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Ionic liquids in transdermal drug delivery system: Current applications and future perspectives

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ABSTRACT

The transdermal drug delivery (TDD) shows considerable advantages over other administration pathways. However, conventional enhancing permeation methods face a series of challenges owing to barrier function provided by the skin, of which enhancing abilities either are so strong that it results in toxicity and irritation, or too weak to achieve desirable therapeutical effects. To address these issues, it is an urgent need to develop a novel method to overcome the limitations of current measures. Fortunately, in the preceding decades, ionic liquids (ILs) have been extensively studied and increasingly applied in pharmaceutical drug delivery due to their unique physicochemical and biological properties. What is more, tunability of structure resolves the challenges in processing active pharmaceutical ingredient (API) formulation, such as polymorphism and poor solubility of drugs. Thus, the presence of ILs provides an ample design space for the transdermal drug delivery system (TDDS). This review discusses the shortcomings of conventional enhancing permeation methods and introduces the application of ILs in transdermal delivery from three aspects: i) ILs are applied as enhancers to weaken the barrier function of the stratum corneum (SC). ii) As counterions, ILs are combined with API to modify the physicochemical properties of drugs. iii) ILs assist in the design of transdermal preparation for perfecting formulation. This review comprehensively introduces the major breakthroughs made in the applications of ILs, which can serve as guidance to provide novel ideas for formulation scientists who hit the bottleneck in the development of TDD.

1. Introduction

Ionic liquids (ILs) have been increasingly investigated and extensively applied to various science fields in recent decades. ILs refer to organic salts whose melting points are below 100 °C, as found by Paul Walden [1]. They possess numerous characteristics as materials or excipients, such as high viscosity, negligible vapor pressure, thermal stability, biodegradability, and low inflammability, derived from their unique structures and properties [2]. Early progress made in ILs aimed at developing green and stable solvents owing to their excellent properties mentioned above. Currently, much of the investigation indicated that ILs are widely applied in various fields, including chemical synthesis [3,4], catalysis [5], antimicrobials [6]. ILs are salts composed of cations and various anions by ionic interaction, of which the selection of cations has broadened from a narrow perspective quaternary ammonium, imidazolium, pyrrolidinium, pyridinium, or phosphonium cations [7,8] to bioinspired cholinium and guanidinium cations [9,10]. ILs are considered to tailor desirable structures for various purposes, thus, they were also called 'designer solvent' [11,12]. With such a desirable advantage, ILs have extensive applications in the fields of pharmaceutics, summarized in Table S1 (Supporting information).

Drug delivery *via* the skin allows transport of the drug into the blood circulation or dermis for functioning, which has in recent decades been increasingly popular. It has brought not only systemic effects but also topical ones [13,14]. Transdermal drug delivery (TDD) is utilized to deliver the drug into blood circulation to achieve systemic therapy. TDD preparation comprises conventional preparation with topic effects, including ointments, creams, gels, and modern TDDS, which refers to patches. Compared to other conventional drug delivery systems, TDD possesses several unique advantages, such as i) maintaining a constant plasma concentration, ii) avoiding the first-pass effect, and iii) improving patient compliance. Therefore, TDD has received increasing attention in developing various means of increasing skin permeation of different drugs, an area currently worth several billions of dollars [15]. However, several physicochemical properties of drugs applied for TDD must be rigorously demanded, such as low molecular weight (<400 Da), low melting point (<93.3 °C), low polarity, and low daily dose (<20 mg) [16]. Otherwise, it is hard for the drug to

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cross the skin barrier to enter the blood circulation. Thus, various methods were proposed to improve the permeation of drugs based on the unique structure of the skin, including physical methods (electroporation, sonophoresis), chemical methods (chemical permeation enhancers), and preparations (microemulsions, solid lipid nanoparticles) [17]. In some cases, ILs have more efficient enhancing effects than those of other conventional enhancement strategies, which are attributed to their multiple functions that change the barrier function of skin and modify the physicochemical properties of drugs.

This review discussed the applications of ILs in transdermal delivery from three aspects. The first one mainly concentrates on enhancing the permeation effects, which are as good or better as conventional chemical permeation enhancers. The second highlights the impact of API-ILs strategy associated with counterions on skin permeation of active pharmaceutical ingredient (API). The third describes the use of assisting dosage form to modify the drug release or aiding synthesis of innovative materials for transdermal delivery. This review summarized methods that best utilize the characteristics of ILs to improve drug permeation for better therapeutic effects or control the drug release for longer-lasting effects, based on the structure of the skin and current limitations.

2. Properties of ILs

The formation of ILs is accompanied by an increase in viscosity and a decrease in conductivity relevant to the ionicity used to indicate the degree of closeness between cations and anions, evidenced by the Walden plot [18,19]. ILs are virtually liquid salts and can form solvents to solvate a wide range of drugs. The remarkable ability to dissolve many poorly soluble drugs makes it improve the therapeutical effects [20]. The cations and anions that made up ILs played different roles. Structurally asymmetric cations hindered the interaction with the anion to lower the melting points of the resulting compounds. Anions mainly provide the functional group to increase interaction with the dissolved compounds in ILs, improving their solubility. The most significant advantage of ILs was their unlimited suite of tunable properties, including toxicity, volatility, flammability, and instability [21]. They can tune the hydrophobic/hydrophilic balance to improve the solubility of drugs by changing the length of alkyl chains and molecularly engineering the polarity of the cationic head group [22,23]. In general, poorly soluble and unstable drugs are prepared to be salts with a high melting point to improve water solubility for the purpose of to foster their therapeutic efficacy, but at the cost of decreasing liposolubility [24]. Furthermore, it has the same issues around the solid preparation in aspects of polymorphism. Conventional salts with tight packing crystal structures formed by API and the counterion would create various crystal forms under different conditions, which lead to changes in mechanical characteristics and physicochemical properties, such as solubility, stability, bioavailability, and other unpredictable properties [25]. In contrast, ILs possess distinct structures in which bulky counterion of API increases the steric hindrance and, to some extent, weakens the interaction between charges to neutralize the high entropy. In the case of hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) contained in ILs, melting temperature would further drop by reducing the potential of hydrogen bonding, which achieves the stability of ILs in a more disordered state to avoid the polymorphism and ensure bioavailability [4].

3. ILs as chemical permeation enhancers for transdermal delivery

The skin primarily consists of the epidermis and dermis, where the epidermis is composed of stratum corneum (SC) and viable epidermis (VED) (Fig. S1 in Supporting information). In order to break the barrier of stratum corneum, various kinds of techniques have been developed to improve permeation, including drug manipulation strategies, formulation improvements, physical methods for penetration enhancement, and chemical permeation enhancers (CPEs) (Fig. S2 in Supporting information), of which the most investigated means are chemical permeation enhancers.

Based on the structure and action mechanism of CPEs, ILs strategy provides all kinds of possibilities to design permeation enhancers with more efficient enhancement effects and lower irritation and toxicity. ILs thrive as permeation enhancers, which gain widespread use in drugs with various properties. Not only can macromolecules (proteins) and small molecules (caffeine) be enhanced by lipids extraction [26,27], but also hydrophilic (phenol red) and hydrophobic (tulobuterol) molecules are by means of fluidifying the protein and lipid regions to open the tight junctions in SC [28]. At present, there are several types of ILs as permeation enhancers shown in Table 1: i) Choline-based ILs. They reduce the toxicity of ILs to the most extent attributed to the choline of endogenous substances. The widest application in choline-based ILs is choline and geranate (CAGE) originated from the interaction of choline with geranic acid. Enhancing effects provided by other conventional permeation enhancers pales in comparison to that by CAGE. In fact, it was investigated that increased maximum permeation amount by CAGE is comparable to that by physical methods, but with low toxicity and damage to the skin [29–32]. In addition, choline malate IL (CM-IL) with low toxicity, irritation, and excellent biocompatibility assisted in delivering hydrophilic macromolecule dextran into deep skin layers [33]. Other choline-based ILs were also prepared to foster drug permeation, such as choline-fatty acids ([Cho][FA]) [34], choline-citric acid ([Cho][Cit]) [35]. ii) Imidazolium-based ILs [36–38]. Nitrogen heterocycle-contained ILs are also applied as permeation enhancers because of their special cations, which could insert into the SC and change its surface properties. However, nitrogen heterocycle-based ILs are less suitable for facilitating drug permeation due to toxicity. iii) ILs composed of aliphatic carboxylic acid and aliphatic amine [28]. Highly biocompatible ILs could be prepared by selecting great compatible aliphatic carboxylic acid and aliphatic amine. ILs comprised of isostearic acid (ISA) and diisopropanolamine (DIPA) showed comparable enhancing effects to sodium dodecyl sulfate (SDS) for hydrophilic phenol red. On the other hand, the enhancement of the hydrophobic tulobuterol provided by ILs composed of octanoic acid (OA) and DIPA was almost as effective as that of isopropyl myristate (IPM). Interestingly, these ILs could significantly foster the hydrophilic and hydrophobic drugs but hardly had a morphological influence on the skin compared to IPM and SDS. The mechanism of ILs as CPEs is essentially the same as conventional CPEs, but they are a little different. In the case of CAGE, it delivered insulin by extraction and fluidization of the lipids to act as a solvent. On the other hand, CAGE diffused into lipids in SC to disrupt strongly linked keratinocytes and lipids [26]. Another mechanism is based on the structures of anions and cations. ILs function as a cationic surfactant to disturb the lipid bilayer and hydrophobic tail by fluidifying the lipids. Furthermore, it was investigated that unsaturation was an essential consideration for designing IL as CPEs, which was attributed to increased steric hindrance to further influence structures of the skin [39,40].

The key to balancing permeation enhancement effects and toxicity is the nature of anions and cations, but it also depends on the biosystem. Even though ILs were viewed as an environmentally-friendly solvent, large amounts of published data show that they give rise to various degrees of toxicity ranging from bacterial to human. The cytotoxicity of imidazole-based

Table 1
Examples of ILs as chemical permeation enhancers.

Cations	Anions	API	Skin	Ref.
Choline bicarbonate	Geranic acid	Dextrans	Human	[24,26,27,29]
		Bovine serum albumin	Porcine	
		Insulin	Wistar rat	
		Caffeine		
	Malic acid	Dextrans	Porcine	[33]
			Wistar rat	
	Fatty acids	Antigen peptide	Mouse	[34]
	Sorbic acid	Hyaluronic acid	Porcine	[35]
	Malonic acid			
	Succinic acid			
	Lactic acid			
	Geranic acid			
	Oleic acid			
	Hyaluronic acid			
Dimethylimidazolium	Dimethylphosphate	Acyclovir	Micropig	[36]
Diisopropanolamine	Octanoic acid	Phenol red	Wistar rat	[28]
Triisopropanolamine	Isostearic acid	Tulobuterol		

ILs was evaluated in human keratinocytes (HaCat cells), including [C2mim][Br], [C4mim][Br] and [C6mim][Br]. They showed concentration-dependent cytotoxicity, where the IC_{50} values were 0.10% (v/v) for hexyl, 0.30% (v/v) for butyl and 0.44% (v/v) for the ethyl analogue, indicating that it was easier for [C6mim][Br] to accumulate in cell at higher levels and exhibit a higher cytotoxicity [41]. Furthermore, Ropel found that toxicity of ILs not only originated from the cation moiety, but also from the anion moiety. The skin permeation of bis(trifluoromethanesulfonyl)imide (TFSI) salt was 40 times than that of other anion salts, such as tetrafluoroborate (BF4) [42]. However, the proportion of viable cells decreased and necrotic cells increased significantly in 3D reconstructed human skin models after treatment of ILs containing the TFSI as anionic parts, which implied that the obvious cell toxicity [43]. For one thing, recent studies have shown that ILs with short alkyl chains performed poor biodegradability and compatibility but had lower toxicity than long alkyl chains, which possessed better biodegradability and liposolubility accompanied by higher toxicity [44]. Although the compatibility improved progressively between imidazolium-based ILs and lipids of SC as the length of alkyl chains increased, toxicity also increased, as is made evident by the molecular dynamic simulation [45]. Imidazolium cations were partially inserted into the phosphatidylcholine lipid bilayer. It would penetrate deeper as the length of alkyl chains increased, which explained the relationship between toxicity and transdermal enhancing effects of imidazolium-based ILs. On the other thing, ILs have specific inhibitory effects on enzymes. Their inhibition role is derived from the cations where pyridinium or imidazolium exerted more potent inhibition than others. The toxicity of cationic moiety was assessed and graded as follows: choline < piperidinium < pyrrolidinium < morpholinium < pyridinium = imidazolium < ammonium < phosphonium [46].

Therefore, choline-based ILs are the most extensively researched ILs enhancers with the lowest toxicity and irritation. GRAS (generally recognized as safe) is an index determining the safety of additives or chemicals. CM-IL did not show any signs of irritation and toxicity toward mice skin and human epidermal cells due to components of CM-IL, both belonging to the GRAS [33]. Thus, toxicity and irritation to the skin could be avoided by screening to fall constituents of ILs within the GRAS. In conclusion, in addition to their fundamental enhancing effects, comprehensive evaluations of biocompatibility and safety must be carried out because they tend to intrude upon the conception of designing ILs.

Table 2
Listed here are some of applications of API-ILs to enhance transdermal drug delivery.

API	Counterion	Ref.
Lidocaine	Sodium docusate	[52]
Salicylic acid	Diethylamine	[72]
	Dipropylamine	
	Triethylamine	
	Triethanolamine	
Indapamide	Acetic acid	[63]
	Maleic acid	
	Oxalic acid	
Felbinac	Triethylamine	[64]
Loxoprofen	Ethanolamine	
	Diethanolamine	
	Triethanolamine	
Lidocaine	Diclofenac	[55,56]
	Etodolac	
	Ibuprofen	

4. API-ILs/ion pair techniques

4.1. The classification of API-ILs

ILs as permeation enhancers consist of anions and cations where both of them are indispensable, but each additional exogenous substance means more risk of inducing adverse effects. Therefore, a key consideration in more effective and safe transdermal delivery is modifying the physicochemical properties of drugs by adding one of two types of ions alone. As a result, the third evolution of ILs, API-ILs, has appeared. API-ILs are defined as ILs combined with API, firstly introduced by Davis in 1998 [47]. The tunable feature of ILs was associated with the combination of anions and cations with various characteristics [48]. The innovative conception of API-ILs is based on taking advantage of the difference of pK_a between API and counterions (at least $\Delta pK_a > 3$) to generate proton transfer, modifying the intermolecular packing of drugs and their polarity (Table 2) [49]. The mechanism of the ion-pair strategy was in line with the API-ILs, but it was not within the definition of the ILs [50,51]. Accordingly, the ion-pair strategy could be regarded as the "special API-ILs". It also lowered the melting point of the parent drug and increased its skin permeation. As a result, we put it under this chapter.

Currently, there are two main formulations in the development of API-ILs for transdermal delivery. The first category contains the combination of ionizable API and counterion. Lidocaine was clin-

ically used as local analgesia by intradermal injection, but it was reported low compliance relevant to pain, and patients complained that they had difficulty self-administrating. Thus, lidocaine contained ILs were prepared. Lidocaine-docusate, composed of lidocaine hydrochloride and non-pharmacologically active sodium docusate, was prepared to improve thermal stability and heighten local analgesia [52]. In addition, either colawet MA-80 or sulfacetamide approved by FDA is also applied combined with lidocaine to form ILs [53,54]. The second category includes a combination of two APIs with different pK_a to form ILs. Permeation of poorly water-soluble etodolac (ETO) has increased 9.3-fold across the Yucatane Micro Pig (YMP) skin after adding the lidocaine with the composition ratio of 1:1. It deserves a special note that although etodolac–lidocaine ILs pass through the skin, their skin permeation amount failed to have synchronous growth. Investigators found that lidocaine self-sacrificially improved the permeation of ETO [55]. The first production of API-ILs is MRX-7EAT (Etodolac-Lidocaine Topical Patch) to treat ankle sprains. What's more, lidocaine-ibuprofen (Lid-Ibu) permeation rate through an artificial membrane increased compared with conventional ionized lidocaine or ibuprofen salts in solvents [56,57]. Local anesthesia of lidocaine-ibuprofen took effect within 20 min, significantly faster than the commercially-available eutectic mixture of local anesthetics (EMLA), which needs at least 1 h.

4.2. The enhancement mechanism of API-ILs

In general, the solubility of a permeant in the SC lipid domain is one of the determinants of the permeation ability [58]. Moreover, the drug with a lower melting point tends to attain greater skin permeation because the more depressed melting point of drugs is, the higher concentration gradient between matrix and skin they could produce to pass through the skin at a more rapid pace [59]. Additionally, the permeation rate also depends upon the thermodynamic activity resulting from activity proportional to the concentration. Higuchi detailed the relationship between the activity of drugs in matrix and permeation flux as follows (Eq. 1):

$$J_s = (\sigma_v/\gamma_s)AD/H \quad (1)$$

where σ_v and γ_s are the activity of drugs in the matrix and the skin, respectively. A is defined as the permeation area, D and H are diffusion coefficient, and the thickness of the boundary.

In summary, the permeation rate promotes by screening proper counterion to depress the melting point of the parent drug. One of the reasons contributing to the high melting point is the highly ordered structure mediated by the electrostatic force. Thus, bulky and asymmetric counterions would increase the distance between positive and negative charges to disturb the lattice packing of parent drugs, resulting in a depressed melting point. As a side benefit, charge density further decreases with the increased steric hindrance attributed to the counterion enabling the electrostatic force to be weak enough to offset the high entropy, maintaining the structural stability in the case of liquids. Solid ibuprofen with low skin permeability was converted into the liquid to form API-ILs following combination with proline ethylester (ProOEt), resulting in 10-fold skin permeation enhancement [60]. Moreover, the hydrogen bond also helped to increase the melting point. Choline chloride (ChCl)/urea possessed a higher melting point because of hydrogen bonds between salt and HBD [61], whose mechanism was clarified by molecular dynamics simulations that the number of hydrogen bonds was inversely correlated with melting point [62]. HBD contained in the structure of the drug was also involved in the permeation process [63]. Tayar pointed out that many HBA groups (ester groups, phosphate groups, *etc.*) existed in the lipid phase of SC, prone to bind with protonic compounds to form stable hydrogen bonding and restrain the drug diffusion [64]. As a result, it was speculated that the formation of API-ILs transferred protons in drugs to result in fewer chances of binding with HBA, increasing the drug permeation.

In addition, the skin consists of hydrophobic SC filled with different sorts of lipids and hydrophilic VED. In other words, only could drug with suitable solubility between the oil and water phase permeate the skin into the systemic circulation. Therefore, the 1-octanol-water partition coefficient (log$P_{o/w}$) is considered as one of the indicative indexes for assessing drug permeability [65]. The log$P_{o/w}$ of the parent drug is changed by selecting counterions with different lengths of alkyl chains to modify drug permeation. Song *et al.* applied the ion pair strategy by selecting four counterions (fumaric acid (F), maleic acid (M), tartaric acid (T), and benzenesulfonic acid (B)) to control the permeation behavior of bisoprolol (BSP) to achieve long-acting delivery. The results showed that the resulting ion-pair restrained the permeation of BSP with the decrease of log$P_{o/w}$ and increase of molecular weight [66]. However, skin permeation of the given API-ILs is not always improved with the increase of log$P_{o/w}$ as a result of API-ILs that is not a totally combined chemical entity, and their properties may be changed in various environments. In general, oral drugs have experienced from acid to weak basic environments followed by the absorption in the intestine. Thus, API salts are significantly protonated when the pH value of the environment is lower than the pK_a value of weakly acidic API, converting the API into free acid to recrystallize [67]. In fact, the transdermal permeation process is also accompanied by gradual changes in pH values and polarity. The surface of normal skin performs weak acidity, and its pH values are from 5.5∼7.0, prone to be influenced by external and internal factors [68]. The transdermal permeability coefficient of ibuprofen decreased with increased pH values [69]. In addition, the change of polarity is also an essential factor [70]. Zhao *et al.* selected a series of homologous fatty acids with different lengths of alkyl chains as counterions of BSP to comprehensively investigate the molecular mechanism of ion-pair in transdermal delivery. Molecular weight and melting point, which were thought of as factors affecting transdermal permeation, were excluded as a result of insignificant correlation with logk_p. Furthermore, it was discovered that a negative correlation between logk_p and log$P_{o/w}$ in ion-pair as opposed to positive correlation, which was in contradiction with previous investigations. Thus, the ^{1}H NMR study and molecular dynamic simulation were well utilized for a better understanding of the mechanism. They found ion-pair was stable in the polar environment but not in the nonpolar environment. Accordingly, based on phenomenon and characterization, they concluded that ion-pair was more stable in SC compared to that in VED, where it tended to dissociate into BSP [71].

Until now, systematic investigation on selecting the counterion structure to improve the skin permeation of API-ILs was still missing. Yang *et al.* detailed how the counterion structure affected the formation of API-ILs and skin permeation. They selected a series of anti-inflammatory drugs as parent drugs and five basic compounds used to be as counterions. They found a positive correlation between the volume of counterion and the declined degree of melting point owing to decreased ionic interaction and increased van der Waals force. Nevertheless, API-TAA (triamylamine) with the lowest ΔT_{mean} failed to provide significant enhancing effects. On the one hand, the molecular weight was responsible for drug permeation. On the other hand, API-TAA with the highest polarizability resulted in stronger interaction between ILs and components of skin and fewer drugs permeation. Therefore, the authors finally chose diethylamine (DEA) with medium M.W., log$P$, and polarizability as the counterion [72]. According to the above investigations of designing API-ILs, it was found that it is not enough to consider decreasing melting point and log$P_{o/w}$ merely. Other aspects of resulting API-ILs, including molecular weight and molecu-

lar volume, should also be considered [73]. In practical terms, API-ILs play a dual-regulatory role in TDD. On the one hand, API-ILs can increase the skin permeation of drugs to improve transdermal delivery efficiency. On the other hand, the given API-ILs could depress transdermal absorption of drugs with high permeation flux to design the long-acting formulation. Therefore, the properties of parent drugs could be modified by screening proper counterions to design API-ILs to meet the practical needs of transdermal delivery.

5. Design of ILs-assisted dosage form

In addition to being enhancers to weaken the barrier function of SC by disturbing lipids or as a moiety of the parent drug to change physicochemical properties of API to improve the skin permeation, ILs also have come into use in the transdermal preparation as excipients, such as microemulsions, pressure-sensitive adhesive and gel.

5.1. ILs based microemulsions

At present, investigators aim at developing ILs-based microemulsions (MEs) in their potential to increase drug loading and skin permeability by drawing on ILs. The flexibility to tune physiochemical properties enables ILs to be added in MEs as oil phase, water phase, or surfactants. Therefore, IL-based MEs fall into two categories, including IL in oil (IL/o) and IL in water (IL/w) MEs (Fig. 1). ILs are used to constitute the hydrophilic core for solubilizing poorly soluble drugs in IL/o microemulsions. It was reported that hydrophilic ILs was an effective means to enhance the solubility of acyclovir (ACV) [74]. Based on this, IL/o have potential to develop the MEs for poorly water-soluble drugs required in high does. In IL/w microemulsions, ILs were utilized to substitute the oil phase that showed limited capability of dissolving drugs and permeability, such as isopropyl myristate (IPM) [75].

Conventional w/o MEs enhance the limited skin permeation of water-soluble drugs caused by the SC with nonpolar properties. Since the solubility of API in the water phase has determined the drug-loading capacity, so much so that the transdermal delivery capability of MEs for water-soluble drugs can vary only within certain limits. Poor compliance of commercial creams containing 5-fluorouracil (5-FU) was reported as a result of low permeability and irritation [76]. Goindi *et al.* developed the IL/o-based ME, of which the water phase was substituted with 1–butyl–3-methylimidazolium bromide (BMIMBr) to triple the solubility of 5-FU. More than that, nanosized globules distributing the 5-FU were

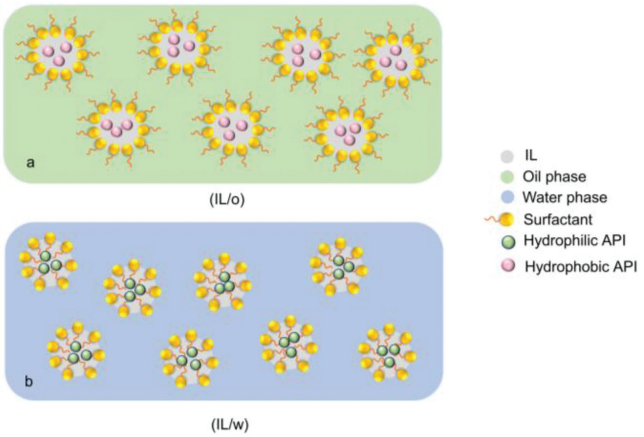

Fig. 1. Schematic diagrams of ILs-based microemulsions: (a) IL-in-oil (IL/o MEs), (b) IL-in-water (IL/w MEs).

responsible for enhanced release of API and volatilization of partial volatile components to lead to a supersaturation system, increasing the skin permeation [77]. The most popular cationic components of ILs are the substituted imidazolium cations $[C_nmim]^+$, which interact with drugs or surfactants to increase the stability of MEs [78]. Moreover, coordinating anion with strong HBA in ILs was more efficient as disperse phase in the case of the same cationic moiety [79]. ILs also substitute the oil phase to prepare IL/w-based MEs. IPM with a small molecular volume is commonly applied as the oil phase because the minimum concentration of surfactants (Tween-80) required for emulsifying the IPM-based oil phase indicates the maximum emulsify efficiency compared with other commonly applied oil, such as castor oil, Capmul, and oleic acid [80]. However, the dissolving capacity of drugs in IPM limits thermodynamic activity and permeability. Solubility of ETO in 1-butyl-3-methylimidazolium hexafluorophosphate ($BMIMPF_6$) increased double as much as that in IPM. *Ex-vivo* permeation study showed that the 24-h cumulative penetration percentage of ETO-loaded IL/w based-ME (99.030% ± 0.921%) was higher than that of ETO-loaded o/w ME (61.548% ± 1.875%) and oily solution of ETO (48.830% ± 2.488%) [73]. Further, ILs manifested amphiphilic properties by changing the length of the alkyl chain to be used as surfactants. Not only that, but surfactants prepared by ILs also reduced the toxicity after the polar groups were introduced into the alkyl side chain [81,82]. ILs as surfactants improve the finite skin permeation of drugs mainly from two aspects. On the one hand, hydrophile-lipophile balance (HLB) values of emulsifiers would be changed following the polarity of ILs modulated to improve the stability of MEs [83]. On the other hand, cationic moiety in ILs was able to extract and disturb lipids, and anionic moiety boosted the skin hydration to improve drug penetration [84]. In conclusion, compared with conventional MEs, IL-based MEs more efficiently enhanced the solubility of hydrophilic and hydrophobic drugs in the formulation and skin permeability. What is more, toxicity and irritation are also depressed by tuning ILs structure. Thus, ILs-based MEs with many such advantages have broad application prospects in enhancing transdermal drug delivery.

5.2. Ion-pair strategy for patches

Modern TDDS refers to patches, consisting of an impermeable backing, a rate-controlling membrane, skeleton materials, and a release liner. Drug in adhesive (DIA) patch, a polymeric matrix where drugs are dissolved, has been widely accepted because of its simple manufacturing technology, excellent compatibility, and mechanical properties [85]. DIA principally comprises pressure sensitive adhesive (PSA), drugs, and excipients, where PSA is the key to controlling drug release.

ILs were designed to change the interaction strength of the PSA-drug system to control release rate by introducing the proper counterion into the patch. The patch containing escitalopram (ESP) is hard as the sustained preparation, resulting from excellent skin permeation of the drug [86]. The patch containing the ion-pair formed by ESP and benzoic acid (BA) showed the highest skin flux for three days compared with other ion-pairs and better controlling release performance. The results showed that the transdermal process was dominated by drug release from the patch. A key consideration in controlling release rate is the interaction between PSA and the drug or ion-pair. C=O of PSA merely interacted with ESP, whose N and O atoms were weak HBAs by dipole-dipole interaction [87], which implied that weak interaction and sink condition sped the drug release. However, the deprotonated COO^- group of BA following the formation of ion-pair formed strong hydrogen bonding with OH of PSA to delay the ESP release, making the patch have the potential to offer three-day therapeutic effects [88]. The proton transfer is incomplete for API-ILs formed by weak acid

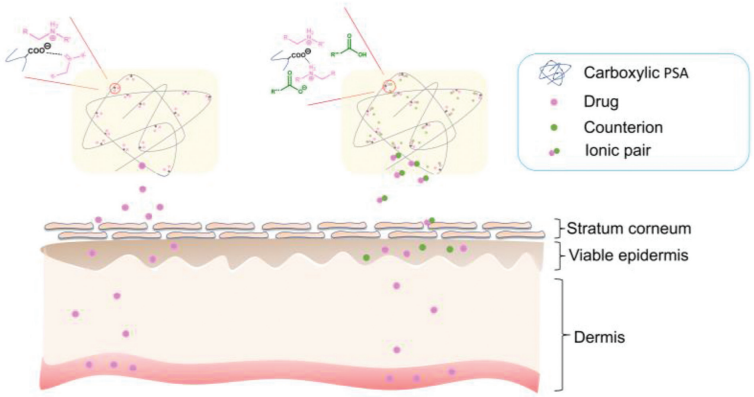

Fig. 2. Molecular interactions involved in the controlling release processes of ion-pair in pressure sensitive adhesive. Reproduced with permission [91]. Copyright 2018, Elsevier B.V.

and base in pharmaceutical applications compared with the proton of general salts, which transfers entirely from the strong acid to base [89,90], which means that the unpredictable location of the proton would lead to complex interaction. BSP-C_{12} (lauric acid) ion-pair patch showed lower values of C_{max} and longer mean residence time than those of the BSP patch, which indicated that BSP-C_{12} possessed better controlling release effects. In this situation, a competitive relationship existed between PSA and lauric acid because the –COOH of PSA and lauric acid both had a chance of forming ionic and hydrogen bonding interaction with the weak base drug (BSP). They detailed that partially dissociated $BSPH^+$ formed ionic H-bond with PSA-COO^- to provide a similar release rate from the thermodynamic view; the formation of doubly ionic hydrogen bond between undissociated C_{11}–COO^- $BSPH^+$ and PSA-COO^- virtually controlled the drug release more efficiently from kinetics (Fig. 2) [91]. Apart from the API-ILs-PSA interaction, the ion-pair would influence the molecular mobility of PSA to modify the drug release rate from the transdermal patch [92]. Thus, the interaction involved in the API-ILs based patch should be thoroughly clarified, helping to modify the drug release in the case of not changing the cumulative permeation amount.

ILs are also designed to be used as recrystallization inhibitors in patches. The drug is usually loaded into PSA at saturated or closed to saturated concentration contributing to minimizing the surface area of patches and maximizing the drug's thermodynamic activity in the matrix [93]. On the contrary, a high concentration of drugs in the patch increases the risk of recrystallizing and affects dosage and therapeutic efficacy [94]. Moreover, tack, peel and shear strengths were reduced with the advent of drug crystals [95]. Neupro® containing rotigotine and Duragesic® containing fentanyl were recalled because of recrystallization [96]. In general, recrystallization inhibitors are introduced in PSA to avoid the presence of crystals, such as polyvinylpyrrolidone (PVP) and crosslinked polyvinylpyrrolidone (CPVP) [97,98]. However, the drug release rate was promoted after CPVP was incorporated into polyisobutylene-based PSA [99,100], unfavorable to the sustained release of drugs. Still, CPVP also increased the cohesive strength of the matrix and affinity to the skin [101]. Thus, desirable additives inhibit the recrystallization from improving drug loading and enhancing permeation if not affecting the drug release rate. Room-temperature ionic liquids (RT-ILs), defined as ILs which keep the liquid-like state at ambient conditions, avoid the polymorphism [102]. RT-ILs inhibited from recrystallizing in two aspects. On the one hand, the bulky counterion increased the distance between drugs to reduce the interaction probabilities. On the other hand, the counterion decreased charge density, further weakening the ionic interaction to hold the liquid-like state. The phenomenon that counterions provided inhibition effects on recrystallization in patches was firstly observed by Weng *et al.*, who found that fatty acids significantly inhibited the presence of crystals of risperidone (RISP) compared with PVP, polyethylene glycol (PEG), and surfactants attributed to the interaction between RISP and fatty acid [103]. Until recently, the mechanism of API-ILs used as recrystallization inhibitors in the patch was thoroughly clarified. Naproxen (NPX) was able to be loaded in PSA containing a carboxyl group to prepare the patch because of ion-ion repulsion and the H-bond interaction between drug and PSA [104]. It started to emerge drug crystals after 1 month of storage if the drug loading of the patch exceeded 3%, but the NPX loading rose to 30% without recrystallization after converting the NPX into ILs by using TAA [105]. The higher drug loading was attributed to the complex interaction between NPX-TAA and PSA, whose mechanism was different with changes in drug loading. NH^+ of TAA as HBD interacted with COO^- of NPX and COO^- of PSA to form ionic hydrogen bonds in the case of low NPX-TAA loading. However, at the high drug loading, besides the ionic hydrogen bond, excess NPX-TAA derived from the strong ionic interaction interacted with the carbonyl group of PSA. In other words, a combination of these interactions was responsible for higher drug loading in the patch. Interestingly, the patch containing 30% NPX-TAA had a similar drug release percent and rate to that containing 2% NPX.

In conclusion, the application of ILs strategy in the patch avoids the compromise between the drug loading and release. Not only does it control the drug release to reduce dosing frequency and extend therapeutic efficacy, but it also inhibits recrystallization and increases the drug loading, which implies that the ILs technique offers a promising strategy for overcoming the limitations in practical application.

5.3. Other IL-based transdermal preparation

Microneedle technology has received increasing attention because of its less pain, tissue harm, and better compliance in contrast to the conventional hypodermic needle, attributed to produced 200 μm depth by microneedle, which did not damage the dermis [106]. Conventional enhancing permeation strategy by disturbing lipids in SC is dwarfed by delivery strategy puncturing the skin provided by microneedle strategy [107]. Microneedle patches provide attractive means to break through the limitation of molecular weight, which deliver drugs that cannot be delivered by traditional transdermal techniques, such as biological macromolecules, including insulin, and vaccines [108,109]. It has been reported that a potent humoral immune response can be generated by microneedle to deliver the influenza vaccine against the influenza

virus in mice [110]. Even though microneedle patches offer excellent delivery efficiency, micro-channels formed by tiny needles also bring bacteria to induce the infection [111]. ILs showed excellent antibacterial activity capable of damaging charged, and hydrogen bonding networks existed within polypeptides and polysaccharides [112], which originated from cationic moiety, including imidazolium [113], pyrrolidinium [114], quaternary ammonium [115], *etc.* Poly(ionic liquids) (PILs) polymerized by ILs containing imidazolium are introduced into microneedle patches to be bacteriostatic agents and carriers [116,117]. It was observed that salicylic acid-loaded PIL-microneedles showed more efficient therapeutic effects on acne induced by *Propionibacterium acnes* (*P. acnes*) and prolonged treatment time as a result of the strong electrostatic interaction between imidazolium cations and salicylic acid anions (SA^-) introduced by anion exchange with bromide anions [118]. In fact, there is little research on the application of ILs in microneedles, but there is no doubt that ILs have significant development potential in aspects of bacteriostasis and controlling drug release from microneedle patches.

Gel with a good appearance, considerable stability, and excellent drug release characteristics is the most popular among the semisolid preparation used in the topical formulation [119,120]. Gels are divided into hydrogels composed of an aqueous phase and organogels consisting of an aqueous and organic phase, where hydrogels are extensively applied in the transdermal delivery field [121,122]. ILs are applied in gels from two aspects. One is as chemical enhancers and bacteriostatic agents added in gel formulation [123], but the rheological properties and viscosity should be taken into account because ILs risk interacting with gelling agents to be absorbed to lead to depressed viscosity and changes of the tensile strength [124]. Another is preparing gel-based material containing ILs, called ionogel, by one-pot photopolymerization to obtain a three-dimensional network structure diffusing throughout ILs to overcome shortcomings of the gel, including easy freezing and drying, resulting from outstanding thermal stability and less inflammability displayed by ILs [125–128]. Hydrophilic ILs substituted for the water phase to prepare hydrogels with excellent mechanical strength and transparency [129]. Even underwater, the resulting gels polymerized by hydrophobic ILs and monomers possessed strong adhesiveness. To our knowledge, ionogels mentioned above principally focus on the field of skin sensors to monitor the minor strains with high sensitivity but less application in topical or transdermal drug delivery. However, it is undeniable that the combination of ILs and gels is promising because the resulting material can avoid water evaporation or freezing which is favorable for drug release.

6. Future perspectives

Over the last few decades, ILs have been extensively used in varied fields due to their excellent performance and tunability, which can gratify different demands. Compared with other administration pathways, the unique advantages of transdermal drug delivery are much evident, which is limited by the strong skin barrier function, whereas a combination of ILs and augmentation strategies offers breakthroughs in transdermal delivery. The application of ILs in the transdermal field is no more a novel means of enhancing skin permeation, practically applied of which for drug permeation enhancement is dwarfed by all types of ILs obtained through an arbitrary combination between cations and anions. A design of optimal ILs for transdermal delivery from numberless types of ILs requires an in-depth understanding of factors affecting the skin permeation, including the barrier of SC, physicochemical properties of drugs, and formulation limitations. Therefore, ILs are able to offer personalized approaches, *i.e.,* tailoring the most suitable ILs for individual drugs to enhance the drug loading and permeation amount.

ILs as CPEs overcome the inefficiency of traditional CPEs due to excessive lipophilic or polar properties with the tuning of amphiphilicity by screening cations and anions with different lengths of alkyl chains and polar groups to adjust the amphiphilicity for more efficiently insertion into lipids to weaken the barrier provided by the skin. Therefore, ILs enhance skin permeation of not only for lipophilic and hydrophilic drugs but also for small molecular and macromolecular drugs, the boundaries of which are readily apparent, ILs have greater toxic effects on cells with increasing alkyl chains. Future studies should first aim to elucidate how structures of CPEs affect the permeation enhancing efficiency and toxicity and irritation to design more effective, less toxic, and irritative ILs. More importantly, the combined use of ILs and traditional CPEs should be taken into account, utilizing the advantages of both ILs and CPEs to reduce the toxicity and irritation while not reducing enhancing effects due to their complementary strengths. Therefore, there is a reasonable prospect of designing the near-ideal CPEs by exploiting the advantages of ILs.

API-ILs formed by the drug and counterion increase the limited permeation caused by the adverse physicochemical properties of the drug. In other words, ILs provide a strategy for transdermal delivery by individually tailoring the most appropriate counterion to the properties and deficiencies of the parent drug to maximize permeation amount or reduce the permeation for prolonged therapeutic effects. ILs dissociate with the change in environmental polarity to release active ingredients, which is preferable to prodrugs that depend on limited enzymes in the skin. Furthermore, they provide a perfect solution to polymorphism by converting solid API into a liquid-like state to improve the stability of the drug in formulation by repressing recrystallization more efficiently. One question that arises for ILs is an abundance of counterions available for weak acidic or basic drugs that needs in-depth analysis for key pharmaceutical parameters of APIs, which would otherwise cause problems in screening for suitable counterion. However, present counterions are difficult to alter multiple physicochemical parameters of drugs. Thereby, it would be a daunting task for formulation scientists to synthesize the counterion for the parent drug with poor properties to obtain the desired permeation behaviors. Although API-ILs modified the physicochemical properties and increased skin permeation of the parent drug, the long-term safety and stability of these altered drugs remained unknown, the therapeutical effects of which would not be guaranteed the same as the parent drug in clinical application no matter how well done.

In addition, ILs as excipients rely on their flexibility make it possible to solve various issues existing in the current formulation. ILs as solvents improve the solubility of drugs or other excipients in the formulation, with derived from advantages of negligible vapor pressure, thermal stability, and biodegradability, among which the lipophilic and hydrophilic ILs serve as oil and water phase respectively to dissolve different polar drugs, while amphiphilic ILs act as surfactants for solubilization and bacteriostasis. Theoretically, the addition of any excipients other than drugs to the formulation would negatively affect the mechanical properties of the resulting formulation and the release behaviors of drugs, while the addition of counterion or ILs could enable the preparation to achieve desirable release behaviors by introducing various interactions (hydrogen bond, ionic interaction, and ionic hydrogen bond) with predictable effects on mechanical performance. If the three aspects of the application of ILs in transdermal delivery were freely combined, there was the promise of producing perfect transdermal preparation with appropriate skin permeability, non-toxicity, non-irritation, and prolonged therapeutical effects.

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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.06.054.

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