Asian Journal of Pharmaceutical Sciences 19 (2024) 100900

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/AJPS

Review Article

Ionic liquids as the effective technology for enhancing transdermal drug delivery: Design principles, roles, mechanisms, and future challenges

Xuejun Chen[a], *Ziqing Li*[a], *Chunrong Yang*[a,*], *Degong Yang*[a,b,*]

[a] *Department of Pharmacy, Shantou University Medical College, Shantou 515041, China*
[b] *Guangdong Provincial Key Laboratory of Infectious Diseases and Molecular Immunopathology, Shantou University Medical College, Shantou 515041, China*

ARTICLE INFO

Article history:
Received 28 March 2023
Revised 25 December 2023
Accepted 8 January 2024
Available online 6 March 2024

Keywords:
Transdermal drug delivery system
Ionic liquid
Quantitative structure-activity relationship
Intermolecular interaction

ABSTRACT

Ionic liquids (ILs) have been proven to be an effective technology for enhancing drug transdermal absorption. However, due to the unique structural components of ILs, the design of efficient ILs and elucidation of action mechanisms remain to be explored. In this review, basic design principles of ideal ILs for transdermal drug delivery system (TDDS) are discussed considering melting point, skin permeability, and toxicity, which depend on the molar ratios, types, functional groups of ions and inter-ionic interactions. Secondly, the contributions of ILs to the development of TDDS through different roles are described: as novel skin penetration enhancers for enhancing transdermal absorption of drugs; as novel solvents for improving the solubility of drugs in carriers; as novel active pharmaceutical ingredients (API-ILs) for regulating skin permeability, solubility, release, and pharmacokinetic behaviors of drugs; and as novel polymers for the development of smart medical materials. Moreover, diverse action mechanisms, mainly including the interactions among ILs, drugs, polymers, and skin components, are summarized. Finally, future challenges related to ILs are discussed, including underlying quantitative structure-activity relationships, complex interaction forces between anions, drugs, polymers and skin microenvironment, long-term stability, and *in vivo* safety issues. In summary, this article will promote the development of TDDS based on ILs.

* Corresponding authors.
E-mail addresses: yangchunrong@stu.edu.cn (C. Yang), yangdg@stu.edu.cn (D. Yang).
Peer review under responsibility of Shenyang Pharmaceutical University.

https://doi.org/10.1016/j.ajps.2024.100900

1. Introduction

Transdermal drug delivery system (TDDS) is the third largest drug delivery system after oral and injection, which delivers drugs through the skin to achieve local or systemic therapeutics [1]. TDDS not only avoids the first-pass metabolism, gastrointestinal degradation, and "peaks and valleys" phenomenon of plasma concentration but also improves the patient's compliance [2]. However, for the purpose of effective transdermal absorption, most pharmaceutical molecules need to pass through the highly ordered and dense stratum corneum (SC) intercellular lipids, then enter the comparatively hydrophilic viable epidermis, and finally are distributed into the aqueous dermis for the systemic effect [3]. Thus far, there have been ~24 active pharmaceutical ingredients (APIs) developed into transdermal patches and approved in the market, because the optimal therapeutic compounds for TDDS have strict requirements for dosage (< 10 mg/d), molecular weight (< 500 Da), melting point (< 200 °C), and oil-water partition coefficient (2–4) [4,5]. Therefore, safe and effective transdermal penetrating technology is urgently required to improve skin permeation, which promotes the development of TDDS [6,7].

Ionic liquids (ILs) are organic salts with melting points below 100 °C, which are usually composed of organic cations and inorganic anions with large volume differences and asymmetrical structures [8]. Therefore, ILs were designed at the molecular level for achieving the expected goal, including enhancing the permeability of skin and the dissolution behavior of insoluble drugs, mainly by changing anions and cations [9–12]. These characteristics of ILs also show the unique advantages in TDDS; thus, the use of ILs has become a new direction and growing point of current studies of ILs [13]. For example, the choline and geranic acid (CAGE) ILs were employed for transdermal transport of nanosensors for thrombotic disease detection [14]. The ILs-based microemulsion formulation considerably increased the solubility of rosiglitazone and bezafibrate, which suggested that ILs-based microemulsion was adequate delivery carrier for hydrophobic drugs [15]. Using fatty acids as counterions, hydrophilic drugs were converted into oil-soluble drug-ILs, which improved their abilities to penetrate the skin [16]. As the antibiotic carrier, the hydrogel was prepared via copolymerization of microwave-responsive ILs and transdermal enhancer ILs, which performed excellently in microwave thermal therapy and facilitated transdermal drug delivery for addressing deep tissue infection [17].

Based on these results, we summarized different roles and mechanisms of ILs in promoting drug skin permeation. At present, the efficient ILs are obtained by means of numerous blind screening experiments. In comparison, systematic investigations on the quantitative structure-activity relationship between the structure and efficacy of ILs have not been performed. In particular, the underlying molecular mechanisms of ILs are still scarce [18,19]. Therefore, the review systematically elucidates the design principles, different roles and mechanisms of ILs, which provides scientific guidance for the development of ILs in TDDS.

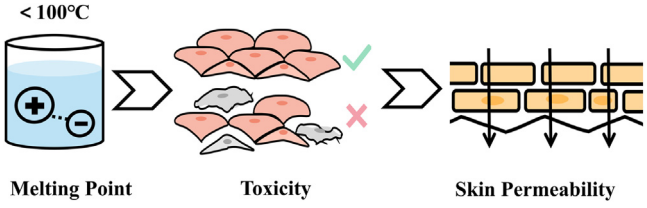

Fig. 1 – Design principles of ILs for the TDDS.

2. Design principles of ILs for the TDDS

The ideal ILs can be obtained by tuning the melting point, skin permeability, and toxicity of ILs (Fig. 1) [20–22]. ILs are composed of cations and anions, and their physicochemical properties are affected by the molar ratios, types, and functional groups of ions [23–25].

2.1. *Effects of ILs structures on melting points*

The melting point is chosen as the criteria based on the definition of ILs. ILs are organic salts with melting points below 100 °C. A study showed that the melting point of ILs is closely related to skin permeability [26]. Generally, the melting point ranging between −80 °C and 25 °C (room temperature) was considered suitable because the corresponding ILs exhibiting low lattice energy were used as solvents [13]. Compared with traditional organic salts, most ILs maintained the liquid state in the large temperature range [27]. The solid–liquid transition temperature of ILs was usually defined by the melting point (or glass transition temperature), which depended on the microchemical structures of anions and cations, including size, flexibility of carbon chain, charge distribution, and interaction (Table 1) [21,28,29].

The ILs with the bulky, asymmetric, and charge-delocalized ions displayed a lower melting point because the frustrated coordination and minimized interactions weakened the lattice energy of ILs [8,30,31]. The large structural entropy, rather than kinetic entropy, was proposed as the main factor contributing to the low melting points of ILs [32]. In general, the longer the alkyl chain of cation was, the higher the melting point of ILs was. For n-alkyl-n-methylimidazolium salts, the melting point sharply increased for alkyl chains with more than seven carbon atoms [33]. When the number of charges was same, anion with larger radii had lower melting point.

Table 1 – Melting point of ILs with different structures.

Cation	Anion	Molar ratio	T_m/T_g (°C)	Refs
$C_{14}min^+$	$N(CN)_2^-$	1:1	65.2	[34]
$C_{14}min^+$	$CF_3SO_3^-$	1:1	58.0	[34]
$C_{14}min^+$	$N(SO_2CF_3)_2^-$	1:1	41.1	[34]
$C_{16}min^+$	Tf_2N^-	1:1	46.9	[33]
$C_{18}min^+$	Tf_2N^-	1:1	53.5	[33]
$C_{20}min^+$	Tf_2N^-	1:1	62.5	[33]
Choline	Geranic acid	2:1	−88.9	[37]
Choline	Geranic acid	1:1	−71.8	[37]
Choline	Geranic acid	1:2	−77.5	[37]
Choline	Geranic acid	1:4	−76.8	[37]

Table 2 – Skin penetration amount of ILs with different structures.

Cation	Anion	Molar ratio	Cumulative skin penetration amount ($\mu g/cm^2$)	Refs
C_6	Bisoprolol	1:1	1318.7 ± 226.7 (8 h)	[42]
C_{12}	Bisoprolol	1:1	353.6 ± 35.3 (8 h)	[42]
C_{18}	Bisoprolol	1:1	246.3 ± 11.1 (8 h)	[42]
HEPP	Zaltoprofen	1:1	59.73 ± 1.60	[43]
HEPP	Zaltoprofen	1:1	59.57 ± 3.41	[43]
TEOA	Zaltoprofen	1:1	18.53 ± 2.53	[43]
DEA	Flurbiprofen	1:1	~2500 (24 h)	[21]
DEA	Loxoprofen	1:1	~1800 (24 h)	[21]
DEA	Mefenamic acid	1:1	~300 (24 h)	[21]
Lidocaine	Flurbiprofen	1:1	~100 (Lid 12 h) ~20 (Flu 12 h)	[44]

For 1-tetradecyl-3-methylimidazolium salt, the melting point was linearly related to the volume of anion, and larger anion produced lower melting point of ILs [34]. The composition ratio of anion and cation also affected the melting point of ILs. Nuthakki et al. studied the melting points of three ILs (ethanolammonium acetate, 2-methylbutylammonium formate, and pentylammonium formate) at the equimolar acid/base ratio and in the presence of excess acid and base. The dynamic scanning calorimetry results indicated that the melting points of ILs decreased with the addition of excess acid or amine [35]. The interactions between anions and cations are also important factors affecting the melting point of ILs. For example, the π-π ring stacking interaction considerably increased the melting point of anilinium salt [36].

2.2. *Effects of ILs structures on skin permeability*

The skin permeability of ILs is mainly affected by their physical and chemical properties, which in turn depend on the structures (Table 2). Wang et al. demonstrated that lidocaine and ibuprofen dissolved in ethanol as complex [Lid][Ibu] had strong intermolecular hydrogen bonds, which allowed simultaneous membrane transport of both APIs at higher rates than their corresponding commercial crystalline salts. In addition, they found that the mode and rate of transdermal transport of two APIs varied with their respective proportions in the ILs, which enabled the modulation of the membrane transport rate [38]. Wu et al. converted ibuprofen into ILs using aromatic, tetraalkylammonium and tetraalkylphosphonium salts. Compared with conventional sodium salts, the synthetic ILs showed enhanced skin permeability, which was associated with the higher ionic degree, higher log *P* values and lower water solubility [39].

Mechanistic studies revealed that hydrophobic molecular interactions between ibuprofen and alkyl counterions facilitated ion conjugation and ion pair formation, promoting transdermal penetration [39]. Using the quantitative structure-activity relationship (QSAR) model, Yang et al. found that the polarizability, molecular weight, and log *P* of counterions affected skin permeability of ILs [21]. The results suggested that van der Waals interactions between ILs and skin played an important role in disturbing the ordered arrangement of lipids [40,41].

Table 3 – Toxicity of ILs to human skin cells.

Cation	Anion	Molar ratio	Toxicity	LC_{50}/IC_{50}	Refs
2HEA	Ol	1:1	HaCaT cells	< 0.1 mg/l	[50]
BHEA	Ol	1:1	HaCaT cells	0.196 mg/l	[50]
m-2HEA	Ol	1:1	HaCaT cells	< 0.1 mg/l	[50]
C_4C_1pyr	NTf_2	1:1	NHDF cells	7.29 mM	[54]
C_6C_1pyr	NTf_2	1:1	NHDF cells	2.68 mM	[54]
C_8C_1pyr	NTf_2	1:1	NHDF cells	0.21 mM	[54]
C_4py	NTf_2	1:1	NHDF cells	1.39 mM	[54]
$C_2C_1C_1$im	NTf_2	1:1	NHDF cells	1.87 mM	[54]
$C_1OC_2C_1$im	NTf_2	1:1	NHDF cells	1.64 mM	[54]
HOC_2C_1im	NTf_2	1:1	NHDF cells	5.18 mM	[54]
C_4C_1pip	NTf_2	1:1	NHDF cells	0.32 mM	[54]
C_4C_1py	NTf_2	1:1	NHDF cells	2.81 mM	[54]
N_{4111}	NTf_2	1:1	NHDF cells	2.22 mM	[54]
C_4C_1im	TFO	1:1	NHDF cells	4.42 mM	[54]
C_4C_1im	OAc	1:1	NHDF cells	5.2 mM	[54]

2.3. *Effects of ILs structures on their toxicity*

ILs are considered as the green solvents. However, recent research has displayed that some ILs are poisonous [45–47]. The toxicity of ILs is related to nuclear structures and groups of anions and cations (Table 3). Furthermore, the toxicity of ILs is dependent on the cations structures [48]. Thus, ILs with imidazolium, pyrrolidinium, morpholinium, piperidinium, and ammonium cations usually show obvious toxicity and low degradability [49]. In contrast, the ILs containing choline and protic cations have fairly good biocompatibility [50]. In another work, the anions have exerted a considerable effect on overall toxicity. Hydrophilic anions have little contribution to toxicity of ILs, such as chlorine, bromine, organic carboxylate, alkyl sulfate, alkyl sulfonate, alkyl benzene sulfonate, and amino acid [51,52]. In contrast, ILs with anions containing fluorine, such as bis(trifluoromethanesulfonyl) amide, induce abnormal heart rate and liver damage in zebrafish [53]. The bis(trifluoromethanesulfonyl) amide anion also increased the cytotoxicity on normal human dermal fibroblasts, attributed to the enhanced lipophilicity of fluorinated alkyl side chain [54].

In addition to the core structure of ion, the length of the alkyl side chain also increases the toxicity of ILs [55]. Long alkyl chains (C > 4) endowed ILs with high hydrophobicity, which facilitated their insertion into the phospholipid bilayer and destroyed the integrity of cell membranes [56,57]. In addition, the functional groups of ILs are directly related to the overall toxicity. Polar groups, such as ether, ester, and hydroxyl groups, reduce the toxicity of ILs [58]. Hydrophobic aromatic groups enhance the toxicity of ILs [59].

In summary, melting point, skin permeability, and toxicity of ILs are three indexes considered important in the design of ILs for TDDS applications. The three indexes are interrelated and depend on cations and anions because the interactions between both components affect the lattice energy and thermodynamic activity. The weaker total interactions decrease the lattice energy. Regarding skin permeability and toxicity of ILs, the interactions between cations and anions affect the interaction between ILs and skin/cell membranes, that is, the interaction with adequate strength increases skin permeability. Therefore, the structures of cations and anions in terms of physicochemical parameters are the focus of research, such as polarizability (van der Waals interactions) and polar surface area (ability to form hydrogen bonds). The alkyl chains of ions have shown the substantial influence on the polarizability. In particular, longer alkyl chains cause non-optimal packing and the correspondingly lower melting point, albeit also causing the strong dipole–dipole interaction with the skin, which improves the skin penetration of ILs. The functional groups of ions, such as the hydroxyl group, affect polar surface area; when hydrogen bonds occupy main interaction sites of ions, the ability to form ionic interactions is weakened. In contrast with ionic interaction, hydrogen bond and dipole-dipole interactions are both weak noncovalent interactions. Therefore, increasing the strength of noncovalent interactions will be the research direction in the design of new ILs.

3. Roles and mechanisms

At present, the applications of ILs in the pharmaceutical field have received considerable attention, especially in the TDDS. The roles of ILs for TDDS are divided into the following four categories: skin penetration enhancers, solvents, active pharmaceutical ingredients-ILs (API-ILs) and Poly (ILs) (Fig. 2) [60–63].

3.1. *ILs as novel skin penetration enhancers*

The skin barrier prevents the loss of useful substances in the body and the invasion of harmful substances from the outside [64]. It plays an important role in maintaining the stability of the human body environment. However, it also brings difficulties for the percutaneous penetration of drugs, especially the brick-wall structure of SC [65]. Chemical penetration enhancers (CPEs) overcome the SC barrier in a simple and effective manner [66]. Owing to their unique physicochemical properties, the ILs have received extensive attention as novel CPEs [67–69].

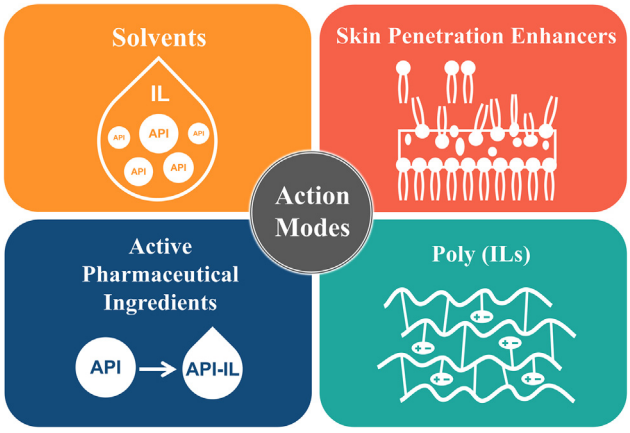

Fig. 2 – Different roles of ILs for the TDDS.

Currently, the ILs with high skin penetration enhancement ability mainly contain imidazole, amino acid ester and choline [70–72]. Among them, ILs with amino acid ester and choline have become research hotspots due to their superior biodegradability and transdermal delivery of biomacromolecules [73–76]. Other ILs are under development, such as cyclic onium salt, menthol/capric acid (Table 4) [77]. Therefore, manipulating the micro-structures of ILs has been proven to be an efficient way to improve their penetration-enhancing abilities.

ILs could enhance drug transdermal transport through cellular and intercellular pathways [89]. Hydrophilic ILs promote paracellular transport primarily by enhancing the fluidization of protein and lipid regions. Hydrophobic ILs facilitate the trans-cellular transport of lipid regions by providing channels [71,90]. Banerjee et al. used CAGE to enhance the transdermal penetration of insulin (Fig. 3A), which significantly reduced the blood glucose level of rats (Fig. 3B) [91]. After CAGE treatment, SC lipids were extracted, and the proportion of disordered protein structures was increased (Fig. 3C and 3D). Dynamic FTIR results revealed that ILs extracted skin components and changed the SC structures (Fig. 3E) [92]. It was also found that 1–butyl–3-methylimidazolium bromide enhanced the transdermal penetration by affecting the lipid mobility and keratin, depending on the appropriate molecular size, hydrogen bonding capability, and octanol-water partition coefficient [93].

Strong interaction forces are key factors for enhancing drug transdermal delivery. In particular, hydrogen bonds play an important role in promoting drug transport in the hydrophobic region of the skin [81]. Amphiphilic ILs interact with aliphatic carboxylic acid through hydrogen bonds in the excess acid state, and their skin penetration-enhancing ability is substantially enhanced compared with that in the neutral state [88]. Zhao et al. developed the novel ILs containing amino acid and citric acid for transdermal delivery of mesoporous silica nanoparticles (MSNs), which were strongly covalently bonded to ILs, resulting in high skin permeability stemming from the drag effect of ILs (Fig. 4A and B) [18]. Regarding safety and efficacy, Qi et al. revealed that ILs had the

Table 4 – Skin penetration enhancement of ILs.

ILs	Model drugs	Animals	Enhancement ratio	Refs
[L-LeuC12]Cl	5-Fluorouracil	Rat	7.14	[71]
[L-LeuC12]Cl	Hydrocortisone	Rat	2.28	[71]
[OIm]Cl	Testosterone	Mouse	3.69	[78]
[OMIm]Cl	Testosterone	Mouse	3.13	[78]
[OMMIm]Cl	Testosterone	Mouse	3.56	[78]
[C_{12}dabco]Br	Diltiazem	Rat	4.00	[67]
[C_4dabco]Br	Diltiazem	Rat	2.70	[67]
[$C_{10}C_1$Mor]Br	Diltiazem	Rat	1.40	[67]
[Choline][Geranic acid]	Mannitol	Pig	5.00	[79]
[Choline][Geranic acid]	Cefadroxil	Pig	6.20	[79]
[Choline][Geranic acid]	Methotrexate	Pig	6.00	[80]
[Choline][Geranic acid]	Nobiletin	Rat	3.00	[81]
[Choline][Malate]	Dextran	Pig	2.00	[72]
[Choline][Glycolate]	Cu^{2+}	Pig	6.60	[82]
[Choline][Analinate]	Ibuprofen	–	1.30	[83]
[Choline][Serine]	Ferulic acid	–	1.60	[84]
[Choline][C18:1]	Antigen peptide	Mouse	28.00	[61]
[Betaine][Malate]	Copper glycyl-histidine-tripeptide	Mouse; Pig	2.39	[85]
[Matrine][Coconutoleic acid]	Conotoxins	Mouse	5.70	[86]
[L-(-)-carnitine][DL-malic acid]	Insulin	Mouse	6.00	[15]
[EDMPC][Lin]	Ovalbumin	Mouse; Pig	15.14	[87]
[TIPA][OA]	Phenol red	Rat	18.00	[88]
[DIPA][ISA]	Phenol red	Rat	25.00	[88]

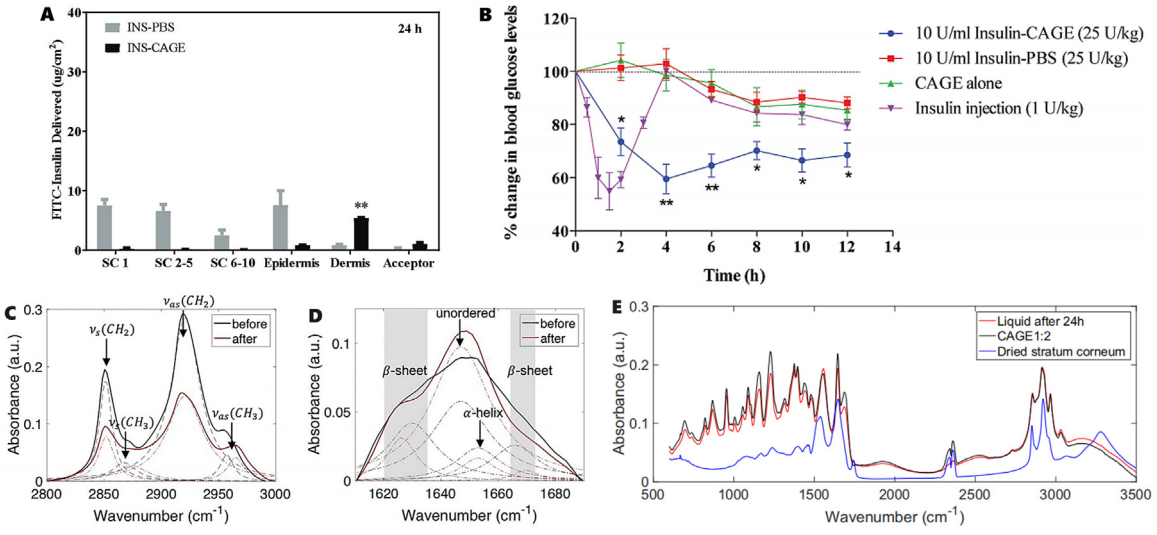

Fig. 3 – (A) Transdermal delivery of insulin with CAGE treatment *in vitro* ($n = 3$, $^{**}P < 0.005$); (B) Evaluation of CAGE as a transdermal insulin delivery material *in vivo* ($n = 6$, transdermal groups; $n = 3$, subcutaneous injection group; $^{*}P < 0.01$ and $^{**}P < 0.001$). (Reproduced with permission from [91], Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim). (C) FTIR spectra for SC samples with deconvoluted peaks in high wavenumber lipid region and (D) amide region; (E) FTIR spectra of SC by dynamic measurement. (Reproduced with permission from [92], Copyright 2019 Elsevier B.V. All rights reserved).

Hansen solubility parameter close to that of skin, thereby outperforming conventional CPEs (Fig. 4C). That was because ILs had adequate polar interaction and hydrogen bonding with the skin, which caused the ideal cohesive energy density range and good compatibility [94].

Novel ILs as skin penetration enhancers have been extensively studied, thus promoting the development of TDDS. However, two major issues need to be addressed: (1) the quantitative analysis of ILs is lacking, which results in blindness and uncertainty of screening of ILs in formula optimization. (2) comprehensive studies on skin enhancement mechanisms of ILs, especially the dissociation behavior of ILs in SC and active epidermis, are still required.

3.2. *ILs as novel solvents*

Solubility is an important parameter that directly affects skin absorption and the bioavailability of drugs. Most drugs are

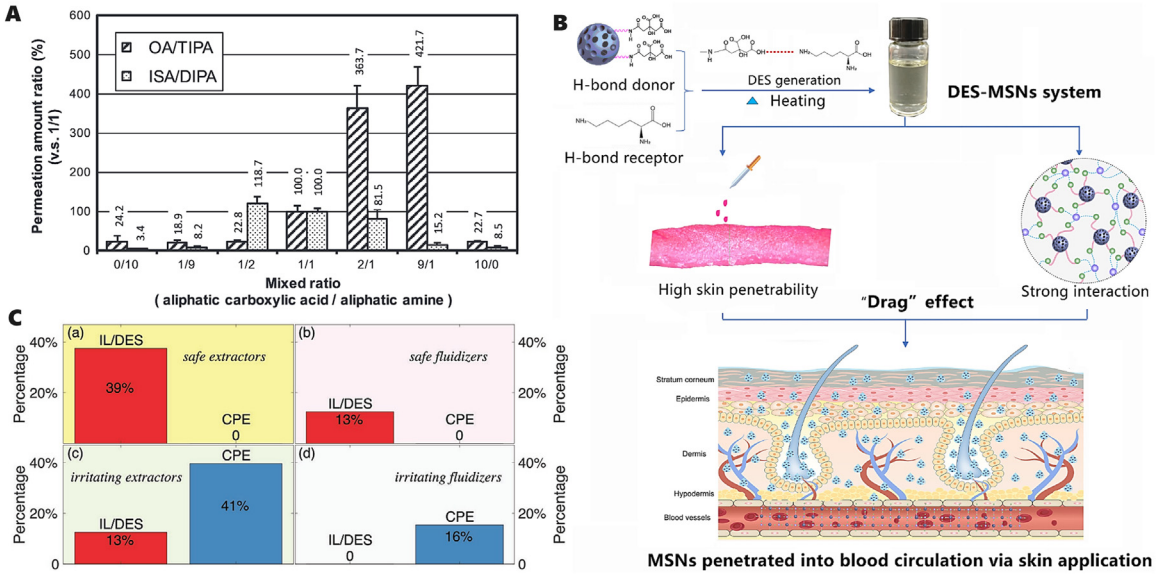

Fig. 4 – (A) Skin permeation amount ratio of phenol red incorporated in the liquid salt mixture (Reproduced with permission from [88], Copyright 2016 Published by Elsevier B.V.). (B) Preparation and action mechanism of DES-MSNs (Reproduced with permission from [18], Copyright 2022 Elsevier B.V. All rights reserved). (C) Comparison of percentages of ILs/DESs and CPEs causing spectral changes of SC (Reproduced with permission from [94], Copyright 2020 Wiley-VCH GmbH).

Table 5 – Solubility of drugs in ILs.

Cation	Anion	Molar ratio	Model drug	Solubility (mg/ml)	Refs
ProEt	Fer	1:1	Luteolin	42.5	[98]
ProEt	Cou	1:1	Luteolin	27.5	[98]
ProEt	Ben	1:1	Luteolin	10	[98]
Choline	Oleate	1:1	Paclitaxel	5	[99]
Choline	Glycine	1:1	Acyclovir	250 ± 17	[100]
Choline	Alanine	1:1	Acyclovir	210 ± 15	[100]
Choline	Serine	1:1	Acyclovir	135 ± 11	[100]
Menthol	Capric acid	3:7[a]	Risperidone	367	[101]
Menthol	Capric acid	5:5[a]	Risperidone	335	[101]
Menthol	Capric acid	7:3[a]	Risperidone	167	[101]
L-(-)-carnitine	DL-malic acid	1:1	Rosiglitazone	10[b]	[15]
L-(-)-carnitine	DL-malic acid	1:1	Bezafibrate	11.25[b]	[15]
Choline	Geranic acid	1:1	Ketoconazole	8.6[b]	[102]
DC-7	NTf_2	1:2	Amphotericin B	0.7	[103]
Choline	Hexanoate	1:1	Amphotericin B	6	[103]

[a] Mass ratios. [b] mg/g.

weak acidic or alkaline, and their water solubility is poor, which is the main obstacle in the development of new drug formulations. In this context, the ILs increase the solubility of insoluble small molecules and biomolecules, elevating their potential for drug delivery (Table 5) [95–97].

ILs are used to improve the solubility of hydrophilic, lipophilic and amphiphilic drugs by reducing the interfacial tension between drugs and solvent medium [104–106]. Owing to superior amphiphilic properties, ILs are used to improve the stability of lipid formulations [107–112]. Islam et al. developed the ILs-in-oil microemulsion for transdermal delivery of insulin using choline-fatty acids (Fig. 5A) [60]. In the ILs-assisted delivery system for cancer immunotherapy, the ILs containing choline and propionic acid formed the complex with ovalbumin (OVA), then was uniformly dispersed in the oil phase of isopropyl myristate (IPM) (Fig. 5B) [113]. Uddinet et al. reported that the ILs as the surfactants increased the stability, drug-loading capacity, and drug encapsulation in the ILs-in-oil nano-dispersions (Fig. 5C) [114]. Esson et al. synthesized the novel hydrophobic dicationic cholinium-based ILs, and the hydrophobic and hydrophilic regions of ILs mimicked the amphiphilicity of amphotericin B (AmB), thereby increasing the solubility of AmB [103]. In the effective ternary system, ILs also improved the solubility of acyclovir (ACV) (Fig. 5D) [100]. And the ternary system containing ILs was also suitable for water-soluble drugs [115].

In general, ILs improve the solubility through interactions with solutes [116,117]. Kunov et al. demonstrated the method

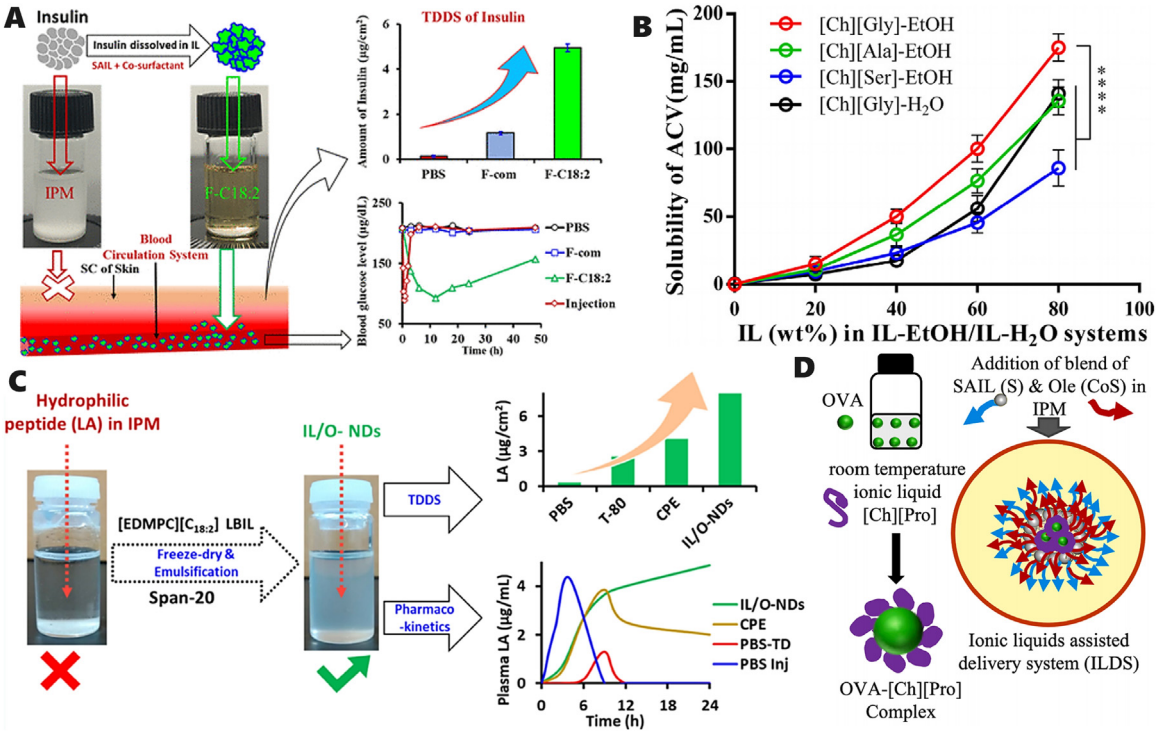

Fig. 5 – (A) Preparation of ILDS (Reproduced with permission from [60]. Copyright 2021 American Chemical Society). (B) Enhanced insulin solubility in surface-active ILs (Reproduced with permission from [113]. Copyright 2021 Elsevier B.V. All rights reserved). (C) ILs-in-oil nanodispersions (Reproduced with permission from [114] Copyright 2021 American Chemical Society). (D) Solubility of ACV in the IL-EtOH and IL-H_2O systems (Reproduced with permission from [100]. Copyright 2020 Elsevier B.V. All rights reserved).

for selecting ILs based on cosmo-RS calculations, revealing that the ability to accept hydrogen bonds was the most important factor [118]. The ILs based on proline ethyl ester phenolate facilitated the solubilization of bioactive compound luteolin (LUT) through multiple hydrogen bonds, π-π interactions, and cation-π interactions between LUT and ILs [98]. In the surface-active IL-assisted nonaqueous micelle, the multiple hydrogen bonds, π-π interactions and cation-π interactions between paclitaxel and SAIL[Cho][Ole] enhanced the solubility of paclitaxel in the micelle [99].

Due to the interaction between ions of ILs and specific groups of solutes, changes in the composition and structure of ILs lead to different solubilities of the solute [119,120]. Cholinium-based ILs with different anions showed different solubility enhancement ratios for naproxen and ibuprofen [121]. The solubility of risperidone, a hydrophobic drug, was improved using ILs containing menthol and capsaicin, which was increased with increased capsaicin content [101]. Wu et al. studied the solubility of ketoconazole, a hydrophobic drug, in ILs with different carboxylic and amino acids. They found that the differences in the lengths and branches of the alkyl chains and the number of hydroxyl and carboxyl groups were the main reasons for the solubility difference of drug in ILs. In addition, the same groups in different systems also exerted different effects on the solubilities of drugs [102].

ILs, as novel solvents, play an important role in enhancing drug solubility, mainly attributed to increasing interaction strength between drugs and excipients. Since the interactions between anions and cations are reversible, and ILs interact with acidic and alkaline drugs. In terms of safety, more attentions are paid to the dosage of ILs.

3.3. *ILs as novel APIs*

Using an API and a counterion or two different APIs, API-ILs are formed and used in the transdermal, oral, and injectable drug delivery systems [122–124]. Therefore, the screening of suitable counterions is very important [125–127]. API-ILs effectively control skin permeability, drug-polymer miscibility, release performance and pharmacokinetic behaviors of drugs (Fig. 6) [128–131]. In addition, some ILs exhibit biological activities, which synergistically enhance the efficacy of the APIs [132–134].

3.3.1. *Regulating drug skin permeability*

Transforming insoluble API into API-ILs increases the penetration amounts [135,136]. Furukawa et al. prepared API-ILs containing non-steroidal anti-inflammatory drugs with proline ethyl ester (counteraction), which enhanced the transdermal penetration of drugs [137]. Moshikur et al. used n-methyl-2-pyrrolidone (NMP) as an effective biocompatible counterion for the preparation of API-ILs. The resulting NMP-ILs showed better physico-thermal stability, enhanced skin penetration, and enhanced drug accumulation 2.6 times in

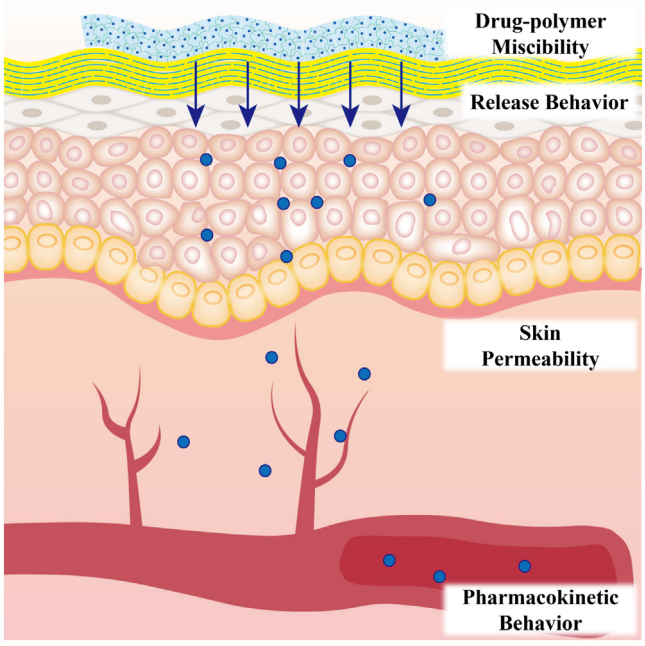

Fig. 6 – Different roles of API-ILs.

Table 6 – Regulating drug-polymer miscibility utilizing API-ILs.

Cation	Anion	Molar ratio	Polymer	Refs
Lidocaine	Ibuprofen	1:1	PVDF	[142]
Lidocaine	Naproxen	1:1	PVDF	[142]
Lidocaine	Diclofenac	1:1	PVDF	[142]
Choline	Citrate	1:1	Gelatin	[140]
Naproxen	Triamylamine	1:1	PSA	[129]
Cholinium	ibuprofenate	1:1.05	BC	[143]
Cholinium	ketoprofenate	1:1.05	BC	[143]
Cholinium	naproxenate	1:1.05	BC	[143]
Lidocaine	Diclofenac	1:1	Eudragit NE 30 D	[145]
Choline	Glycolic acid	1:1	PVA, PDA	[82]

the target tissue [138]. The skin penetration of ketoprofen was also improved after the addition of piperine (molar ratio: 1:1) [139]. The main contents are illustrated in detail in Section 2.2.

3.3.2. *Regulating drug-polymer miscibility*

Polymers are often used for the development of sustained and controlled release preparations. Choline citrate, a bio-based IL, was shown to stabilize homogeneous gelatin–lignin UV-shielding films with excellent antimicrobial and mechanical properties [140]. In addition, API-ILs are also used to improve the drug-loading in the polymers (Table 6). The carboxylic pressure-sensitive adhesive (PSA) effectively inhibited API-ILs recrystallization and increased the drug loading [129]. It was shown that a strong ionic hydrogen bond was formed between API-ILs and PSA-COO^-, and a normal hydrogen bond was formed between API-ILs and carbonyl group of PSA, which synergistically increased the drug capacity in PSA [141]. Abednejad et al. synthesized the dual biofunctional ILs with analgesic and anti-inflammatory properties using lidocaine-derived cations and hydrophobic NSAID-derived anions. The API-ILs were successfully blended with the hydrophobic polyvinylidene fluoride membrane as the top layer of the reservoir [142]. To incorporate low water-soluble API, namely ibuprofen, ketoprofen, and (S)-naproxen, into bacterial cellulose membranes, Chantereau et al. converted these drugs into choline-based ILs and fabricated BC-ILs membranes, which exhibited the improved rehydration capability compared with that of pure BC [143]. Halayqa et al. developed a novel drug delivery system based on grafted-Poly(L-lactide) (API-ILs-LA) nanoparticles, finding that API-ILs-LA reached a maximum encapsulation efficiency of 92.0% ± 2.7% [144]. The above studies show that API-ILs regulate the miscibility between drugs and polymers, thus facilitating the development of new drug delivery systems.

3.3.3. *Regulating drug release behavior*

The interactions between drugs and polymers exert the considerable influence on the drug release, such as ionic bonds, hydrogen bonds, and van der Waals forces [146,147]. The interaction nature and strength of these interactions are related to the types of donor and acceptor [148]. Accordingly, the formation of API-ILs changes the interactions between API and polymer, thereby modifying the drug release amount and rate (Table 7). Lozoya-Agullo et al. designed the ILs with brilliant blue to achieve a slow release by encapsulating them in polymer nanoparticles (NPs). *In vitro* release studies showed that the release of NPs was pH-dependent and exhibited a suitable release profile [149]. Zhou et al. converted gliclazide into API-ILs using tributyl(tetradecyl) phosphonium. *In vitro* dissolution tests showed that a sustained drug release of 88.17% in transdermal patches was achieved within three d [128]. Wu et al. transformed donepezil into API-ILs and prepared a controlled release DIA transdermal patch. This was mainly due to the higher molecular mobility of API-ILs DIA patch, which enhanced drug release [150]. Yang et al. investigated the release characteristics of two active ingredients of API-ILs. They found that release amounts of two drugs of API-ILs in four PSAs were all significantly

Table 7 – Regulating drug release behavior utilizing API-ILs.

Cation	Anion	Molar ratio	Drug cumulative release (%)	Refs
Brilliant blue	Atenolol[a]	1:1	100	[149]
$P_{6,6,6,14}$	Gliclazide[a]	1:1	88.17 ± 3.59	[128]
Triethylamine	Ketoprofen[a]	1:1	~70	[130]
Lidocaine[a]	Ibuprofen	1:1	~90	[142]
	Naproxen	1:1	~85	[142]
	Diclofenac	1:1	~75	[142]
Choline	Mefenamic acid[a]	1:1	100	[144]
Lidocaine	Ibuprofen[a]	1:1	>90	[151]
C4MIm		1:1	~79	[151]

[a] Detected drug.

different, proving that the two components were not released synchronously. This was because PSAs participated in interionic interaction with the API-ILs and reduced the release of drugs [44].

3.3.4. *Regulating drug pharmacokinetic behavior*

API-ILs regulate the pharmacokinetic behavior mainly by promoting drug absorption, protecting drugs from degradation, slowing drug elimination and enhancing drug targeting distribution [152–154]. A study has shown that the high delivery efficacy of CAGE is attributed to inhibition of proteolytic enzymes [155]. Mohamed et al. used a series of structurally related amine counterions for investigating the stability of theophylline ILs and their active uptake in A549 lung cells. The results showed that the theophylline with the polyamine as counterion enhanced cell accumulation, which provided the novel strategy for the regulation of the pharmacokinetic behavior [156].

In summary, API-ILs strategy has shown a great advantage in regulating skin permeability, miscibility, release performance and pharmacokinetic behaviors of drugs. The design of new API-ILs requires a comprehensive and systematic investigation of the whole TDDS process instead of focusing on a specific step, as has been done to date. More importantly, identifying changes in the original pharmacological action of API upon formation of API–ILs is very crucial for the clinical applications of API–ILs.

3.4. *Poly (ILs) as novel polymers*

Poly (ILs), as the new type of polymers, are formed using ILs as monomers, which combine the low volatility and thermal and electrochemical stability of ILs with mechanical durability of polymers [157,158]. Poly (ILs) are mainly used for the development of intelligent devices and drug carriers [159–162]. For example, the gel ionic conductor composed of polymeric gelant PMMA-r-PBA and ILs[EMI][TFSI] was proved to be highly stretchable, mechanically robust, and deformation durable, which was used in human motion sensors [163]. The problems of freezing and degradation of hydrogels at low temperatures were addressed by using the anti-freeze hydrogel based on amphoteric poly-ILs for multimodal artificial skin, which provided a new strategy for the development of sophisticated stimuli-responsive skins with multifunction and environmentally adaptable properties [164]. Poly(tetrabutylphosphonium styrenesulfonate), owning pH/thermal dual responsiveness, was used as a shell to prepare the drug nanocarrier with controlled drug release [165]. Cationic poly (ILs) with antibacterial activity have been used to construct novel TDDS [12]. The introduction of poly (ILs) into PVA hydrogel effectively improves the bactericidal activity, mechanical strength and tensile deformation of hydrogel [166]. Microneedle patches based on poly (ILs) synthesized using imidazolium-type ILs were loaded with salicylic acid and used to treat acne infections on account of their antibacterial and anti-inflammatory activity, which stemmed from electrostatic and hydrophobic interactions between the bacterial membrane and poly (ILs) [63]. A hydrogel wound dressing was prepared using deferoxamine (DFO) and halogen-free imidazolium poly (ILs). Under the exposure of hyaluronidase, the hydrogel degraded and continuously released DFO and poly (ILs), effectively promoting wound healing [167].

Nowadays, poly (ILs) as novel polymers have garnered considerable attention owing to their designability of ILs. However, studies on the application of poly (ILs) for TDDSs are still scarce owing to the complex synthesis and purification of poly (ILs), the limited availability of ILs monomers, and monomer residue problems. As a result, the screening of suitable ILs and optimization of the synthesis of poly (ILs) are still the subject.

4. Conclusions and challenges

ILs have great potential for the development of TDDS through different roles: as novel skin penetration enhancers for enhancing transdermal absorption of drugs, as novel solvents for improving the solubility of drugs in carriers or solvents, as novel APIs for regulating drugs and preparations properties, and as novel polymers for the development of smart medical materials. The investigations of the mechanisms of action of ILs contribute to the development and application of ILs. For instance, numerous research studies have proved that the functions of ILs are closely related to the structures. Specifically, the ion type, proportion, and functional group of ILs influence the functions owing to microscopic molecular force. However, further knowledge on the mechanisms of ILs is still required for their clinical application. Based on the current literature, the following challenges are proposed: (1) It is very necessary to construct valid quantitative structure-activity relationship models, which will provide basic design principles for the design of biocompatible ILs with specific functions. (2) Detailed studies on the action mechanism of ILs are still scarce. The underlying action mechanisms need to be unveiled according to changes in interionic interactions between cations and anions. (3) The investigation of the long-term stability of ILs is highly desirable, which may determine their efficacy and safety, in terms of the reversible noncovalent bonds between cations and anions. (4) The *in vivo* behaviors of ILs are still not clear, which may cause safety issues. So, studies on the pharmacokinetics of ILs are required. (5) Poly (ILs) as novel polymers combining the unique characteristics of ILs and polymers have drawn widespread attention. However, biocompatibility and biodegradability issues of poly (ILs) are still being explored.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Acknowledgments

This research was funded by the National Natural Science Foundation of China (82273881 and 82304386),

Guangdong Basic and Applied Basic Research Foundation (2022A1515110476), the Open Fund of Guangdong Provincial Key Laboratory of Infectious Diseases and Molecular Immunopathology (GDKL202214) and SUMC Scientific Research Initiation Grant (510858046 and 510858056).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2024.100900.

REFERENCES

[1] Qindeel M, Ullah MH, Fakhar-Ud-Din AN, Rehman AU. Recent trends, challenges and future outlook of transdermal drug delivery systems for rheumatoid arthritis therapy. J Control Release 2020;327:595–615.
[2] Ng LC, Gupta M. Transdermal drug delivery systems in diabetes management: a review. Asian J Pharm Sci 2020;15(1):13–25.
[3] Narangifard A, den Hollander L, Wennberg CL, Lundborg M, Lindahl E, Iwai I, et al. Human skin barrier formation takes place via a cubic to lamellar lipid phase transition as analyzed by cryo-electron microscopy and EM-simulation. Exp Cell Res 2018;366(2):139–51.
[4] Wiedersberg S, Guy RH. Transdermal drug delivery: 30+ years of war and still fighting!. J Control Release 2014;190:150–6.
[5] Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. Br J Pharmacol 2015;172(9):2179–209.
[6] Niu JX, Yuan M, Zhang ZW, Wang LY, Fan YL, Liu XH, et al. Hyaluronic acid micelles for promoting the skin permeation and deposition of curcumin. Int J Nanomed 2022;17:4009–22.
[7] Lee H, Park J, Kim YC. Enhanced transdermal delivery with less irritation by magainin pore-forming peptide with a N-lauroylsarcosine and sorbitan monolaurate mixture. Drug Deliv Transl Res 2018;8(1):54–63.
[8] Dean PM, Pringle JM, MacFarlane DR. Structural analysis of low melting organic salts: perspectives on ionic liquids. Phys Chem Chem Phys 2010;12(32):9144.
[9] Berton P, Di Bona KR, Yancey D, Rizvi SAA, Gray M, Gurau G, et al. Transdermal bioavailability in rats of lidocaine in the forms of ionic liquids, salts, and deep eutectic. ACS Med Chem Lett 2017;8(5):498–503.
[10] Marrucho IM, Branco LC, Rebelo LPN. Ionic liquids in pharmaceutical applications. Annu Rev Chem Biomol Eng 2014;5(1):527–46.
[11] Wang BS, Qin L, Mu TC, Xue ZM, Gao GH. Are ionic liquids chemically stable? Chem Rev 2017;117(10):7113–31.
[12] Gao YR, Zhang WX, Li LY, Wang ZJ, Shu Y, Wang JH. Ionic liquid-based gels for biomedical applications. Chem Eng J 2023;452:139248.
[13] Agatemor C, Ibsen KN, Tanner EEL, Mitragotri S. Ionic liquids for addressing unmet needs in healthcare. Bioeng Transl Med 2018;3(1):7–25.
[14] Bekdemir A, Tanner E, Kirkpatrick J, Soleimany AP, Mitragotri S, Bhatia SN. Ionic liquid-mediated transdermal delivery of thrombosis-detecting nanosensors. Adv Heal Mater 2022;11(11):e2102685.
[15] Lu BB, Bo YY, Yi MJ, Wang ZY, Zhang JC, Zhu ZY, et al. Enhancing the solubility and transdermal delivery of drugs using ionic liquid-in-oil microemulsions. Adv Funct Mater 2021;31(34):2102794.
[16] Md MR, Shimul IM, Uddin S, Wakabayashi R, Moniruzzaman M, Goto M. Transformation of hydrophilic drug into oil-miscible ionic liquids for transdermal drug delivery. ACS Appl Mater Interfaces 2022;14(50):55332–55341.
[17] Gao YR, Hao YN, Zhang WX, Wei YA, Shu Y, Wang JH. Microwave-triggered ionic liquid-based hydrogel dressing with excellent hyperthermia and transdermal drug delivery performance. Chem Eng J 2022;429:131590.
[18] Zhao ZY, Li MJ, Zheng LY, Yang Y, Cui XM, Xu TR, et al. Noninvasive transdermal delivery of mesoporous silica nanoparticles using deep eutectic solvent. J Control Release 2022;343:43–56.
[19] Zhang TH, Peng X, Li FL, Toufouki S, Yao S. Risk-focused investigation on ionic liquids against their applied background in transdermal delivery. J Mol Liq 2022;353:118770.
[20] R Md Moshikur, MdR Chowdhury, Fujisawa H, Wakabayashi R, Moniruzzaman M, Goto M. Design and characterization of fatty acid-based amino acid ester as a new “green” hydrophobic ionic liquid for drug delivery. ACS Sustain Chem Eng 2020;8(36):13660–71.
[21] Yang DG, Liu C, Ding DW, Quan P, Fang L. The molecular design of drug-ionic liquids for transdermal drug delivery: mechanistic study of counterions structure on complex formation and skin permeation. Int J Pharm 2021;602:120560.
[22] Gonçalves ARP, Paredes X, Cristino AF, Santos FJV, Queirós CSGP. Ionic liquids-a review of their toxicity to living organisms. Int J Mol Sci 2021;22(11):5612.
[23] Yavir K, Marcinkowski Ł, Marcinkowska R, Namieśnik J, Kloskowski A. Analytical applications and physicochemical properties of ionic liquid-based hybrid materials: a review. Anal Chim Acta 2019;1054:1–16.
[24] Oshizaka T, Inaba R, Isono M, Takei C, Takeuchi I, Mori K, et al. Effects of physicochemical properties of constituent ions of ionic liquid on its permeation through a silicone membrane. Chem Pharm Bull 2022;70(10):716–19.
[25] Zhou HC, Chen LF, Wei Z, Lu YJ, Peng C, Zhang B, et al. Effect of ionic composition on physicochemical properties of mono-ether functional ionic liquids. Molecules 2019;24(17):3112.
[26] Tsakovska I, Pajeva I, Al Sharif M, Alov P, Fioravanzo E, Kovarich S, et al. Quantitative structure-skin permeability relationships. Toxicology 2017;387:27–42.
[27] Chen R, Lascaris E, Palmer JC. Liquid–liquid phase transition in an ionic model of silica. J Chem Phys 2017;146(23):234503.
[28] Brooks NJ, Castiglione F, Doherty CM, Dolan A, Hill AJ, Hunt PA, et al. Linking the structures, free volumes, and properties of ionic liquid mixtures. Chem Sci 2017;8(9):6359–74.
[29] Lindenberg EK, Patey GN. Melting point trends and solid phase behaviors of model salts with ion size asymmetry and distributed cation charge. J Chem Phys 2015;143(2):024508.
[30] Pringle JM, Golding J, Baranyai K, Forsyth CM, Deacon GB, Scott JL, et al. The effect of anion fluorination in ionic liquids—physical properties of a range of bis(methanesulfonyl)amide salts. New J Chem 2003;27(10):1504–10.
[31] Yoshida Y, Muroi K, Otsuka A, Saito G, Takahashi M, Yoko T. 1-Ethyl-3-methylimidazolium based ionic liquids containing cyano groups: synthesis, characterization, and crystal structure. Inorg Chem 2004;43(4):1458–62.
[32] Endo T, Sunada K, Sumida H, Kimura Y. Origin of low melting point of ionic liquids: dominant role of entropy. Chem Sci Camb 2022;13(25):7560–5.
[33] Murray SM, O’Brien RA, Mattson KM, Ceccarelli C, Sykora RE,

West KN, et al. The fluid-mosaic model, homeoviscous adaptation, and ionic liquids: dramatic lowering of the melting point by side-chain unsaturation. Angew Chem Int Ed Engl 2010;49(15):2755–8.
[34] Nelyubina YV, Shaplov AS, Lozinskaya EI, Buzin MI, Vygodskii YS. A new volume-based approach for predicting thermophysical behavior of ionic liquids and ionic liquid crystals. J Am Chem Soc 2016;138(32):10076–9.
[35] Nuthakki B, Greaves TL, Krodkiewska I, Weerawardena A, Burgar MI, Mulder RJ, et al. Protic ionic liquids and ionicity. Aust J Chem 2007;60(1):21.
[36] Baker B, Cockram CJ, Dakein S, DeMaria JM, George DM, Malyk KR, et al. Synthesis and characterization of anilinium ionic liquids: exploring effect of π-π ring stacking. J Mol Struct 2021;1225:129122.
[37] Tanner EEL, Ibsen KN, Mitragotri S. Transdermal insulin delivery using choline-based ionic liquids (CAGE). J Control Release 2018;286:137–44.
[38] Wang H, Gurau G, Shamshina J, Cojocaru OA, Janikowski J, MacFarlane DR, et al. Simultaneous membrane transport of two active pharmaceutical ingredients by charge assisted hydrogen bond complex formation. Chem Sci 2014;5(9):3449.
[39] Wu H, Deng ZZ, Zhou BJ, Qi MH, Hong MH, Ren GB. Improved transdermal permeability of ibuprofen by ionic liquid technology: correlation between counterion structure and the physicochemical and biological properties. J Mol Liq 2019;283:399–409.
[40] Tian Q, Quan P, Fang L, Xu H, Liu C. A molecular mechanism investigation of the transdermal/topical absorption classification system on the basis of drug skin permeation and skin retention. Int J Pharm 2021;608:121082.
[41] Yang DG, Liu C, Quan P, Fang L. A systematic approach to determination of permeation enhancer action efficacy and sites: molecular mechanism investigated by quantitative structure-activity relationship. J Control Release 2020;322:1–12.
[42] Zhao HQ, Liu C, Quan P, Wan XC, Shen MY, Fang L. Mechanism study on ion-pair complexes controlling skin permeability: effect of ion-pair dissociation in the viable epidermis on transdermal permeation of bisoprolol. Int J Pharm 2017;532(1):29–36.
[43] Cui HX, Quan P, Zhou Z, Fang L. Development of a drug-in-adhesive patch combining ion pair and chemical enhancer strategy for transdermal delivery of zaltoprofen: pharmacokinetic, pharmacodynamic and *in vitro/in vivo* correlation evaluation. Drug Deliv 2016;23(9):3461–70.
[44] Yang DG, Chen XJ, Li ZQ, Yang CR. Mechanistic study of release characteristics of two active ingredients in transdermal patch containing lidocaine–flurbiprofen ionic liquid. Pharmaceutics 2022;14(10):2158.
[45] De Jesus SS. Maciel Filho R. Are ionic liquids eco-friendly? Renew Sustain Energy Rev 2022;157:112039.
[46] Marchel M, Cieslinski H, Boczkaj G. Deep eutectic solvents microbial toxicity: current state of art and critical evaluation of testing methods. J Hazard Mater 2022;425:127963.
[47] Wei P, Pan X, Chen CY, Li HY, Yan X, Li C, et al. Emerging impacts of ionic liquids on eco-environmental safety and human health. Chem Soc Rev 2021;50(24):13609–27.
[48] Mano B, Jesus F, Gonçalves FJM, Ventura SPM, Pereira JL. Applicability of heuristic rules defining structure-ecotoxicity relationships of ionic liquids: an integrative assessment using species sensitivity distributions (SSD). Green Chem 2020;22(18):6176–86.
[49] Miao S, Atkin R, Warr G. Design and applications of biocompatible choline amino acid ionic liquids. Green Chem 2022;24(19):7281–734.
[50] Ortega Vega MR, Baldin EK, Pereira DP, Martins MCS, Pranke P, Horn F, et al. Toxicity of oleate-based amino protic ionic liquids towards Escherichia coli, Danio rerio embryos and human skin cells. J Hazard Mater 2022;422:126896.
[51] Flieger J, Flieger M. Ionic liquids toxicity-benefits and threats. Int J Mol Sci 2020;21(17):6267.
[52] Cho CW, Pham TPT, Zhao YF, Stolte S, Yun YS. Review of the toxic effects of ionic liquids. Sci Total Environ 2021;786:147309.
[53] Padilla MS, Bertz C, Berdusco N, Mecozzi S. Expanding the structural diversity of hydrophobic ionic liquids: physicochemical properties and toxicity of gemini ionic liquids. Green Chem 2021;23(12):4375–85.
[54] Musiał M, Zorębski E, Malarz K, Kuczak M, Mrozek-Wilczkiewicz A, Jacquemin J, et al. Cytotoxicity of ionic liquids on normal human dermal fibroblasts in the context of their present and future applications. ACS Sustain Chem Eng 2021;9(22):7649–57.
[55] Bubalo MC, Radosevic K, Redovnikovic IR, Halambek J, Srcek VG. A brief overview of the potential environmental hazards of ionic liquids. Ecotoxicol Env Saf 2014;99:1–12.
[56] Jesus F, Passos H, Ferreira AM, Kuroda K, Pereira JL, Gonçalves FJM, et al. Zwitterionic compounds are less ecotoxic than their analogous ionic liquids. Green Chem 2021;23(1):3683–92.
[57] Pan X, Li L, Huang HH, Wu JL, Zhou XX, Yan XL, et al. Biosafety-inspired structural optimization of triazolium ionic liquids based on structure-toxicity relationships. J Hazard Mater 2022;424:127521.
[58] Weaver KD, Kim HJ, Sun J, MacFarlane DR, Elliott GD. Cyto-toxicity and biocompatibility of a family of choline phosphate ionic liquids designed for pharmaceutical applications. Green Chem 2010;12(3):507–13.
[59] Abramenko N, Kustov L, Metelytsia L, Kovalishyn V, Tetko I, Peijnenburg W. A review of recent advances towards the development of QSAR models for toxicity assessment of ionic liquids. J Hazard Mater 2020;384:121429.
[60] MdR Islam, S Uddin, MdR Chowdhury, Wakabayashi R, Moniruzzaman M, Goto M. Insulin transdermal delivery system for diabetes treatment using a biocompatible ionic liquid-based microemulsion. ACS Appl Mater Interfaces 2021;13(36):42461–72.
[61] Tahara Y, Morita K, Wakabayashi R, Kamiya N, Goto M. Biocompatible ionic liquid enhances transdermal antigen peptide delivery and preventive vaccination effect. Mol Pharm 2020;17(10):3845–56.
[62] Sahbaz Y, Williams HD, Nguyen T-H, Saunders J, Ford L, Charman SA, et al. Transformation of poorly water-soluble drugs into lipophilic ionic liquids enhances oral drug exposure from lipid based formulations. Mol Pharm 2015;12(6):1980–91.
[63] Zhang TK, Sun B, Guo JN, Wang MY, Cui HQ, Mao HL, et al. Active pharmaceutical ingredient poly(ionic liquid)-based microneedles for the treatment of skin acne infection. Acta Biomater 2020;115:136–47.
[64] Harris-Tryon TA, Grice EA. Microbiota and maintenance of skin barrier function. Science 2022;376(6596):940–5.
[65] Mojumdar EH, Kariman Z, van Kerckhove L, Gooris GS, Bouwstra JA. The role of ceramide chain length distribution on the barrier properties of the skin lipid membranes. Biochim Biophys Acta 2014;1838(10):2473–83.
[66] Ita KB. Chemical penetration enhancers for transdermal drug delivery-success and challenges. Curr Drug Deliv 2015;12(6):645.
[67] Monti D, Egiziano E, Burgalassi S, Chetoni P, Chiappe C, Sanzone A, et al. Ionic liquids as potential enhancers for transdermal drug delivery. Int J Pharm 2017;516(1):45–51.
[68] Zhang Y, Liu C, Wang JQ, Ren SJ, Song YL, Quan P, et al. Ionic liquids in transdermal drug delivery system:

current applications and future perspectives. Chin Chem Lett 2023;34(3):107631.
[69] Liu YW, Wu YJ, Liu JM, Wang WX, Yang QL, Yang GS. Deep eutectic solvents: recent advances in fabrication approaches and pharmaceutical applications. Int J Pharm 2022;622:121811.
[70] Santos DAT, Julio A, Saraiva N, Fernandes AS, Araujo M, Baby AR, et al. Choline- *versus* imidazole-based ionic liquids as functional ingredients in topical delivery systems: cytotoxicity, solubility, and skin permeation studies. Drug Dev Ind Pharm 2017;43(11):1858–65.
[71] Zheng L, Zhao Z, Yang Y, Li YM, Wang CX. Novel skin permeation enhancers based on amino acid ester ionic liquid: design and permeation mechanism. Int J Pharm 2020;576:119031.
[72] Wu XY, Chen ZJ, Li Y, Yu Q, Lu Y, Zhu QG, et al. Improving dermal delivery of hydrophilic macromolecules by biocompatible ionic liquid based on choline and malic acid. Int J Pharm 2019;558:380–7.
[73] Pereira R, Silva SG, Pinheiro M, Reis S, Vale MLD. Current status of amino acid-based permeation enhancers in transdermal drug delivery. Membranes 2021;11(5):343.
[74] Li XD, Ma NN, Zhang LJ, Ling GX, Zhang P. Applications of choline-based ionic liquids in drug delivery. Int J Pharm 2022;612:121366.
[75] Ossowicz-Rupniewska P, Klebeko J, Świątek E, Bilska K, Nowak A, Duchnik W, et al. Influence of the type of amino acid on the permeability and properties of ibuprofenates of isopropyl amino acid esters. Int J Mol Sci 2022;23(8):4158.
[76] Boscariol R, Oliveira Junior JM, Baldo DA, Balcão VM, Vila MMDC. Transdermal permeation of curcumin promoted by choline geranate ionic liquid: potential for the treatment of skin diseases. Saudi Pharm J 2022;30(4):382–97.
[77] Ali MK, Moshikur RM, Goto M, Moniruzzaman M. Recent developments in ionic liquid-assisted topical and transdermal drug delivery. Pharm Res 2022;39(10):2335–51.
[78] Zhang D, Wang HJ, Cui XM, Wang CX. Evaluations of imidazolium ionic liquids as novel skin permeation enhancers for drug transdermal delivery. Pharm Dev Technol 2017;22(4):511–20.
[79] Zakrewsky M, Lovejoy KS, Kern TL, Miller TE, Le V, Nagy A, et al. Ionic liquids as a class of materials for transdermal delivery and pathogen neutralization. Proc Natl Acad Sci 2014;111(37):13313–18.
[80] Shu Y, Xue R, Gao Y, Zhang WX, Wang JH. A thermo-responsive hydrogel loaded with an ionic liquid microemulsion for transdermal delivery of methotrexate. J Mater Chem B 2023;11(24):5494–502.
[81] Hattori T, Tagawa H, Inai M, Kan T, Kimura S, Itai S, et al. Transdermal delivery of nobiletin using ionic liquids. Sci Rep 2019;9(1):20191.
[82] Gao YR, Zhang WX, Wei YN, Li Y, Fei T, Shu Y, et al. Ionic liquids enable the preparation of a copper-loaded gel with transdermal delivery function for wound dressings. Biomater Sci 2022;10(4):1041–52.
[83] Yuan J, Wu JY, Yin TX. Solubility and permeation enhancement of poor soluble drug by cholinium-amino acid based ionic liquids. J Drug Deliv Sci Technol 2020;60:102037.
[84] Yuan J, Zhou NN, Wu JY, Yin TX, Jia YB. Ionic liquids as effective additives to enhance the solubility and permeation for puerarin and ferulic acid. RSC Adv 2022;12(6):3416–22.
[85] Liu TQ, Zhang LG, Lu BB, Li DP, Bo YY, Wang W, et al. Noninvasive and efficient peptide delivery by a novel biocompatible ionic liquid. ACS Sustain Chem Eng 2022;10(50):16611–23.
[86] Liu TQ, Zhang LG, Lu BB, Li DP, Bo YY, Wang W, et al. Noninvasive and efficient peptide delivery by a novel biocompatible ionic liquid. J Mol Liq 2022;367:120529.
[87] Uddin S, Islam MdR Md, Moshikur R, Wakabayashi R, Kamiya N, Moniruzzaman M, et al. Transdermal delivery of antigenic protein using ionic liquid-based nanocarriers for tumor immunotherapy. ACS Appl Bio Mater 2022;5(6):2586–97.
[88] Kubota K, Shibata A, Yamaguchi T. The molecular assembly of the ionic liquid/aliphatic carboxylic acid/aliphatic amine as effective and safety transdermal permeation enhancers. Eur J Pharm Sci 2016;86:75–83.
[89] Liu TQ, Zhang DL, Pan ZH, Yang H, Ruan B, Bo YY, et al. Lysine-based ionic liquid enables peptides to reverse skin photoaging: from leaves to roots. Adv Funct Mater 2023;22(33):2300723.
[90] Huda MN, Deaguero IG, Borrego EA, Kumar R, Islam T, Afrin H, et al. Ionic liquid-mediated delivery of a BCL-2 inhibitor for topical treatment of skin melanoma. J Control Release 2022;349:783–95.
[91] Banerjee A, Ibsen K, Iwao Y, Zakrewsky M, Mitragotri S. Transdermal protein delivery using choline and geranate (CAGE) deep eutectic solvent. Adv Healthc Mater 2017;6(15):1601411.
[92] Qi QM, Mitragotri S. Mechanistic study of transdermal delivery of macromolecules assisted by ionic liquids. J Control Release 2019;311-312:162–9.
[93] Goindi S, Arora P, Kumar N, Puri A. Development of novel ionic liquid-based microemulsion formulation for dermal delivery of 5-Fluorouracil. AAPS PharmSciTech 2014;15(4):810–21.
[94] Qi QM, Duffy M, Curreri AM, Balkaran JPR, Tanner EEL, Mitragotri S. Comparison of ionic liquids and chemical permeation enhancers for transdermal drug delivery. Adv Funct Mater 2020;30(45):2004257.
[95] Tanigawa H, Suzuki N, Suzuki T. Application of ionic liquid to enhance the nose-to-brain delivery of etodolac. Eur J Pharm Sci 2022;178:106290.
[96] Halayqa M, Pobudkowska A, Domanska U, Zawadzki M. Studying of drug solubility in water and alcohols using drug-ammonium ionic liquid-compounds. Eur J Pharm Sci 2018;111:270–7.
[97] Li LS, Tai ZG, Wu XY, Wu JC, Zhang TR, Chen ZJ, et al. Ionic liquids: momentous tools in transdermal delivery of biomacromolecules. Adv Ther 2023;6(6):2200332.
[98] Shimul IM, Moshikur RM, Minamihata K, Moniruzzaman M, Kamiya N, Goto M. Amino acid ester based phenolic ionic liquids as a potential solvent for the bioactive compound luteolin: synthesis, characterization, and food preservation activity. J Mol Liq 2022;349:118103.
[99] MdK Ali, Moshikur RM, Wakabayashi R, Moniruzzaman M, Goto M. Biocompatible ionic liquid-mediated micelles for enhanced transdermal delivery of paclitaxel. ACS Appl Mater Interfaces 2021;13(17):19745–55.
[100] MdR Islam, MdR Chowdhury, Wakabayashi R, Tahara Y, Kamiya N, Moniruzzaman M, et al. Choline and amino acid based biocompatible ionic liquid mediated transdermal delivery of the sparingly soluble drug acyclovir. Int J Pharm 2020;582:119335.
[101] Daadoue S, Al-Remawi M, Al-Mawla L, Idkaidek N, Khalid RM, Al-Akayleh F. Deep eutectic liquid as transdermal delivery vehicle of risperidone. J Mol Liq 2022;345:117347.
[102] Wu XY, Yu Q, Wu J, Li T, Ding N, Wu W, et al. Ionic liquids containing ketoconazole improving topical treatment of T. Interdigitale infection by synergistic action. Int J Pharm 2020;589:119842.
[103] Esson MM, Mecozzi S. Preparation, characterization, and formulation optimization of ionic-liquid-in-water

nanoemulsions toward systemic delivery of amphotericin B. Mol Pharm 2020;17(6):2221–6.
[104] Buettner CS, Cognigni A, Schröder C, Bica-Schröder K. Surface-active ionic liquids: a review. J Mol Liq 2022;347:118160.
[105] McNamee CE, Kawakami H. Effect of the surfactant charge and concentration on the change in the forces between two charged surfaces in surfactant solutions by a liquid flow. Langmuir 2020;36(8):1887–97.
[106] Froba AP, Wasserscheid P, Gerhard D, Kremer H, Leipertz A. Revealing the influence of the strength of coulomb interactions on the viscosity and interfacial tension of ionic liquid cosolvent mixtures. J Phys Chem B 2007;111(44):12817–22.
[107] Williams HD, Ford L, Igonin A, Shan Z, Botti P, Morgen MM, et al. Unlocking the full potential of lipid-based formulations using lipophilic salt/ionic liquid forms. Adv Drug Deliv Rev 2019;142:75–90.
[108] Balk A, Wiest J, Widmer T, Galli B, Holzgrabe U, Meinel L. Transformation of acidic poorly water soluble drugs into ionic liquids. Eur J Pharm Biopharm 2015;94:73–82.
[109] Williams HD, Ford L, Lim S, Han S, Baumann J, Sullivan H, et al. Transformation of biopharmaceutical classification system class I and III drugs into ionic liquids and lipophilic salts for enhanced developability using lipid formulations. J Pharm Sci 2018;107(1):203–16.
[110] Sahbaz Y, Nguyen TH, Ford L, McEvoy CL, Williams HD, Scammells PJ, et al. Ionic liquid forms of weakly acidic drugs in oral lipid formulations: preparation, characterization, *in vitro* digestion, and *in vivo* absorption studies. Mol Pharm 2017;14(11):3669–83.
[111] Zhang WX, Gao YR, Xue R, Nguyen W, Chen W, Wang JH, et al. Liquid formulations based on ionic liquids in biomedicine. Mater Today Phys 2023;30:100925.
[112] Uddin S, MdR Islam, RMd Moshikur, Wakabayashi R, Moniruzzaman M, Goto M. Modification with conventional surfactants to improve a lipid-based ionic-liquid-associated transcutaneous anticancer accine. Molecules 2023;28(7):2969.
[113] Chowdhury MR, Moshikur RM, Wakabayashi R, Moniruzzaman M, Goto M. Biocompatible ionic liquids assisted transdermal co-delivery of antigenic protein and adjuvant for cancer immunotherapy. Int J Pharm 2021;601:120582.
[114] Uddin S, MdR Islam, MdR Chowdhury, Wakabayashi R, Kamiya N, Moniruzzaman M, et al. Lipid-based ionic-liquid-mediated nanodispersions as biocompatible carriers for the enhanced transdermal delivery of a peptide drug. ACS Appl Bio Mater 2021;4(8):6256–67.
[115] Karpierz E, Niedzicki L, Trzeciak T, Zawadzki M, Dranka M, Zachara J, et al. Ternary mixtures of ionic liquids for better salt solubility, conductivity and cation transference number improvement. Sci Rep 2016;6:35587.
[116] Minnick DL, Flores RA, DeStefano MR, Scurto AM. Cellulose solubility in ionic liquid mixtures: temperature, cosolvent, and antisolvent effects. J Phys Chem B 2016;120(32):7906–19.
[117] Kumar PK, Rani A, Olasunkanmi LO, Bahadur I, Venkatesu P, Ebenso EE. Probing molecular interactions between ammonium-based ionic liquids and N,N -Dimethylacetamide: a combined FTIR, DLS, and DFT Study. J Phys Chem B 2016;120(49):12584–95.
[118] Kunov Kruse AJ, Weber CC, Rogers RD, Myerson AS. The a priori design and selection of ionic liquids as solvents for active pharmaceutical ingredients. Chemistry 2017;23(23):5498–508.
[119] Anwer MK, Muqtader M, Iqbal M, Ali R, Almutairy BK, Alshetaili A, et al. Estimating the solubility, solution thermodynamics, and molecular interaction of aliskiren hemifumarate in alkylimidazolium based ionic liquids. Molecules 2019;24(15):2807.
[120] Ranke J, Othman A, Fan P, Muller A. Explaining ionic liquid water solubility in terms of cation and anion hydrophobicity. Int J Mol Sci 2009;10(3):1271–89.
[121] Sintra TE, Abranches DO, Benfica J, Soares BP, Ventura SPM, Coutinho JAP. Cholinium-based ionic liquids as bioinspired hydrotropes to tackle solubility challenges in drug formulation. Eur J Pharm Biopharm 2021;164:86–92.
[122] Wibel R, Friedl JD, Zaichik S, Bernkop-Schnürch A. Hydrophobic ion pairing (HIP) of (poly)peptide drugs: benefits and draw backs of different preparation methods. Eur J Pharm Biopharm 2020;151:73–80.
[123] Moreira DN, Fresno N, Pérez-Fernández R, Frizzo CP, Goya P, Marco C, et al. Brønsted acid–base pairs of drugs as dual ionic liquids: NMR ionicity studies. Tetrahedron 2015;71(4): 676–685.
[124] Hong MH, Wang QL, Wang K, Li JH, Qi MH, Ren GB. Transdermal delivery of metformin utilizing ionic liquid technology: insight into the relationship between counterion structures and properties. Pharm Res 2022;39(10):2459–74.
[125] Bharate SS. Modulation of biopharmaceutical properties of acidic drugs using cationic counterions: a critical analysis of FDA-approved pharmaceutical salts. Int J Pharm 2021;607:120993.
[126] Gamboa A, Schüßler N, Soto-Bustamante E, Romero-Hasler P, Meinel L, Morales JO. Delivery of ionizable hydrophilic drugs based on pharmaceutical formulation of ion pairs and ionic liquids. Eur J Pharm Biopharm 2020;156:203–18.
[127] Wiest J, Saedtler M, Balk A, Merget B, Widmer T, Bruhn H, et al. Mapping the pharmaceutical design space by amorphous ionic liquid strategies. J Control Release 2017;268:314–22.
[128] Zhou BJ, Liu SY, Yin HM, Qi MH, Hong MH, Ren GB. Development of gliclazide ionic liquid and the transdermal patches: an effective and noninvasive sustained release formulation to achieve hypoglycemic effects. Eur J Pharm Sci 2021;164:105915.
[129] Yang DG, Liu C, Piao HQ, Quan P, Fang L. Enhanced drug loading in the drug-in-adhesive transdermal patch utilizing a drug–ionic liquid strategy: insight into the role of ionic hydrogen bonding. Mol Pharm 2021;18(3):1157–66.
[130] Yang DG, Fang L, Yang CR. Roles of molecular interaction and mobility on loading capacity and release rate of drug-ionic liquid in long-acting controlled release transdermal patch. J Mol Liq 2022;352:118752.
[131] Zhao HQ, Liu C, Yang DG, Wan XC, Shang R, Quan P, et al. Molecular mechanism of ion-pair releasing from acrylic pressure sensitive adhesive containing carboxyl group: roles of doubly ionic hydrogen bond in the controlled release process of bisoprolol ion-pair. J Control Release 2018;289:146–57.
[132] Egorova KS, Gordeev EG, Ananikov VP. Biological activity of ionic liquids and their application in pharmaceutics and medicine. Chem Rev 2017;117(10):7132–89.
[133] Liu LX, Zou DY, Zhang YN, Zhang Q, Feng YR, Guo YL, et al. Pharmaceutical salts/cocrystals of enoxacin with dicarboxylic acids: enhancing *in vitro* antibacterial activity of enoxacin by improving the solubility and permeability. Eur J Pharm Biopharm 2020;154:62–73.
[134] Zandu SK, Chopra H, Singh I. Ionic liquids for therapeutic and drug delivery applications. Curr Drug Res Rev 2020;12(1):26–41.
[135] Gomes A, Aguiar L, Ferraz R, Teixeira C, Gomes P. The emerging role of ionic liquid-based approaches for enhanced skin permeation of bioactive molecules: a snapshot of

the past couple of years. Int J Mol Sci 2021;22(21):11991.
[136] Klebeko J, Krüger O, Dubicki M, Ossowicz-Rupniewska P, Janus E. Isopropyl amino acid esters ionic liquids as vehicles for non-steroidal anti-Inflammatory drugs in potential topical drug delivery systems with antimicrobial activity. Int J Mol Sci 2022;23(22):13863.
[137] Furukawa S, Hattori G, Sakai S, Kamiya N. Highly efficient and low toxic skin penetrants composed of amino acid ionic liquids. RSC Adv 2016;6(90):87753–5.
[138] Moshikur RM, Chowdhury MR, Wakabayashi R, Tahara Y, Kamiya N, Moniruzzaman M, et al. Ionic liquids with N-methyl-2-pyrrolidonium cation as an enhancer for topical drug delivery: synthesis, characterization, and skin-penetration evaluation. J Mol Liq 2020;299:112166.
[139] Hassan SA, Gad SF, Abdu-Allah H, Qayed WS, AbouElmagd SA, Ibrahim EA. Ionic liquid of ketoprofen-piperine modulates the pharmaceutical and therapeutic characters of ketoprofen. Int J Pharm 2022;620:121724.
[140] Mehta MJ, Kumar A. Ionic liquid stabilized gelatin-lignin films: a potential UV-shielding material with excellent mechanical and antimicrobial properties. Chemistry 2019;25(5):1269–74.
[141] Makowska A, Dyoniziak E, Siporska A, Szydlowski J. Miscibility of ionic liquids with polyhydric alcohols. J Phys Chem B 2010;114(7):2504–8.
[142] Abednejad A, Ghaee A, Morais ES, Sharma M, Neves BM, Freire MG, et al. Polyvinylidene fluoride–hyaluronic acid wound dressing comprised of ionic liquids for controlled drug delivery and dual therapeutic behavior. Acta Biomater 2019;100:142–57.
[143] Chantereau G, Sharma M, Abednejad A, Neves BM, Sèbe G, Coma V, et al. Design of nonsteroidal anti-Inflammatory drug-based ionic liquids with improved water solubility and drug delivery. ACS Sustain Chem Eng 2019;7(16):14126–34.
[144] Halayqa M, Zawadzki M, Domańska U, Plichta A. Polymer-ionic liquid-pharmaceutical conjugates as drug delivery systems. J Mol Struct 2019;1180:573–84.
[145] Suksaeree J, Maneewattanapinyo P. Ionic liquid drug-based polymeric matrices for transdermal delivery of lidocaine and diclofenac. J Polym Environ 2020;28(10):2771–9.
[146] Lim PT, Irwan RM, Li Z, Goh KB. Quantifying how drug-polymer interaction and volume phase transition modulate the drug release kinetics from core-shell microgels. Int J Pharm 2022;622:121838.
[147] Jia L, Wang R, Fan YN. Encapsulation and release of drug nanoparticles in functional polymeric vesicles. Soft Matter 2020;16(12):388–95.
[148] Song Y, Yang X, Chen XH, Nie HC, Byrn S, Lubach JW. Investigation of drug-excipient interactions in lapatinib amorphous solid dispersions using solid-state NMR spectroscopy. Mol Pharm 2015;12(3):857–66.
[149] Lozoya-Agullo I, Planelles M, Merino-Sanjuán M, Bermejo M, Sarmento B, González-Álvarez I, et al. Ion-pair approach coupled with nanoparticle formation to increase bioavailability of a low permeability charged drug. Int J Pharm 2019;557:36–42.
[150] Wu H, Fang F, Zheng L, Ji WJ, Qi MH, Hong MH, et al. Ionic liquid form of donepezil: preparation, characterization and formulation development. J Mol Liq 2020;300:112308.
[151] Jouannin C, Tourné-Péteilh C, Darcos V, Sharkawi T, Devoisselle J-M, Gaveau P, et al. Drug delivery systems based on pharmaceutically active ionic liquids and biocompatible poly(lactic acid). J Mater Chem B 2014;2(20):3133–41.
[152] Liu C, Guan YI, Tian Q, Shi XY, Fang L. Transdermal enhancement strategy of ketoprofen and teriflunomide: the effect of enhanced drug-drug intermolecular interaction by permeation enhancer on drug release of compound transdermal patch. Int J Pharm 2019;572:118800.
[153] Ren SJ, Liu C, Sun YT, Zhang Y, Ruan JH, Fang L. Formulation development and molecular mechanism characterization of long-acting patches of asenapine for efficient delivery by combining API-ILs strategy and controlled-release polymers. J Pharm Sci 2023;112(7):1850–62.
[154] Lv XY, Chen KH, Shi GL, Lin WJ, Bai HZ, Li HR, et al. Design and tuning of ionic liquid-based HNO donor through intramolecular hydrogen bond for efficient inhibition of tumor growth. Sci Adv 2020;6(45):eabb7788.
[155] Banerjee A, Ibsen K, Brown T, Chen R, Agatemor C, Mitragotri S. Ionic liquids for oral insulin delivery. Proc Natl Acad Sci 2018;115(28):7296–301.
[156] Mohamed Sofian Z, Harun N, Mahat MM, Nor Hashim NA, Jones SA. Investigating how amine structure influences drug-amine ion-pair formation and uptake via the polyamine transporter in A549 lung cells. Eur J Pharm Biopharm 2021;168:53–61.
[157] Qian W, Texter J, Yan F. Frontiers in poly(ionic liquid)s: syntheses and applications. Chem Soc Rev 2017;46(4):1124–59.
[158] Zhang SY, Zhuang Q, Zhang M, Wang H, Gao ZM, Sun JK, et al. Poly(ionic liquid) composites. Chem Soc Rev 2020;49(6):1726–55.
[159] Zheng SJ, Li WZ, Ren YY, Liu ZY, Zou XY, Hu Y, et al. Moisture-wicking, breathable, and intrinsically antibacterial electronic skin based on dual-gradient poly(ionic liquid) nanofiber membranes. Adv Mater 2022;34(4):e2106570.
[160] Xu J, Fang H, Su Y, Kang Y, Xu DL, Cheng YY, et al. A 3D bioprinted decellularized extracellular matrix/gelatin/quaternized chitosan scaffold assembling with poly(ionic liquid)s for skin tissue engineering. Int J Biol Macromol 2022;220:1253–66.
[161] Liu B, Fu RZ, Duan ZG, Zhu CH, Deng JJ, Fan DD. Ionic liquid-based non-releasing antibacterial, anti-inflammatory, high-transparency hydrogel coupled with electrical stimulation for infected diabetic wound healing. Compos Part B 2022;236:109804.
[162] Zhang YW, Yuan B, Zhang YQ, Cao QP, Yang C, Li Y, et al. Biomimetic lignin/poly(ionic liquids) composite hydrogel dressing with excellent mechanical strength, self-healing properties, and reusability. Chem Eng J 2020;400:125984.
[163] Kim YM, Moon HC. Ionoskins: nonvolatile, highly transparent, ultrastretchable ionic sensory platforms for wearable electronics. Adv Funct Mater 2019;30(4):1907290.
[164] Liu ZY, Wang Y, Ren YY, Jin GQ, Zhang CC, Chen W, et al. Poly(ionic liquid) hydrogel-based anti-freezing ionic skin for a soft robotic gripper. Mater Horiz 2020;7(3):919–27.
[165] Fan SY, Hao YN, Zhang WX, Kapasi A, Shu Y, Wang JH, et al. Poly(ionic liquid)-gated $CuCo_2S_4$ for pH-/thermo-triggered drug release and photoacoustic imaging. ACS Appl Mater Interfaces 2020;12(8):9000–7.
[166] Ahmed M, Bhat AR, Verma AK, Patel R. Collagen–PVA films plasticized with choline acetate ionic liquid for sustained drug release: UV shielding, mechanical, antioxidant, and antibacterial properties. ACS Appl Bio Mater 2023;6(2):663–73.
[167] Yang JX, Zeng WN, Xu P, Fu XX, Yu XJ, Chen L, et al. Glucose-responsive multifunctional metal–organic drug-loaded hydrogel for diabetic wound healing. Acta Biomater 2022;140:206–18.