL is also essential to the functionality of the formulation demonstrating the effectiveness the anion portion of the IL has to the solubility properties.

Recently, Ahmed et al used choline acetate IL as a plasticizer for collagen PVA films with antioxidant properties. Interestingly, they noticed the solubility of ciprofloxacin was lower with choline acetate IL compared to glycerol. The explanation for this finding was that choline acetate increases hydrogen bonding with biopolymers leaving less ability to hydrogen bond with water. Despite this, collagen PVA films with choline acetate IL as a plasticizer showed to have great antioxidant properties whereas films with glycerol had no antioxidant effect, which the authors mentioned is necessary for wound healing. Also, incorporation of choline acetate IL increases the roughness of the films which enhances their adhesive properties, concluding IL based biofilms can be further developed for biomedical applications [65].

Besides overcoming poor solubility with IL, they can also act as a delivery vehicle for toxic drugs and prevent toxicity while increasing transdermal penetration and therapeutic effect. For example, navitoclax (NAVI) is a hydrophobic chemotherapeutic drug that is currently being researched for its anti-cancer and anti-fibrotic activity due to its ability to induce apoptosis by inhibiting BCL-2/BCL-xL. However, since NAVI is known to induce

thrombocytopenia in the blood the need for an effective carrier to deliver the drug to the site of disease will increase the treatment efficacy while limiting toxicity. In our lab, we have developed an IL formulation of choline and octanoic acid (COA) to dissolve NAVI as a topical agent to treat nonmalignant melanoma and skin fibrosis. COA not only effectively increased penetration of NAVI to the dermal layer and retained it over an extended period, but it did also not reach systemic circulation and prevented cytotoxic effects. Also, the IL formulation effectively delivered the drug to the diseased sites of both melanoma and skin fibrosis and induced apoptosis of the disease cells without causing skin irritation [66,67]. Another interesting development into the investigation of ILs is their use for transforming drugs into an IL based treatment. Using ILs in these ways improve drug solubility and skin permeation. A recent example demonstrated by Tang et al. where the solubility and physiochemical properties were tested with naproxen based IL compared to naproxen and naproxen sodium salt described as naproxen anion, choline naproxen ([Ch][Nap]), tetrade-cyldimethylbenzyl ammonium naproxen ([Ben][Nap]), and 1-octyl-3-methylimidazole naproxen ([Omim][Nap]). The solubility of each one was tested in both water and ethanol at 25 and 37 °C. In water, the solubility of all increased with temperature, however it was demonstrated that naproxen IL [Ch][Nap] had the highest solubility of each with naproxen alone having the lowest. In ethanol [Ch][Nap] had a similar solubility as in water and demonstrated low toxicity. The polarity of solvent (water and ethanol) is necessary property to dissolve the solute, meaning the higher the polarity the greater the ability to dissolve the solute. The polarity of water and hydrophilic nature of the naproxen based IL allowed for greater dissolution of [Ch][Nap] [68].

2.4. Using IL for small molecule systems

Small molecule ILs are simple mixtures of drugs and ILs that can enhance drug solubilization and improve drug permeability. Small molecule ILs can be prepared by mixing drugs and ILs in a suitable solvent or by direct synthesis of drug-IL complexes. Simplistic formulation, high drug loading capacity, and good biocompatibility of small molecule IL make them good options for IL formulation development; however, they are also limited by low stability, high viscosity, and potential toxicity. IL has also shown emerging potential in the topical delivery of immunomodulators. For instance, Zhao et. al. has demonstrated that a CAGE IL can enhance topical delivery of immunomodulators-imiquimod (IMQ) and triamcinolone acetonide (TCA) via skin and the transportation rate as much as 50%, which is 10 fold higher than commercially available IMQ formulation [69].

IL-based microemulsions form thermodynamically stable nano-sized droplets with high drug-loading capacity by combining oil, water, surfactant, and IL. A conventional microemulsion can be converted into an IL-based microemulsion by simply combining ILs within the formulation or by replacing one or more components with ILs. Microemulsions-based ILs are advantageous due to their high solubilization capacity, low interfacial tension, and adjustable droplet size. However, they are also associated with multiple drawbacks, including their complex preparation, low stability, and potential for irritation.

For instance, Islam et. al. developed IL-in-oil microemulsion formulations (MEFs) to delivery insulin through the transdermal route using choline-based fatty acids. Insulin was

dissolved by the fatty acid IL and then incorporated into MEF. They stated that lipid fluidization the MEF enhanced penetration of insulin. Low dosing of insulin within the MEF was shown to decrease glucose in the blood by 56% and maintained a higher systemic circulation half-life compared to standard injection [70].

Zhang *et. al.* represented a novel IL-based microemulsion system with a deep eutectic compound to deliver poor water-soluble artemisinin, an antimalarial drug. The microemulsion, which consists of 1-hydroxyethyl-3-methylimidazolium chloride as the IL, lidocaine ibuprofen as the oil phase, and water as the aqueous phase, increased the solubility of artemisinin from 0.02 mg/mL to 0.95 mg/mL. The in-vitro penetration showed a 3-fold increase of the drug transdermally by the microemulsion system. Studying the mechanism of action of the microemulsion on the stratum corneum, the main barrier of the skin, using various analytical techniques, they found that the microemulsion disrupts the regular arrangement of keratin in the stratum corneum facilitating the penetration of artemisinin. Furthermore, the micro-emulsion containing lidocaine ibuprofen, a deep eutectic compound showed anti-inflammatory and analgesic effects [71].

Drugs can be solubilized and transported more efficiently through IL-mediated micelles, self-assembled aggregates of amphiphilic molecules containing ILs in their cores and shells. Micelles made of covalently attached ILs to amphiphilic molecules can be prepared by mixing amphiphilic molecules with ILs. Aside from high drug loading capacity and low critical micelle concentration, IL-mediated micelles are stable and stimuli-responsive. Micelles derived from ILs do, however, have certain limitations, including a complex synthesis process, a slow rate of drug release, and potential toxicity.

The treatment of various cancers requires the use of cytotoxic chemotherapy agents such as paclitaxel (PTX). Its poor solubility in water limits its application. To enhance the efficacy of PTX, researchers have developed drug-polymer formulations, emulsions, micelles, nanoparticles, and liposomes [72–75]. A micelle-based formulation (MF), with its special polymer structure, is very promising for delivering low-water-soluble drugs. According to Korban *et. al.*, they developed a new MF with choline oleate surface active IL and span 20 both of which are biocompatible surfactants shown in Fig. 4. With a SAIL-based MF nanocarrier, PTX was significantly more solubilized than Tween-80-based MF. PTX is significantly more readily absorbed into micelles believed to be due to chemical interactions between PTX and SAIL[Cho] [Ole]. PTX-loaded MF was demonstrated to form spherical micelles between 8.7 and 25.3 nm through DLS and TEM investigations and to have excellent physicochemical stability Fig. 4A. Interestingly, SAIL-based MF delivered substantially better effects than the control formulation, achieving values of 23.47 topical and 89.16 transdermal $\mu g/cm^2$ while also maintaining nontoxicity (Fig. 4C) and demonstrating good long term stability over 4 months (Fig. 4B) [76].

Incorporation of various forms of IL in topical formulation development have the potential to overcome skin barrier, increase drug solubility, and even possess antioxidant and anti-inflammatory effects. A summary of the various forms of ILs can be seen in Table 1, showing their compositions and application feature.

3. Ionic liquid mediated oral delivery

3.1. GI track barriers

Oral delivery is the most widely used route of administration due to ease of use and high patient compliance. Due to the development of controlled-release tablets dosing frequency is also advantageous. Large molecules such as antibodies, mRNA, siRNA, or peptides suffer from low bioavaility due to their poor absorption into intestinal epithelium. Drug transportation is hindered by epithelial cells in which drug delivery systems overcome this obstacle by facilitating drug transport via passive or active diffusion [77]. Intestinal mucus is another physical barrier. It is composed of glycosylated proteins that may trap drugs before interaction with intestinal epithelium. However, the mucus barrier lining within the GI tract poses the delivery greatest challenge to oral delivery. Formulations with ability to modulate the mucus membrane have been successful at enhancing intestinal absorption [77]. For example, choline geranate and choline glycolate (CGLY) IL have shown improvement of oral transportation of insulin and immunoglobulin (IgG) by modulating the mucus layer. Along the same line, another IL composed of Choline and maleic acid (CMLC) has shown significant enhancement of diffusion (about 4 folds) of 4 kDa cationic dextran via mucin solution. The ILs have shown to to reduce mucus viscosity without compromising the native mucus gel structure.

Other physical barriers are chemical entities in GI tract such as bile salt, gastric acids, and proteases. The microbiome in our GI tract also affects absorption of drugs. Many factors affect the absorption and systemic circulation of orally administered drugs. Here, we describe some of the main factors that affect the absorption and systemic circulation of drugs from the gastrointestinal tract summarized in Fig. 5A. An IL composed of choline and glycolate (CGLY), has demonstrated their ability to oral delivery and transportation of antibodies [78]. The CGLY IL has not only shown their ability to protect the antibody from the harsh gastric environment but their ability to overcome barriers within intestine and thereby increase their transportation to the systemic circulation significantly. Additionally, CAGE IL shows that the formulation has a significant impact and effect on glucagon-like peptide-1 (GLP-1). Besides CAGE enhance oral transportation GLP1, the IL improve stability and half-life of this peptide-based therapeutic, significantly [79].

The stability of a drug molecule in the gastrointestinal tract plays a pivotal role in its absorption. The acidic and enzymatic conditions of the gastrointestinal tract can exert detrimental effects on drug molecules, leading to their degradation and subsequent loss of bioactivity or reduced bioavailability. To counteract these challenges, various strategies such as chemical modification or pro-drug approaches can be employed to safeguard drug molecules from degradation, thereby enhancing their stability and facilitating optimal absorption. These protective measures aim to increase the overall effectiveness of drug delivery systems and promote successful therapeutic outcomes [80,81].

The formulation of an orally administered drug significantly influences its absorption within the gastrointestinal tract. Several factors, including molecular size of the drug, dissolution rate, and the presence and nature of excipients, can impact the drug’s solubility and subsequent absorption into the systemic circulation, directly influencing its bioavailability.

Additionally, the selection and inclusion of appropriate excipients in the formulation can further optimize the drug's solubility and absorption, ultimately enhancing its therapeutic efficacy [82]. Modifications in drug formulation have demonstrated the potential to enhance the absorption of orally administered drugs within the gastrointestinal tract. Various methodologies, including prodrug formation [83], solid dispersions [84], self-emulsifying drug delivery systems [85], nanoparticles [86], liposomes [87], modified release systems, and pH-sensitive formulations [88], have been extensively investigated to improve crucial aspects such as drug solubility, stability, permeability, and bioavailability. Among these approaches, IL have emerged as promising drug delivery systems and formulations [15]. These innovative formulations play a substantial role in optimizing drug dissolution, protecting drugs from degradation, improving drug absorption, and ultimately enhancing therapeutic outcomes. The ongoing exploration of advanced drug delivery systems and formulations holds great promise for overcoming the challenges associated with oral drug delivery and maximizing therapeutic efficacy.

Drug absorption within the gastrointestinal tract is influenced by several physiological factors. The pH conditions prevailing in different regions of the gastrointestinal tract, including the stomach, small intestine, and colon, significantly impact drug solubility and dissolution. The presence of digestive enzymes within the gastrointestinal lumen can also influence drug metabolism and degradation, affecting drug availability for absorption. Additionally, the presence of food in the stomach and small intestine can alter drug absorption kinetics and bioavailability, as it may impact drug dissolution, gastric emptying, and intestinal motility. Understanding and considering these physiological factors are crucial for optimizing oral drug delivery strategies and ensuring the desired therapeutic outcomes.

Gastroprotective formulations are designed to extend the residence time of a drug in the gastrointestinal tract, specifically in the stomach or upper intestine [89,90]. By extending contact time, these formulations can improve absorption, especially of drugs that are poorly permeable or undergo rapid metabolism. Technologies such as floating systems [91], mucoadhesive formulations [92], or controlled-release systems [93], can be used to increase the retention of a drug in the stomach. Besides, oral administration, CAGE IL has shown their potential of buccal mucosa delivery of insulin as reported by Vaidya et. al. A sandwich-like composition made with CAGE and a polymeric patch was prepared to load insulin within the core of the patch. Pharmacokinetics and dynamics were investigated using a rodent animal model and they observed around 50% reduction of blood glucose level [94].

It is essential to acknowledge that each drug possesses unique characteristics and can be influenced by multiple factors that impact the absorption of orally administered drugs. These factors may act individually or in combination, affecting the overall drug absorption process. An in-depth understanding of these factors is crucial for optimizing strategies aimed at promoting effective oral drug absorption and facilitating systemic circulation. This understanding becomes particularly significant in the context of IL-mediated oral drug delivery systems, as briefly mentioned earlier, where a comprehensive understanding of the biological and physical factors involved is paramount. Below, we discuss in depth the biological and physical factors that influence the systemic absorption of drugs by utilizing

IL-mediated drug delivery systems specifically designed for oral administration of drugs of which IL structures are seen in Fig. 6.

3.2. Using IL as solubilizers

The physicochemical properties such as solubility, stability, and molecular weight of a drug have a significant impact on the absorption of orally administered drugs in the body [95,96]. Lipophilicity of a drug refers to its affinity for lipids and is an important factor in oral absorption. Lipophilic drugs tend to diffuse more readily and passively through lipid-rich GI cell membranes than hydrophilic drugs [97]. The permeability of a drug through the cell membranes of the gastrointestinal tract is influenced by its molecular weight. In general, smaller, and lighter molecules exhibit higher permeability due to their ability to traverse the tight junctions present in the gastrointestinal epithelium. This phenomenon can be attributed to the ease with which smaller molecules can navigate through the narrow gaps between cells, facilitating their absorption and bioavailability [98]. Also, by default, drugs must be dissolved in digestive fluids to be absorbed into the body. As the size of a molecule increases, so does the resistance to its absorption, which can impede or restrict its rate of penetration through cell membranes. Larger molecules may encounter challenges in traversing the tight junctions and other transport mechanisms in the gastrointestinal tract, thereby potentially limiting their absorption. The solubility of a drug in the digestive fluids is a critical factor in determining its bioavailability and subsequent therapeutic efficacy [99]. Techniques such as reducing particle size or using solubilizing agents can improve solubility and increase drug absorption [100].

Banerjee et. al. evaluated CAGE as a solubilizing agent for oral insulin delivery. They found CAGE used as a solvent for long term insulin storage at room temperature and 4 °C over 4 months did not affect the biological activity of insulin. While CAGE has previously been shown to be an effective solubilizing agent, the group also highlighted some interesting properties when analyzing concentration of two dyes, Lucifer yellow a hydrophilic drug, and Coumarin 6 a hydrophobic drug. Demonstrated in Fig. 5D and 5B respectively, CAGE enhanced the transport of hydrophilic dye lucifer yellow in a caco-2 monolayer but had the opposite effect with hydrophobic dye coumarin 6 [101]. However, IL not only acts a great solubilizer and hydrophilic transporter but can also reduce acidic activity demonstrated in Fig. 5C how IL reduces trypsin activity more than regular saline. The importance of neutralizing acidic environment within the gastrointestinal tract can prevent the degradation of biological molecules especially susceptible to these environments.

Drug hydrophobicity is another factor that limits oral delivery since hydrophobic drugs require more chemical processes to dissolve the drug which are not always suitable for use with patients. In an effort to increase hydrophobic drug solubilization Yujie et. al., used choline bicarbonate and geranic acid (CAGE), for oral delivery of the sorafenib (SRF), a drug with hydrophobic properties [73]. CAGE demonstrated exceptional solubility of SRF, exceeding 500 mg/mL. Upon oral administration to rats, CAGE resulted in a 2.2-fold increase in peak blood concentrations of SRF, increased elimination half-life, and absorption. Moreover, the biodistribution of SRF exhibited significant differences compared to control formulations with higher kidney and lung accumulations. investigations unveiled

that the SRF-CAGE self assembles to an average size of 427 ± 41 nm. This unique structure is likely accountable for the observed alterations in biodistribution in vivo [102]. The study concluded the utilization of CAGE exhibits notable advancements in the solubility of hydrophobic therapeutic drugs, accompanied by a significant augmentation and extension of the drug absorption profile. Consequently, CAGE serves as a valuable platform for extending drug half-life and enhancing both pharmacokinetic and pharmacodynamic properties. Furthermore, by enhancing intestinal permeability, CAGE emerges as a promising drug delivery system capable of improving the oral absorption of water-soluble drugs while effectively modulating their biodistribution to attain desired therapeutic outcomes and mitigate potential side effects.

Some ILs have the special property of significantly enhancing the solubility of insoluble drugs [103]. Choosing the right IL that a particular drug is soluble in can improve the amount of drug absorbed when the drug is dissolved and administered orally. IL-based co-solvent systems [104], or emulsion systems [105], can also improve the solubility of insoluble drugs. Co-solvent systems involve the combination of ILs with other solvents, such as water or organic solvents, to enhance drug solubility. This approach allows for the optimization of drug formulations by taking advantage of the unique properties of ILs and the complementary characteristics of other solvents. When ILs are mixed with other solvents, various physicochemical properties and characteristics of the resulting co-solvent system are altered due to the interactions between the different components [106]. One important aspect that changes in a co-solvent system is polarity. ILs are known for their low polarity, while other solvents can exhibit varying degrees of polarity. By combining ILs with solvents of different polarities, the overall polarity of the co-solvent system can be adjusted [107]. This alteration in polarity can significantly impact the solubility of drugs, as it affects the interactions between the drug molecules and the solvent molecules.

Additionally, the viscosity of the co-solvent system is influenced by the interaction between ILs and other solvents [108,109]. ILs typically possess higher viscosity compared to many organic solvents or water. Therefore, the addition of ILs to a co-solvent system can increase its overall viscosity. This change in viscosity can impact the ease of handling and processing of the system, as well as influence the drug release properties. These changes need to be optimized to facilitate the dissolution of the drug and consequently improve the absorption of the drug. Optimization requires fine-tuning the combination of IL and co-solvent based on the properties of the drug, which also translates into increased formulation flexibility.

To address the very low solubility of favipiravir (FAV), an antiviral drug in clinical trials for use against COVID-19, and the inability to formulate it in common solvents or water, Rahman et. al. synthesized four FAV IL (FAV-ILs). Characterization was conducted on the four synthesized FAV-ILs, which comprised FAV anions and IL-forming cations derived from biocompatible choline, amino acids, and ammonia. The synthesized FAV-ILs demonstrated a significant increase in aqueous solubility, surpassing the solubility of free FAV by at least 78-fold. This enhanced solubility opens the possibility of administering higher doses of FAV through oral or intravenous delivery routes. Moreover, the utilization of FAV-ILs not only improved the solubility of FAV but also resulted in improved pharmacokinetic and pharmacodynamic properties compared to free FAV. In mice, oral

dosing of the β-alanine ethyl ester FAV formulation containing FAV-ILs exhibited a 1.9-fold increase in absolute bioavailability compared to the control FAV formulation. Furthermore, the peak blood concentration, elimination half-life, and mean absorption time of FAV were increased by 1.5-fold, 2.0-fold, and 1.5-fold, respectively, compared to the control. Compared to the control FAV formulation, FAV-ILs led to higher FAV concentrations in the gastrointestinal tract and major organs after oral delivery, indicating enhanced absorption in the gastrointestinal tract [110]. Therefore, the formulation of FAV as an IL presents a promising and versatile drug delivery platform to address the challenges associated with solubility and oral absorption of poorly soluble drugs. Additionally, the biodistribution of FAV can be tuned to achieve therapeutic objectives and reduce side effects. These findings highlight the potential of ILs as a straightforward and scalable strategy to improve the gastrointestinal stability, solubility, and oral absorption of hydrophobic drugs, including FAV.

3.3. Using IL as permeation enhancers

ILs can modulate the permeability of the intestinal epithelium, potentially increasing the absorption of orally administered drugs. Some ILs have been investigated for their potential to enhance the permeability of the intestinal epithelium, thereby improving drug absorption in oral drug delivery. In this case, IL is used as an intestinal permeability enhancer (referred to as an absorption enhancer). Used as intestinal permeability enhancers, ILs temporarily disrupt or modify the structure of cell membranes by interacting with the lipid bilayer of the intestinal epithelium [111]. They also can modify tight junctions between epithelial cells, increasing paracellular drug absorption. These disrupted or deformed cell membranes and tight junctions become loose and lose their adhesion to surrounding cells, allowing drugs to penetrate more easily [112]. One example represented in Fig. 7 by Peng et. al. is the development of a mucoadhesive intestinal CAGE patch for controlled release of insulin. Here, they mixed CAGE with insulin and encapsulated it in PVA, creating the patch. Once the patch is adhered to intestinal epithelium, CAGE is released from the patch, allowing for a slow release of insulin, increasing absorption, and effectively lowering blood sugar levels due to interaction of the IL with tight junctions [113].

Jie et. al. conducted a study aiming to address the challenges of oral absorption and room temperature storage of drugs by developing a multifunctional nanoplatforms. The carrier employed in this nano-system consists of Poly(lactic-co-glycolic acid) (PLGA), IL, and deoxycholic acid (DCA). The IL serves as a non-toxic and environmentally friendly solvent, facilitating the opening of tight junctions between cells and acting as a stabilizing agent at room temperature to enhance the stability of recombinant human growth hormone (rhGH). The endogenous ligand, DCA, enhances the intestinal absorption of nanoparticles through receptor-mediated endocytosis [114]. The nanoplatform presents numerous advantages, including the protection of rhGH from degradation by gastric acid and proteases within the gastrointestinal tract, as well as increased absorption of rhGH in the intestinal tract leading to enhanced bioavailability. Additionally, the storage time of rhGH at room temperature is significantly prolonged as shown in Fig. 8d. These materials are cost-effective, readily accessible, and easily synthesized, thereby providing a promising foundation for the clinical application of rhGH.

3.4. Mucus mediation with ILs

ILs interact with mucus in the mucous membrane, changing the properties of the mucus and affecting the permeation and bioavailability of the drug. Mucus in the gastrointestinal tract acts as a physical barrier to the absorption of orally administered drugs [115]. ILs interact with mucus to change its properties such as viscosity, elasticity, and adhesion. Mucus with reduced physical strength is less effective as a physical barrier to drug absorption. As the physical barrier becomes less functional, the drug is more susceptible to absorption across the mucosal surface and into the body. Some ILs can increase the bioavailability of drugs by interacting with mucus, such as mucin glycoproteins.

The choline cations in the ILs are particularly suited for mucus modulation as they can shield negatively charged mucin domains and reduce the viscosity of mucus without causing significant damage to the mucus structure. Additionally, different anion pairs of IL-based choline can influence the pH and conduction of the formulation. Overall, choline-based ILs present a promising approach for modulating mucus to enhance the oral delivery of therapeutics that are impeded by the mucus barrier. However, it is important to further explore the potential problems and limitations of IL-mediated drug delivery systems through synergistic interactions with mucus. Changes in the physical properties of mucus in the gastrointestinal mucosa can lead to irritation and damage of mucosal tissues; therefore, targeting specific mucosal sites and selective interaction with specific mucins is desirable to avoid this potential threat.

Interestingly, certain ILs have excellent mucosal adhesion properties. Mucosal adhesive properties are the ability of a substance to adhere to the mucosal surfaces of the gastrointestinal tract. Certain ILs can stick to the mucus layer of the mucous membrane of the gastrointestinal tract for longer and have strong adhesion, mainly through interaction with the mucin layer [116,117]. While mucus is commonly recognized as a barrier that hinders effective oral drug delivery, it can also serve as a valuable anchoring mechanism to enhance intestinal residence of drug formulations. Because formulation sticks to the mucus layer longer, the drug stays in the mucus layer longer and has more contact time with the intestinal epithelial cells. Epithelial tissues are organs that absorb not only nutrients but also drugs [118]. Since the drug is in contact with the epithelial cells for a longer period, the chances of absorption in the body are higher. In addition, since it adheres to the epithelial cell tissue present in the mucus layer, it can be moved away from various digestive enzymes, thus avoiding enzymatic degradation. Previously our group has studied and reported that CAGE acts as a fat uptake inhibitor. As demonstrated in Fig. 9, DHA was combined with coumarin 6 to visualize the presence of fat in the intestines over 12 h. Interestingly, even though CAGE is mucoadhesive, it prevents the uptake of hydrophobic molecules in the intestinal tract. Also, CAGE demonstrated the ability to reduce body weight of rats eating a high-fat diet [119].

Additionally, the viscosity of the IL plays a crucial role in the flow and ease of administration. For oral drug delivery, solutions with lower viscosity are generally preferred because they are more dispersible and easier to swallow. However, for general drug delivery, higher viscosity also tends to increase bioavailability by increasing the contact time with the tissue where the drug is absorbed [120,121]. Taste masking has been a relatively

less explored aspect in the study of orally administered drug delivery systems based on IL. However, by considering these physical factors in conjunction with other relevant factors, the integration of ILs in orally administered drug delivery systems can contribute to the development of formulations that improve patient comfort and compliance. Through meticulous selection and formulation of ILs, the taste-masking properties and viscosity characteristics can be optimized, resulting in improved patient experiences during oral drug administration which is the goal of oral drug delivery.

3.5. pH mediation with IL

Most drug delivery systems can be affected by acidic or alkaline environments that alter their inherent properties [122]. Changes in pH can alter the stability of a drug delivery system and its ability to dissolve and efficiency of drugs [123]. Not only that, but the harsh pH environment of the gastrointestinal tract can also be the root cause of a drug's decreased therapeutic effectiveness, including changes in its structure and decreased activity [124]. The potential of certain ILs in protecting drugs from the acidic pH conditions prevailing in the gastrointestinal tract has been demonstrated.

For example, ILs based on weakly acidic or basic components have the potential to be used to modify the pH microenvironment to improve drug stability. These ILs can be applied to act as buffers and maintain a desirable pH environment around the drug to protect it from degradation [125]. Mehrdad et. al. studied IL-based pH-sensitive nanocarriers to deliver Naproxen. An IL monomer imidazolium-based chloride was developed exhibiting intercalation within the montmorillonite layers and underwent copolymerization with methacrylic acid. To assess its potential for colon drug delivery, naproxen, a model drug, was entrapped within these pH-sensitive positively charged nanocarriers. The release profiles of the drug were evaluated separately in enzyme-free simulated gastric fluid (SGF, pH 1) and simulated intestinal fluid (SIF, pH 7.4) in vitro. Notably, a higher release percentage of the drug was observed in SIF, suggesting the suitability of the prepared nanocomposite as a promising carrier for colon-specific drug delivery. A novel controllable drug release system was devised by incorporating positive charges into the structure of organic–inorganic nanocomposites using montmorillonite as a base material. This modification facilitated efficient adsorption of anionic molecules within the carriers, resulting in minimal release under weak acidic conditions. However, with an increase in pH value (pH 7.4), the diffusion of hydrolyzing agents into the carrier was enhanced, leading to an accelerated hydrolysis rate. The discrepancies in hydrolysis rate and release percentage between acidic pH (SGF) and pH 7.4 (SIF) suggest that these carriers hold promise for the targeted delivery of anionic drugs to the colon [126].

3.6. Gut microbiome mediation with IL

Orally administered drugs are subject to the influence of the gut microbiome, which exerts a significant impact on their absorption and metabolism within the body [127,128]. ILs can affect the composition of the gut microbiome, which in turn affects the bioavailability and therapeutic efficacy of orally administered drugs [129]. The gut microbiome not only influences the host's metabolism [130], regulates gene expression [131], and modulates temperament and emotions [132–134], but also affects the bioavailability of

orally administered drugs [135]. Changes in the gut microbiome due to infection with externally administered Helicobacter pylori or consumption of probiotics can alter the pharmacokinetics of orally administered drugs [136–138]. Although there are a few studies that provide conclusions about the relationship between the gut microbiome and orally administered drugs, they are still in their infancy. Furthermore, the study of phenomena caused by the host's gut microbiome, such as metabolic diseases, regulation of gene expression, emotions, and brain disorders [139,140], has a shorter history than other traditional biology-based studies. Moreover, the sheer number of in-depth studies makes it difficult to extrapolate and infer conclusions about the body's absorption and metabolism of orally administered drugs. However, research to date suggests that the gut microbiome alters the pharmacokinetics of orally administered drugs.

Gregory et. al. investigated the effects of exposing mice to two different methylimidazolium IL (BMI and M8OI), each added to drinking water. This study aimed to investigate the potential effects of IL exposure on key target organs, specifically the liver and kidney, as well as the gut microbiome. Adult male mice were orally exposed to drinking water containing ILs at a concentration of 440 mg/L for a duration of 18 weeks. Subsequently, tissues, serum, urine, and gut microbiome samples were collected for analysis. Bacterial DNA was extracted from the gut contents and subjected to targeted 16S rRNA sequencing. The results indicated that IL exposure led to mild effects in the liver and kidney. Specifically, glycogen depletion was observed in the liver, while mild degenerative changes were observed in the kidney. However, no adverse effects were observed in either organ. In contrast, IL exposure had a significant impact on the composition of the gut microbiome, although no significant changes were observed in overall alpha diversity. The proportional abundance of Lachnospiraceae, Clostridia, and Coriobacteriaceae species was notably increased in mice exposed to ILs. Furthermore, predicted KEGG functional pathways associated with xenobiotic and amino acid metabolism were also found to be significantly enriched in the IL-exposed group [141]. These findings indicate that exposure to ILs via drinking water resulted in marked alterations in the gut microbiome of mice, even before any overt pathological effects were observed in the target organs. The changes in microbial composition and predicted functional pathways suggest a potential influence of IL exposure on xenobiotic and amino acid metabolism within the gut microbiota.

Further research is warranted to elucidate the underlying mechanisms and assess the broader implications of these findings. Although the exposure to ILs in this study exhibited limited effects on host organs such as the liver and kidneys, we observed significant taxonomic shifts in the gut microbiota. Additionally, based on predicted metagenomes, we propose that IL exposure resulted in alterations in bacterial function repertoires. It is important to note that changes in gut microbiota composition have been frequently associated with various aspects of host health. Consequently, these findings underscore the necessity for further research to investigate the impact of ILs on humans and their associated microbiota, considering the intricate interaction between the microbiota and the host.

3.7. Nanoparticle systems

ILs within controlled-release systems, such as nanoparticles or microparticles, present a promising avenue. By integrating ILs into these systems, a multitude of benefits can be attained, encompassing drug safeguarding against degradation, protracted drug release, and enhanced drug absorption via an extension of residence duration within the gastrointestinal tract [142]. The noteworthy characteristics of ILs have attracted significant interest, establishing their potential as carriers or excipients in drug delivery systems. Particularly, sustained release formulations based on ILs provide several advantages for improving drug absorption following oral administration [143]. By incorporating drugs into systems based on ILs, it becomes possible to achieve a controlled and prolonged release profile. This, in turn, allows for the maintenance of therapeutic drug concentrations in the bloodstream, an improvement in drug bioavailability, and a decrease in dosing frequency. Within these formulations, ILs act as carriers or encapsulation matrices, providing protection for drugs against degradation within the gastrointestinal tract and facilitating controlled release mechanisms.

An emulsion system of ILs also can be utilized to increase the solubility of insoluble drugs and enhance their oral absorption [144]. An emulsion is a dispersed system of two or more immiscible phases stabilized by an emulsifier or surfactant [145]. Since the two or more immiscible phases are very evenly dispersed, the dissolution of the drug is improved by dispersing the insoluble drug into the soluble phase. This results in improved oral absorption. In addition, the formation of an emulsion increases the surface area, which is directly related to the dissolution of the drug and especially the release of the drug [146]. In addition, ILs are used with stabilizers in emulsion systems to prevent aggregation of the emulsion, thereby increasing the stability of the formulation [147]. Therefore, emulsions can provide a stable vehicle for the drug and help protect the drug in the gastrointestinal tract [148,149]. It all comes down to improving the solubility and bioavailability of insoluble drugs [150]. As with other systems, optimization of emulsion systems requires a detailed evaluation of the optimal combination, considering the physicochemical properties and characteristics of the drug.

Eleni et. al. studied an IL mediated Amphotericin B (AmpB) oral delivery system with self-nano-emulsifying technology [151]. Due to its limited solubility and permeability, the oral bioavailability of AmpB, a frequently employed therapeutic agent against severe fungal infections [152], and life-threatening parasitic diseases like visceral Leishmaniasis, is insignificantly low [153]. To formulate an oral delivery system for AmpB, a self-nano-emulsifying drug delivery system (SNEDDS) comprising medium chain triglycerides and nonionic surfactants was utilized. Additionally, room temperature ILs (RTILs) of imidazolium were incorporated. The inclusion of ILs resulted in a significant enhancement of AmpB solubility while exhibiting low toxicity and promoting AmpB transport across Caco-2 cell monolayers. The combination of RTILs with the lipid formulation represents a promising strategy for augmenting the oral bioavailability of AmpB. In conclusion, the integration of RTIL-lipid-based drug delivery strategies presents intriguing prospects, including high drug-loading capacity and the ability to enhance drug permeation profiles.

The oral administration of certain drugs faces challenges due to barriers and harsh conditions within the gastrointestinal tract, despite their significant therapeutic effects. To achieve successful oral drug delivery, the selection of an appropriate IL should consider factors such as biocompatibility, physicochemical properties, and interactions with specific drugs. The biological and physical factors discussed earlier play a crucial role in IL-mediated oral drug delivery and can interact with each other, impacting the efficiency of drug absorption. Therefore, tailored formulations and strategies are necessary to optimize oral drug absorption and therapeutic efficacy, considering the specific characteristics of the drug and how these factors apply. Researchers should conduct thorough reviews and analyses to understand the application and significance of these factors in IL-mediated oral drug delivery systems. Further research is needed to advance the development, clinical implementation, and commercialization of highly efficient orally administered drug delivery systems. Moreover, potential toxicity concerns associated with IL-based oral drug delivery systems should be carefully considered, studied, and addressed. Table 2 represents a summary of composition various ILs and their benefit for oral delivery.

4. Conclusions and future perspectives

Current research involving IL for noninvasive delivery methods has shown it to be an effective option compared to organic solvents and co-solvents that help improve drug solubility for these systems. ILs have a versatile range of applications since their ionic nature can be tuned to work with a variety of hydrophobic compounds and polymers allowing their use in multiple drug delivery systems. Proper selection of ions during formulation allows the IL to enhance drug solubility while synthesizing specific biological functions depending on the route of administration. Many studies outlined here have shown that ILs used as a solvent or co-solvent greatly improve drug solubility which can be used in various routes of delivery for noninvasive approaches. ILs also increase stability, require minimal volatility, and exhibit customizable physiochemical properties that make them a suitable option to overcome many of the physical and biological barriers of noninvasive delivery methods. Due to these unique properties of ILs, we have demonstrated their ability to work as permeation enhancers due to their compatibility with biological molecules and polymers thus allowing penetration of biological barriers.

Noninvasive drug delivery presents an opportunity to increase patient compliance and therefore provide enhanced treatment for diseases, however, barriers exist for each delivery method that need to be overcome. In the case of oral delivery methods, the harsh nature of gastric fluid in the stomach degrades many drugs and biological molecules due to high pH and limits their effectiveness. Additionally, intestinal mucus, composed of water and mucin lines the entire gastrointestinal tract; this sticky, viscous layer is responsible for absorbing foreign particles as part of the immune system. These two biological barriers require the use of delivery vehicles, such as IL, that will protect drugs and biological molecules from the degrading nature of the GI tract while also facilitating entry and absorption into the mucus layer. For skin-related diseases, topical treatments provide a painless delivery directly on the skin surface. While transdermal delivery of drugs has many advantages, permeation through the skin presents the greatest factor affecting the effective delivery of drugs. Due to the hydrophobic nature, and small pore size of the skin, drugs are not able to penetrate through

the epidermis alone and thus require a vehicle to be delivered into the dermis layer. These factors affecting noninvasive delivery have been extensively covered in this review.

Noninvasive drug delivery involves methods are painless therapeutic administration usually preferred by patients. These noninvasive delivery methods are active areas of research that aim to reduce the need for injectable treatment options through the development of oral medications, topical creams and ointments, and respiratory inhalations. However, APIs, small molecules, and biologics do not have the capabilities to penetrate biological barriers independently due to their large sizes and physiochemical properties suggesting the need for delivery vehicles that are compatible with the biological microenvironment to facilitate entry into cells. Also, solubility of most APIs requires the use of hydrophobic and lipophilic solvents since many of them are not water soluble. Despite obvious advantages, it is still challenging to develop drug delivery systems ensuring high efficiency and bioavailability, the development of formulations that enhance the uptake of therapeutic moieties while also increasing efficacy and safety are needed. Advances in drug delivery systems have led to the development of effective treatments that reduce adverse side effects by creating vehicles that target the diseased area while also controlling the rate and time of release.

While the studies discussed throughout this review demonstrate the effectiveness of ILs to overcome the various barriers of topical and oral noninvasive delivery, more research needs to be done to understand their biocompatible features, their interactions with biological membranes, and their therapeutic activity. For example, the versatility of cation–anion combinations has been shown to improve the bioavailability of hydrophobic drugs in topical delivery by increasing permeation through the skin, however, the specific interactions with the skin barrier are poorly understood; these interactions are important for effective therapeutic drug delivery design. Also reviewed here is the ability of ILs to be effective solubilizers for different drugs and biopolymers, allowing applicability to various delivery routes, however understanding the mechanisms and interactions of the solubilization is key in designing more effective formulations for noninvasive delivery. Although IL-based drug delivery systems for noninvasive approaches are being reported and showing success, the lack of comprehensive studies and mechanistic understanding limits the design of the formulations. Regulatory approval is also required for this novel research which also increases the time for commercialization, however, the results demonstrated so far serve as a positive outlook in the role of ILs in noninvasive drug delivery. Despite these limitations, thus far, ILs are promising in the development of novel noninvasive delivery options, having the potential to improve conventional treatments while enhancing safety and efficacy.

Acknowledgments

The authors are thankful for the support funding received from Cancer Prevention Research Institute of Texas (CPRIT) through Texas Regional Excellence in Cancer Award (TREC) under Award No. RP210153, and National Institutes of Health (NIH) under Award No. R03OD032624. The views presented in this review paper are solely the authors' responsibility and do not represent the views of NIH. Elfa Beaven acknowledges summer fellowship from National Scleroderma Foundation. The graphical abstract was created using Biorender.com. This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2021R1A2C2095113 and 2021R1A6A1A03046418).

Data availability

No data was used for the research described in the article.

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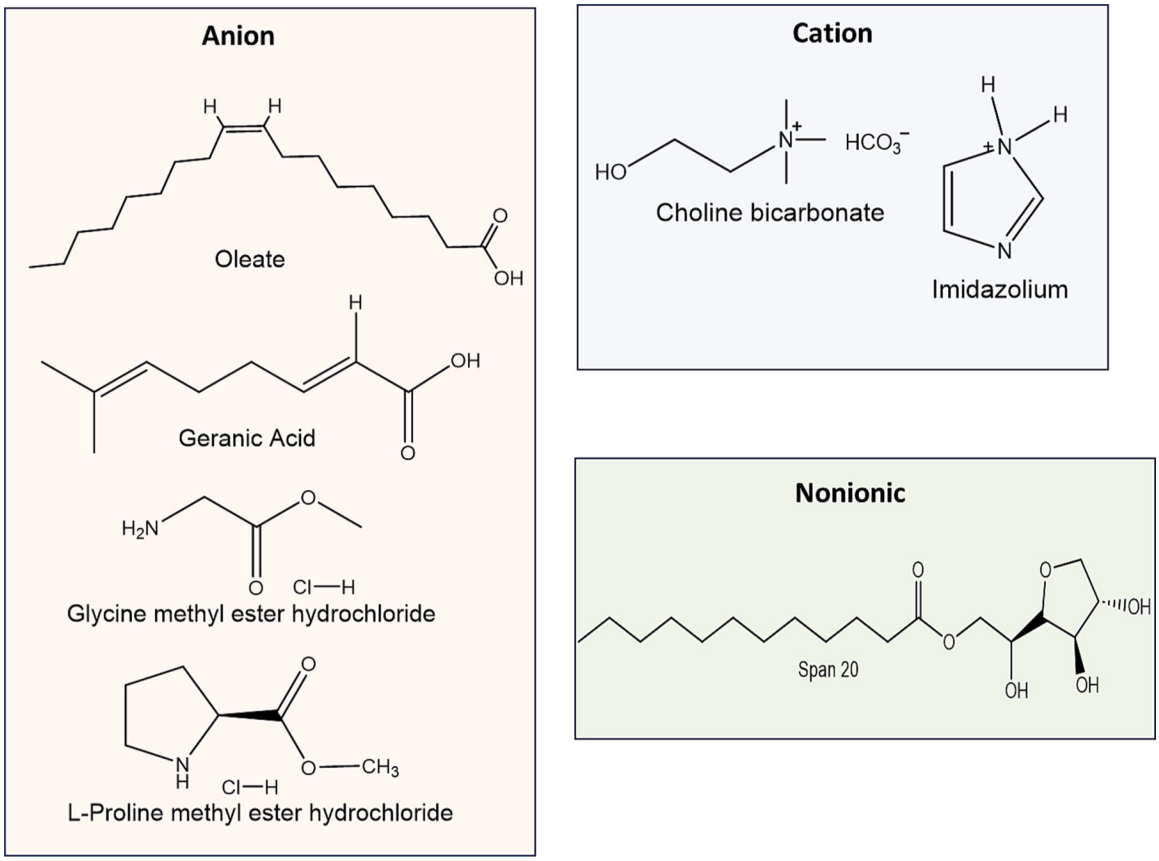
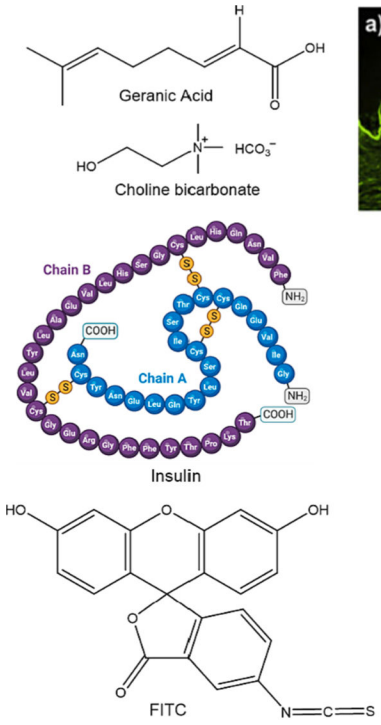
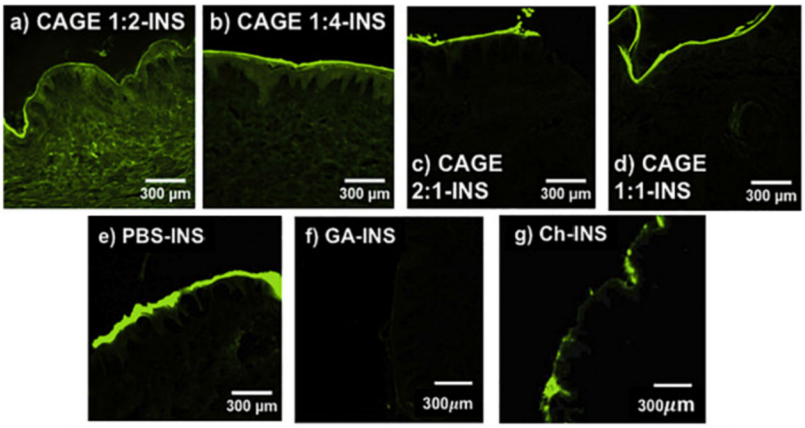


Fig. 1.

Chemical structures of commonly used analogs (cationic and anionic) to prepare IL for transdermal delivery. The cations and anions depicted are discussed in the studies outlined in this review.





Variant	Viscosity/mPa·s	Conductivity/mS m^{-1}	OH Proton/ppm	Diffusion Coefficient/x 10^{-12} m^2 s^{-1}
2:1	737 ± 32	57.55 ± 0.07	5.8	1.8
1:1	492 ± 18	16.28 ± 0.76	5.85	2.6
1:2	568 ± 19	13.79 ± 0.28	10.2	2.2
1:4	223 ± 26	5.28 ± 0.07	11.4	4.3

Fig. 2.

Chemical representation of CAGE, Insulin, and FITC. Insulin was created with BioRender.com. (a–g) are confocal images of rat skin after application of CAGE with FITC-labeled insulin and PBS as control. The table demonstrates the characteristics of the varying ratios of CAGE. Reproduced with permission from ref. [48] Copyright 2018 Elsevier.

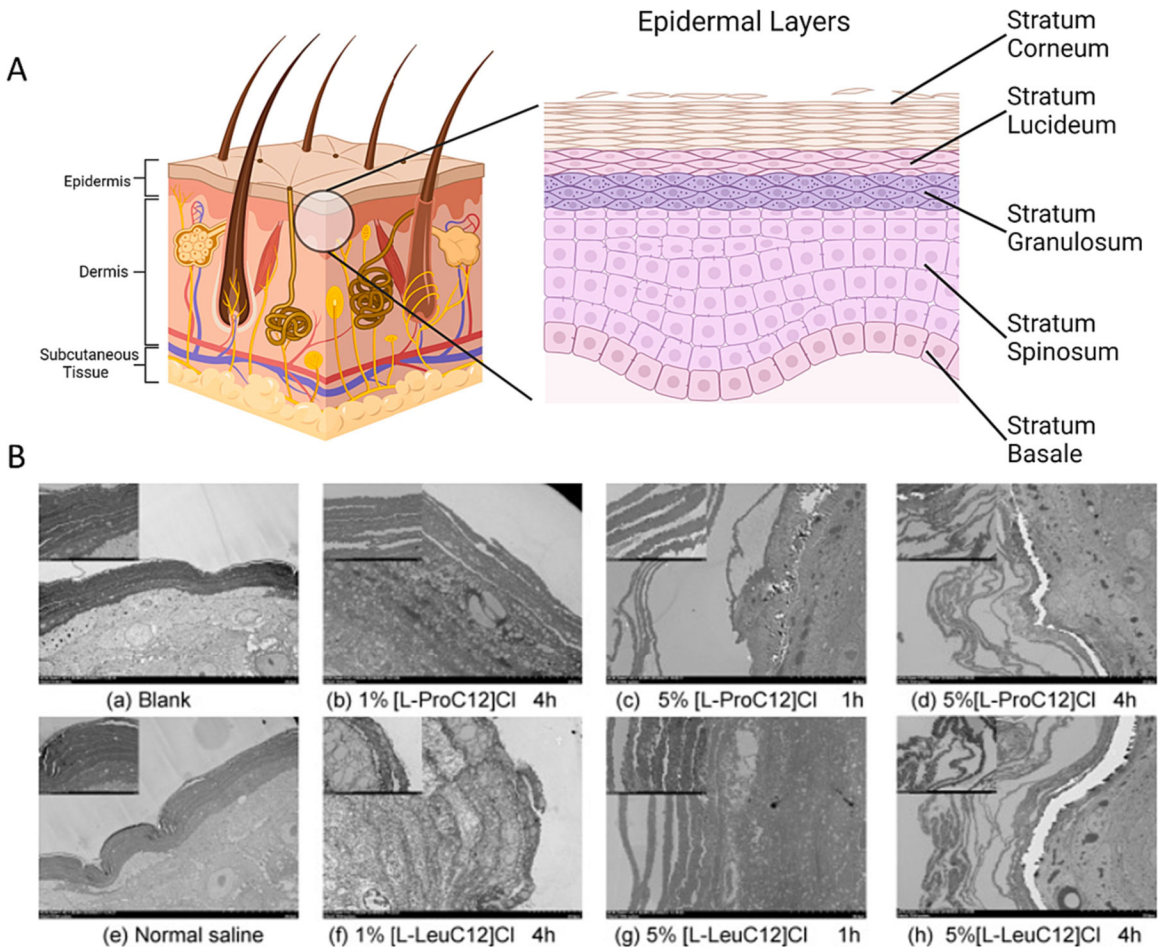


Fig. 3.

(A) Schematic representation of the skin. The skin is composed of three major layers each having various layers with different functions. The epidermis is made up of 5 different layers of varying thickness. The outermost layer, the stratum corneum is the toughest layer composed of dead keratinocytes which form the protective layer of the skin and pose the greatest challenge to transdermal delivery. The deepest layer of the epidermis, the stratum basale, is responsible for supplying the SC with keratinocytes that form a water barrier through the secretion of lipids [54]. Created with BioRender.com. (B) TEM images of amino acid-based IL treatment. Reproduced with permission from ref. [53] Copyright 2020 Elsevier.

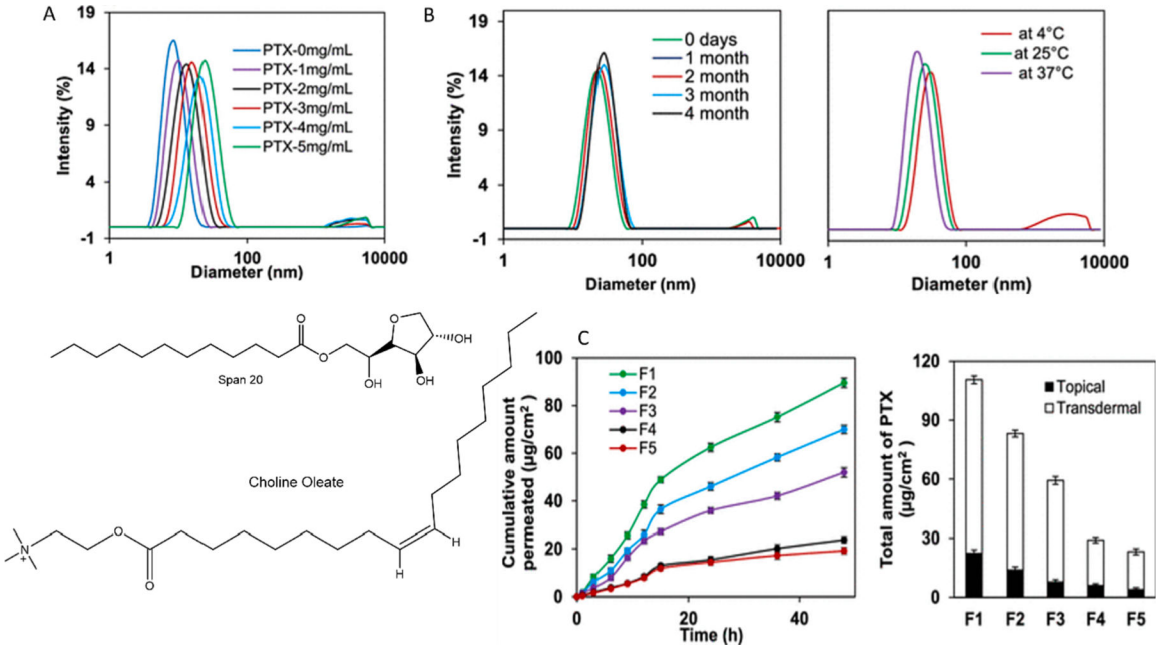


Fig. 4.

Chemical representation of choline oleate and span 20. (A) size distribution of various doses of MF with PTX. (B) Long term stability of MF at 4 °C, 25 °C, and 36 °C over a 4-month period. (C) The cumulative amount of MF permeation and total amount of PTX found topically and transdermal. Reprinted (adapted) with permission from ACS Appl. Mater. Interfaces 2021, 13, 17, 19745–19755. Copyright 2021 American Chemical Society.

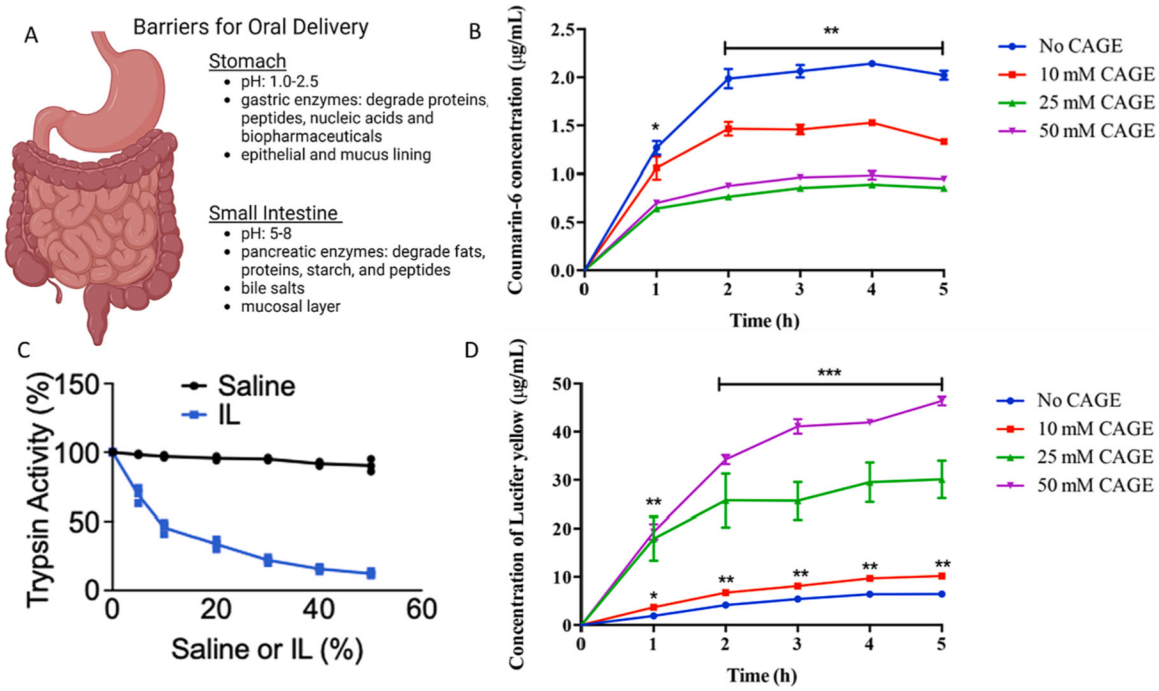


Fig. 5.

(A) Schematic explanation of barriers to oral delivery in the gastrointestinal tract. Created with BioRender.com. (B) and (D) concentration of Coumarin 6 and lucifer yellow with varying mM amounts of CAGE. Reproduced with permission from ref. [101]. Copyright 2018 National Academy of Sciences. (C) IL reduction of acidic activity compared to saline.

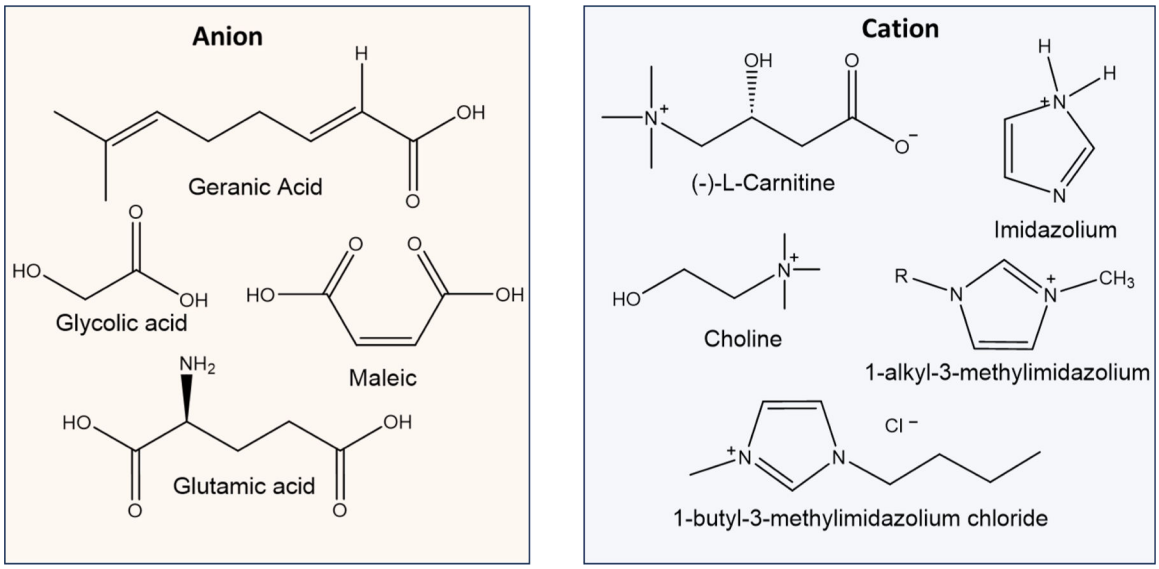


Fig. 6.

Chemical structures of commonly used analogs (cationic and anionic) to prepare IL for oral delivery The cations and anions shown are the ones used in the studies discussed in the oral delivery section.

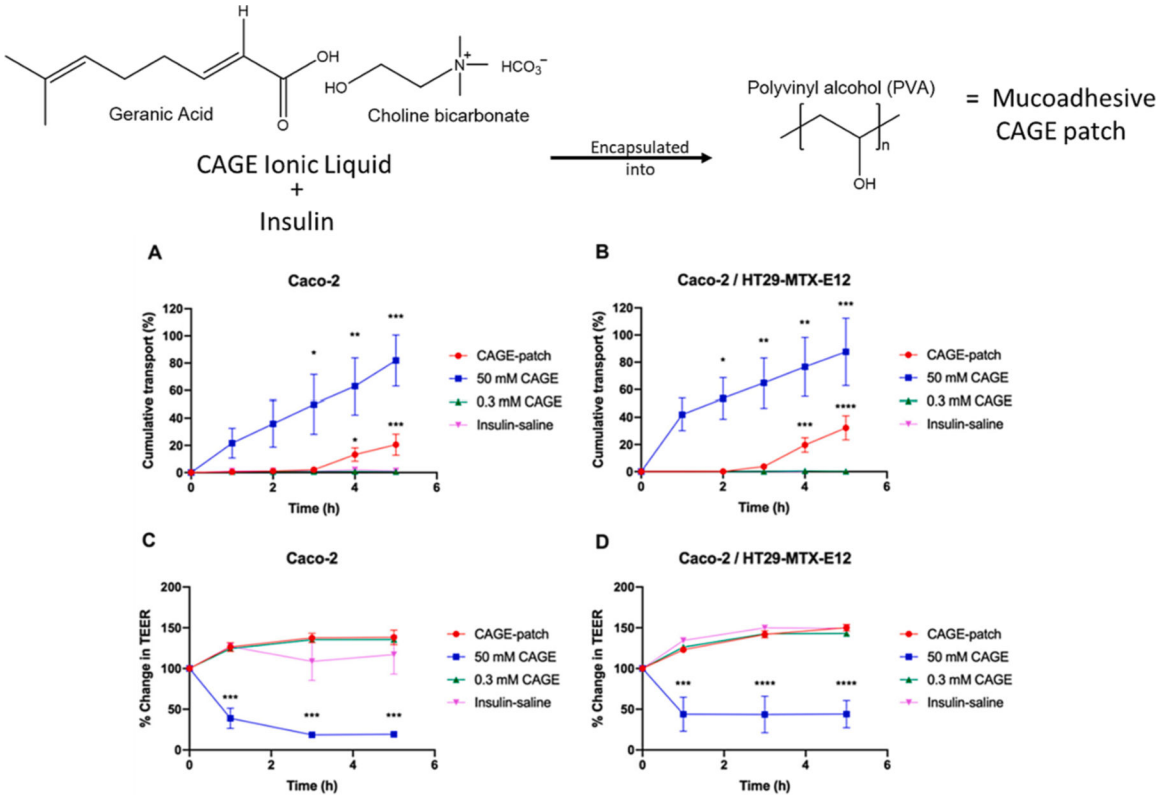


Fig. 7.

Chemical structure representation of oral intestinal patches developed to increase insulin delivery through intestinal epithelium. A and B demonstrate the transport into Caco2 and Caco-2/HT29-MTX-E12 co-culture. C and D show the change in tight junction opening. While 50 mM CAGE shows a higher transport, we can see the opening of the tight junctions does not remain open over an extended period as compared to the patch. Reprinted (adapted) with permission from *ACS Biomater. Sci. Eng.* 2023, 9, 6, 2838–2845. Copyright 2023 American Chemical Society.

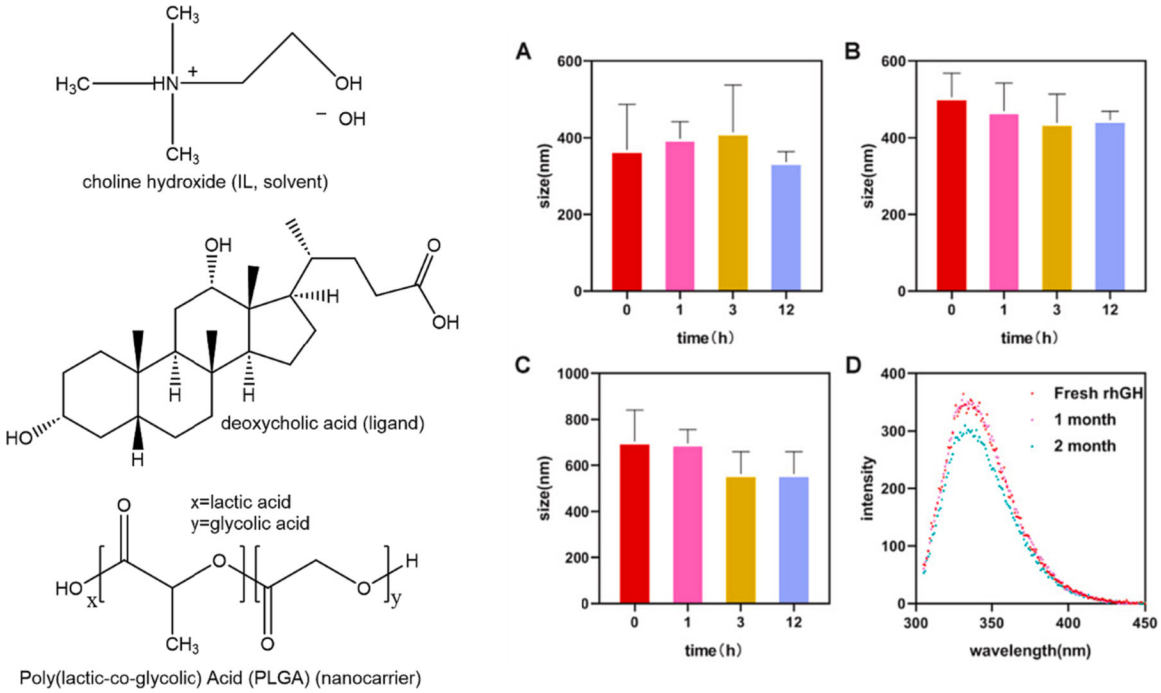


Fig. 8.

Chemical structures for choline hydroxide IL, deoxycholic acid, and PLGA. (a–c) shows the size of the nanoparticle over time. (d) demonstrates the stability of the nanoparticle at room temperature storage for two months. (a–d) reproduced with permission from ref [114] Copyright 2023 Elsevier.

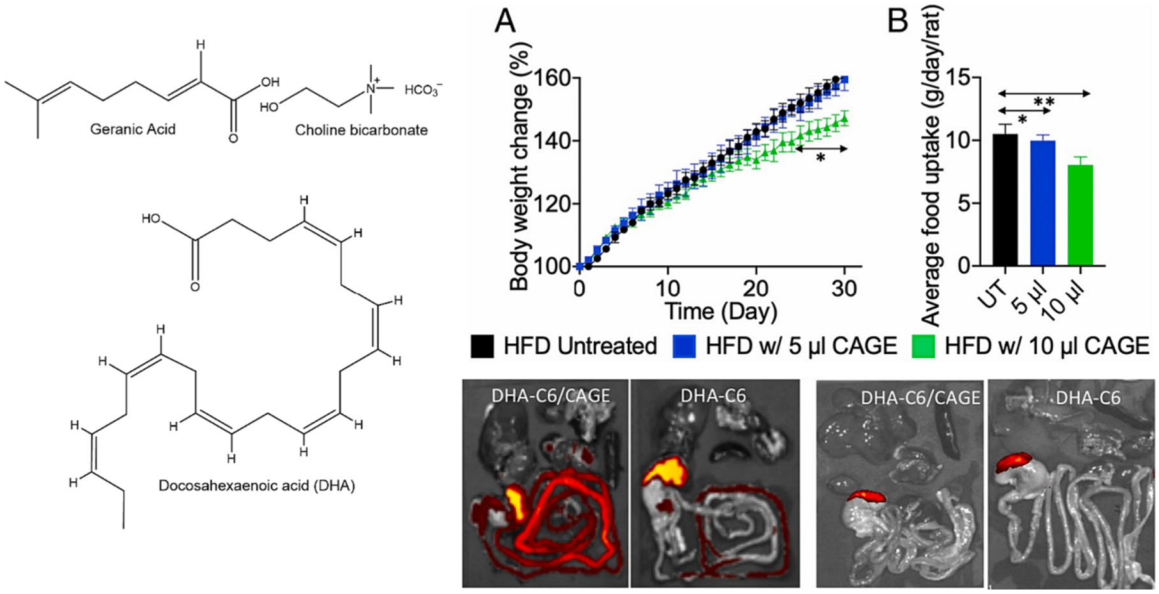


Fig. 9.

Chemical structure of CAGE and DHA. (A) and (B) show the significant reduction of body weight in high fat diet rats with 10 µl of CAGE as compared to untreated and 5 µl dose Reproduced with permission from ref. [119] Copyright 2019 National Academy of Sciences.

Table 1

Topical Ionic Liquid Formulations.

Ionic Liquid Composition	Drug	Disease	Improvement	Ref
Choline bicarbonate and geranic acid (CAGE)	Insulin	Diabetes	Skin permeation by lipid extraction of SC	[48]
Amino acid esters with carbon chain modification: Glycine, L-proline, L-leucine methyl ester hydrochloride	5-Fluorouracil Hydrocortisone	n/a	Skin permeation through lipid extraction of SC	[53]
Cholinium and ellagate	IL absorption in BC membrane	Antioxidant properties	Solubility and skin permeation	[55]
Cholinium and gallate				
Cholinium and caffeate for bacterial cellulose membranes				
Choline and ferulic acid	Finasteride	Androgenic alopecia	Solubility, skin permeation, skin adhesion	[56]
7 variations of Imidazolium-based IL	3,4-methylenedioxybenzoyl-2-thienylhydrazone (LASSBio-294) (cardioactive prototype drug)	n/a	Solubility of water-insoluble drug	[59]
Choline acetate for collagen PVA films	Ciprofloxacin	Wound healing	Adhesion and antioxidant properties	[65]
Choline and octanoic acid (COA	Navitoclax	Skin fibrosis	Drug solubility and skin permeation	[66]
Naproxen based IL: choline and naproxen	Naproxen	Pain and inflammation	Drug solubility	[68]
Choline-based fatty acids-in-oil microemulsions	Insulin	Diabetes	Skin permeation by lipid fluidization	[70]
1-hydroxyethyl-3-methylimidazolium chloride as the IL, lidocaine ibuprofen as the oil phase, and water as the aqueous phase	Artemisinin	Malaria	Solubility of water-insoluble drugs	[71]
Micelle formulation with choline oleate surface active IL and span 20	Paclitaxel	Cancer	Drug solubility of poorly water-soluble drug	[76]

Table 2

Oral Ionic Liquid Formulations.

IL Composition	Drug	Disease	Improvement	Ref
Choline bicarbonate and geranic acid (CAGE)	Insulin	Diabetes	Drug solubility, hydrophilic drug transporter, acidity reduction	[101]
β-alanine ethyl ester IL loaded with favipiravir	Favipiravir	Viral infection	Solubility of poorly soluble drugs and absorption	[110]
Mucoadhesive intestinal CAGE patch encapsulated in PVA	Insulin	Diabetes	Adherence to intestinal epithelium, absorption, controlled release	[113]
of Poly(lactic-co-glycolic acid) (PLGA), choline hydroxide (IL), and deoxycholic acid (DCA) nanoparticles	Recombinant human growth hormone	n/a	Solubility, long-term stability, absorption	[114]
3-methyl-1-[2-(2-methyl-acryloxy)-ethyl]-imidazolium chloride within montmorillonite copolymerization with methacrylic acid	Naproxen	n/a	Drug stability through pH microenvironment modification	[126]
methylimidazolium ILs (BMI and M8OI) in drinking water	n/a	Chronic gastrointestinal diseases	Gut microbiome alterations on xenobiotic and amino acid metabolism pathways	[141]
self-nano-emulsifying drug delivery system (SNEDDS) comprising medium chain triglycerides and nonionic surfactants with imidazolium	Amphotericin B	Fungal infections	Drug solubility and permeability	[152]

Adv Drug Deliv Rev. Author manuscript; available in PMC 2024 January 13.