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Review article

Advancements in transdermal drug delivery using ionic liquids: Design strategies, functional roles, mechanisms, and future challenges

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ABSTRACT

One potential method for improving transdermal medication absorption is ionic liquids (ILs). However, further research is necessary to create effective ILs and clarify their methods of action because of the unique structural characteristics of ILs. This paper examines the basic design concepts of ideal ILs for transdermal drug delivery systems (TDDS), taking into account toxicity, skin permeability, and melting point, all of which are influenced by ion types, molar ratios, functional groups, and inter-ionic interactions. The functions of ILs in developing TDDS are also described in detail, including their use as novel solvents to improve drug solubility in carriers, as innovative skin penetration enhancers to increase transdermal drug absorption, as new active pharmaceutical ingredients (API-ILs) to control drug pharmacokinetics, skin permeability, solubility, and release, and as sophisticated polymers to develop smart medical materials. Additionally, a summary of several action pathways is provided, mainly focusing on the interactions between ILs, medications, polymers, and skin constituents. The discussion concludes with a discussion of ILs' future challenges, including determining quantitative structure-activity relationships, comprehending the intricate forces of interaction between anions, medications, polymers, and the skin microenvironment, guaranteeing long-term stability, and resolving *in vivo* safety issues. In conclusion, the purpose of this essay is to encourage the development of TDDS with ILs.

1. Introduction

Transdermal drug delivery systems (TDDS) are the third most common drug administration mechanism, behind oral and injectable methods. These systems make it possible to administer drugs via the skin, which has therapeutic benefits that are both local and systemic.[1] By eliminating gastrointestinal degradation, avoiding the first-pass metabolism, and reducing variations in plasma concentration, TDDS has a number of benefits that improve patient compliance.[2] To acquire systemic effects, a medicine must first pass through the stratum corneum's highly structured and thick intercellular lipids, then enter the comparatively hydrophilic viable epidermis, and lastly distribute into the watery dermis.[3] There are now around 24 active pharmaceutical ingredients (APIs) that have been authorized for use in transdermal patches. Strict requirements, such as a dose of less than 10 mg/day, a molecular weight of less than 500 Da, a melting point below 200 °C, and an oil-water partition coefficient between 2 and 4,[4,5] should be met by the best therapeutic compounds for TDDS. In order to improve skin penetration and propel the development of TDDS, safe and efficient transdermal penetration technologies must be developed.[6,7]

Organic salts having melting temperatures lower than 100 °C are known as ionic liquids (ILs), and they usually contain inorganic anions and organic cations with asymmetrical structures and significant size differences.[8] By altering anions and cations, ILs, which are molecular engineered to accomplish particular objectives, increase skin permeability and the dissolving behavior of poorly soluble medications [9–12]. These properties make ILs particularly advantageous in TDDS, positioning them as a promising area of research.[13] For example, choline and germanic acid (CAGE) ILs have been used for the transdermal delivery of nanosensors in thrombotic disease detection.[14] Additionally, IL-based microemulsion formulations have significantly increased the solubility of drugs like rosiglitazone and bezafibrate, indicating their suitability as carriers for hydrophobic drugs.[15] Hydrophilic drugs have been converted into oil-soluble forms using fatty acids as countersigns, enhancing

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their skin penetration capabilities.[16] The transdermal distribution of medications for the treatment of deep tissue infections has been made easier by the outstanding performance of hydro-gels made by co polymerizing transdermal enhancer ILs and microwave-responsive ILs as antibiotic carriers in microwave thermal therapy.[17]

We have compiled the different functions and processes of ILs in improving medication skin penetration based on these studies. There is currently a dearth of systematic study on the quantitative structure-activity link between the structure and efficacy of ILs, and successful ILs are frequently found through lengthy trial-and-error studies. Not enough research has been done on the basic molecular processes of ILs.[18,19] In order to provide scientific direction for the development of ILs in TDDS, this paper attempts to methodically clarify the design principles, functions, and processes of ILs.

2. Design guidelines for ILs in TDDS

For TDDS, ILs should be designed with their melting points, skin permeability, and toxicity levels optimized (Fig. 1).[20,21] The molar ratios, kinds, and functional groups of the cations and anions that make up ILs influence their physicochemical characteristics [22–24] (see Fig. 2).

2.1. The impact of IL structures on melting point

One important factor in identifying ILs, which are organic salts with melting temperatures lower than 100 °C, is the melting point. The capacity of ILs to penetrate the skin has been found to be significantly correlated with their melting points.[31] Since ILs in this range have low lattice energy and may act as solvents efficiently, it is ideal for them to have a melting point between −80 °C and 25 °C (room temperature).[13] The majority of ILs stay liquid throughout a broad temperature range, in contrast to conventional organic salts.[32] The anions' and cations' microchemical structures affect the transition from solid to liquid in ILs, which is frequently defined by their melting point or glass transition temperature. This covers elements including inter-ionic interactions, charge distribution, and the size and flexibility of the carbon chains (Table 1).[33,34,35]

ILs featuring bulky, asymmetric, and charge-delocalized ions generally exhibit lower melting points due to decreased lattice energy from frustrated coordination and reduced interactions.[8,42,43] The primary factor contributing to the low melting points of ILs is high structural entropy, rather than kinetic entropy.[44] Generally, ILs with longer alkyl chains on the cation have higher melting points. For instance, in n-alkyl-n-methylimidazolium salts, the melting point increases significantly for alkyl chains with more than seven carbon atoms.[37]

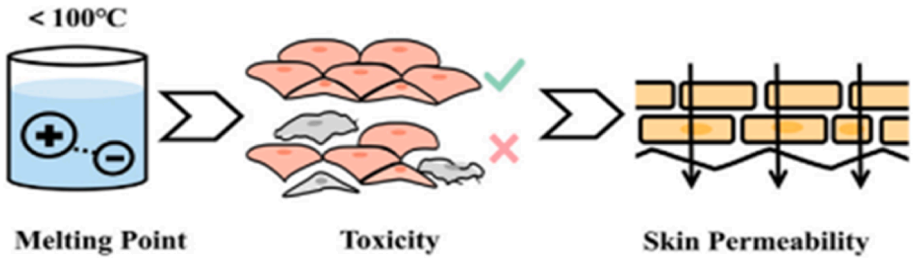


Fig. 1. Design principles of ILs for the TDDS.

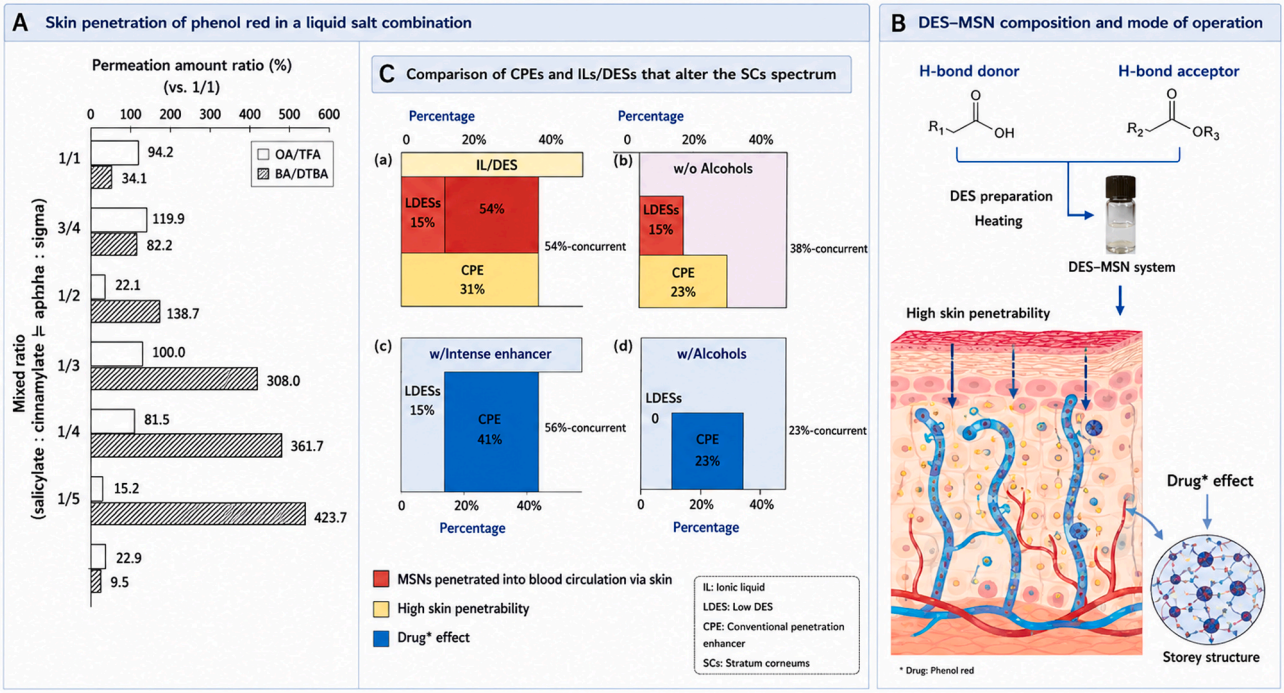


Fig. 2. (A) Skin penetration of phenol red in a liquid salt combination (Source[25], Copyright 2016, Elsevier B.V.). (B) DES-MSN composition and mode of operation (Source[26], Copyright 2020, Wiley-VCH GmbH). (C) Comparison of CPEs and ILs/DESs that alter the SCs spectrum (Source[18], Copyright 2022, Elsevier B.V.).

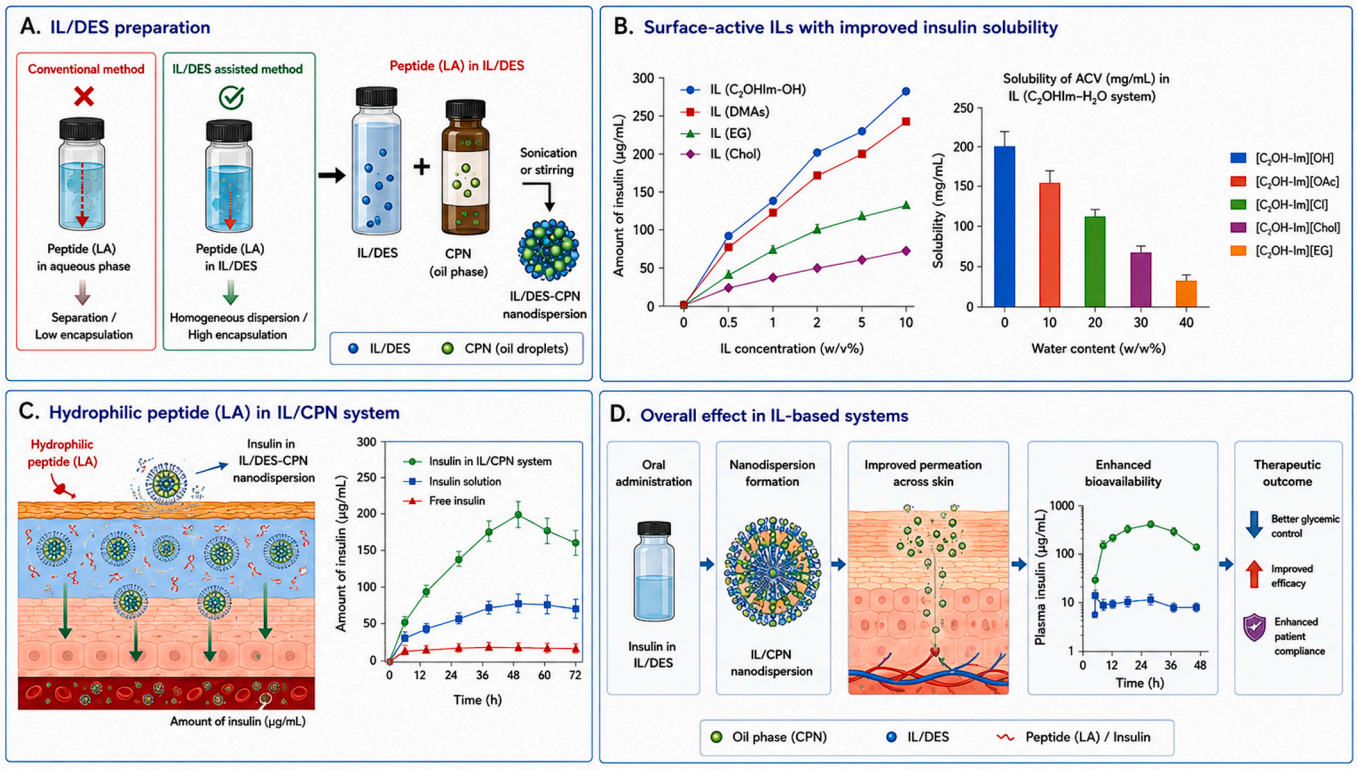


Fig. 3. IL/DES preparation (A), surface-active ILs with improved insulin solubility (B), hydrophilic peptide (LA) in IL/CPN system (C), and overall effect in IL-based system **(D)**. **(A)** Comparison of conventional and IL/DES-assisted preparation of peptide-loaded nanodispersion. **(B)** Effect of different ILs on insulin solubility and solubility of acyclovir (ACV) in IL ($C_2OHIm\text{-}H_2O$) system. **(C)** Enhanced penetration of insulin-loaded IL/CPN nanodispersion across skin and the resulting amount of insulin in blood circulation over time. **(D)** Schematic overview of improved bioavailability and therapeutic outcome via IL-based syetems.

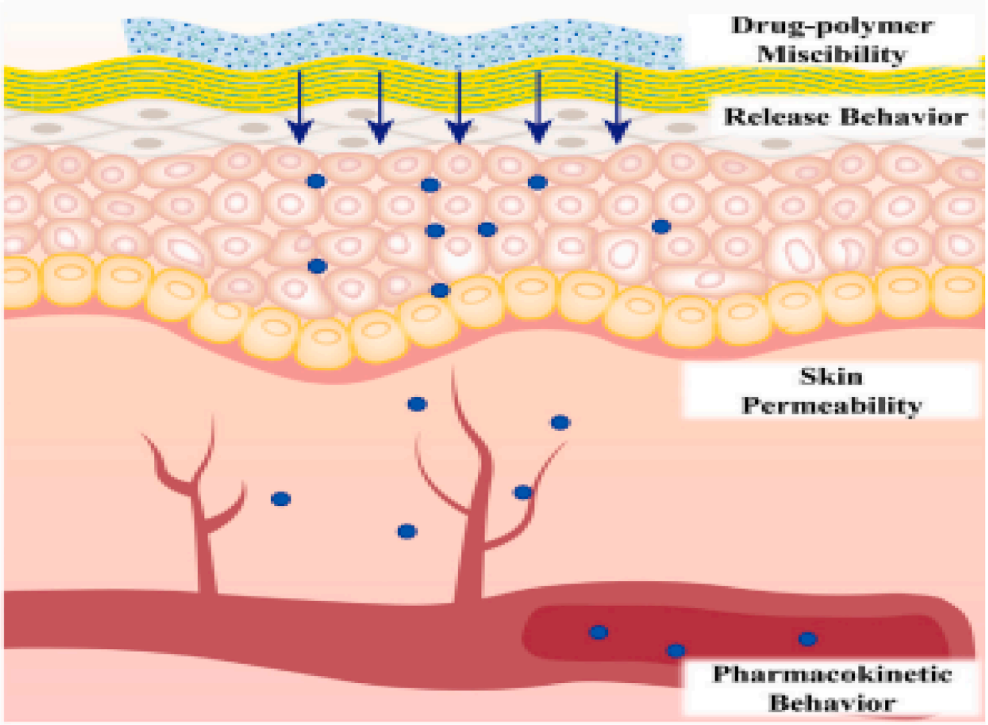


Fig. 4. Different roles of API-ILs.

Furthermore, among ions with the same charge, anions with larger radii typically have lower melting points.

For 1-tetradecyl-3-methylimidazolium salts, there is a direct relationship between the anion volume and the melting point of the ionic liquid. Specifically, larger anions result in a lower melting point of these ILs.[36] Moreover, the proportion of anion to cation is a key factor in

Table 1
Melting point of ILs with different structures[27, 28].

Cation	Anion	Molar Ratio	Tm/T g (°C)	References
C14mim+	CF3SO3-	1:1	58.1	[36]
C18mim+	Tf2N-	1:1	53.5	[37]
Choline	Geranic acid	2:1	−88.9	[38]
BMIM+	Cl-	1:1	70.0	[39]
BMIM+	PF6-	1:1	61.0	[39]
EMIM+	Acetate	1:1	10.0	[40]
EMIM+	Dicyanamide	1:1	−21.0	[40]
Pyridinium	Tetrafluoroborate	1:1	82.0	[41]
Pyridinium	Hexafluorophosphate	1:1	74.0	[41]

determining the melting point. Nuthakki et al. examined how the melting points of ethanol ammonium acetate, 2-methylbutyl ammonium format, and pentyl ammonium format are influenced by equimolar acid/base ratios as well as by excess amounts of either acid or base. Their dynamic scanning calorimetry studies revealed that the melting points decrease when additional acid or amine is added.[45] The interactions between the anions and cations, such as π-π stacking interactions, also have a significant impact. For example, strong π-π interactions notably raise the melting point in anilinium salts.[46]

2.2. The influence of IL structures on skin permeability

ILs' molecular structures govern their physical and chemical characteristics, which in turn affect how well they penetrate the skin (Table 2). Wang et al. found that when lidocaine and ibuprofen were mixed in ethanol to produce the combination [Lid][Ibu], they formed strong intermolecular hydrogen bonds. This characteristic facilitated the simultaneous transdermal transport of both APIs at significantly higher rates compared to their standard crystalline salt forms available commercially. Moreover, they observed that adjusting the proportions of these APIs within the ILs allowed control over both the mode and the rate of membrane transport.[39] Wu et al. and colleagues transformed ibuprofen into ILS using different counterions, including aromatic, tetraalkylammonium, and tetra alkyl phosphonium salts. These synthetically derived ILs demonstrated superior skin permeability in comparison to conventional sodium ibuprofen salts. This enhancement was linked to the ILs' higher ionic nature, elevated log *p* values (a measure of hydrophobicity), and reduced water solubility.[40] (see Table 3)

2.3. Mechanistic Insights into enhanced skin permeability of ibuprofen-based ILs

Ibuprofen and alkyl counterions combine hydrophobically to produce the enhanced skin permeability seen in ibuprofen-based ILs. Transdermal penetration is facilitated by these interactions, which also make it easier for ions to conjugate and form ion pairs.[40] The polarizability, molecular weight, and log *P* of the counterions are important determinants of the skin permeability of ILs, according to a study by Yang et al. that used the Quantitative Structure-Activity Relationship (QSAR) model.[33]. The research highlighted that van der Waals forces between ILs and the skin contribute to the disruption of the orderly structure of skin lipids, thereby enhancing permeability.[41,70]

2.4. Effects of ionic liquid structures on their toxicity

ILs are often heralded as environmentally friendly or "green" solvents due to their low volatility and potential for recyclability. However, recent studies have shown that many ILs exhibit significant toxicity, making it crucial to understand how their structure influences their biological and environmental impact [71–73].

2.4.1. Structural factors influencing toxicity

➢ **Cation Structure**:

Toxic Cations: ILs containing certain cations, such as imidazolium, pyrrolidinium, morpholinium, piperidinium, and ammonium, generally exhibit higher toxicity and lower degradability. These cations are more likely to interact unfavorably with biological systems and resist breakdown in the environment.[74,75]

Biocompatible Cations: In contrast, ILs with choline or protic cations (such as ammonium derivatives) tend to be less toxic and show better biocompatibility. These ILs are more compatible with biological tissues and more readily degradable.[50]

➢ **Anion Structure**:

Low Toxicity Anions: The total toxicity of ILs is largely attributed to hydrophilic anions such as amino acids, carboxylates (organic acids), alkyl sulfates, alkyl sulfonates, alkyl benzene sulfonates, chloride, and bromide. Biological systems are often less disturbed by these anions.[76,77]

High Toxicity Anions: Higher toxicity is linked to anions that contain fluorine, such as bis(trifluoromethanesulfonyl) amide. Such anions, for example, have been connected to enhanced cytotoxicity in human dermal fibroblasts, aberrant heart rate, and liver damage in zebrafish. One important element causing these effects is the increased lipophilicity of fluorinated alkyl chains.[78,51]

➢ **Alkyl Chain Length**:

The length of the alkyl side chains in ILs plays a critical role in their toxicity. Longer alkyl chains (more than four carbons) increase the hydrophobicity of ILs, facilitating their integration into cell membranes and disrupting their integrity. This disruption can lead to cell damage or death [79–81].

Table 2
Skin penetration rate of ILs with various structures.

Cation	Anion	Molar ratio	Cumulative skin penetration amount (μg/cm^2)	Time	References
C6	Bisoprolol	1:1	1,318.70 ± 216.70	8 h	[47]
C12	Bisoprolol	1:1	353.60 ± 34.30	8 h	[47]
C18	Bisoprolol	1:1	246.40 ± 11.20	8 h	[47]
HEPP	Zaltoprofen	1:1	59.73 ± 1.61	N/A	[48]
HEPP	Zaltoprofen	1:1	59.67 ± 3.42	N/A	[48]
TEOA	Zaltoprofen	1:1	18.54 ± 2.54	N/A	[48]
Diethanolamine	Flurbiprofen	1:1	2,600	24 h	[33]
Diethanolamine	Loxoprofen	1:1	1,900	24 h	[33]
Diethanolamine	Mefenamic acid	1:1	300	24 h	[33]
Lidocaine	Flurbiprofen	1:1	100	12 h	[49]

Table 3
The toxicity of ILs on human skin cells[27, 28].

Ionic Liquid	Cation	Anion	Molar ratio	LC50/IC50 Toxicity	References
2HEAOl	2HEA	Oleate	1:1	0.10 mg/L	50
BHEA Ol	BHEA	Oleate	1:1	0.197 mg/L	50
m-2HEAOl	m-2HEA	Oleate	1:1	0.10 mg/L	50
C4C1pyr	C4C1pyr	NTf2	1:1	7.29 mM	51
C6C1pyr	C6C1pyr	NTf2	1:1	2.68 mM	51
C8C1pyr	C8C1pyr	NTf2	1:1	0.21 mM	51
C4py	C4py	NTf2	1:1	1.39 mM	51
C2C1C1im	C2C1C1im	NTf2	1:1	1.87 mM	51
C1OC2C1im	C1OC2C1im	NTf2	1:1	1.64 mM	51
HOC2C1im	HOC2C1im	NTf2	1:1	5.18 mM	51
C4C1pip	C4C1pip	NTf2	1:1	0.32 mM	51
C4C1py	C4C1py	NTf2	1:1	2.81 mM	51
N4111	N4111	NTf2	1:1	2.22 mM	51
C4C1im	C4C1im	TFO	1:1	4.42 mM	51
C4C1im	C4C1im	OAc	1:1	5.20 mM	51

Table 4
Skin penetration improvement of ILs[27, 28].

ILs	Model medication	Animals	Enhancement ratio	References
[l-LeuC12] Cl	5-Fluorouracil	Rat	7.15	52
[L-LeuC12] Cl	Hydrocortisone	Rat	2.29	52
[OIm]Cl	Testosterone	Mouse	3.68	53
[OMMIm]Cl	Testosterone	Mouse	3.57	53
[C12dabco] Br	Diltiazem	Rat	4	54
[C4dabco] Br	Diltiazem	Rat	2.71	54
[C10C1Mor] Br	Diltiazem	Rat	1.41	54
[Choline] [Geranic acid]	Methotrexate	Pig	7	55
[Choline] [Geranic acid]	Nobiletin	Rat	4	56
[Choline][Malate]	Dextran	Pig	3	57
[Choline][Glycolate]	Cu2+	Pig	6.61	58
[Choline][Analinate]	Ibuprofen	Pig	1.31	59
[Choline][Serine]	Ferulic acid	Pig	1.61	60
[Choline][C18:1]	Antigen peptide	Mouse	29	61
[Betaine][Malate]	Copper glycyl-histidine-tripeptide	Mouse; Pig	2.38	62
[Matrine][Coconutoleic acid]	Conotoxins	Mouse	5.71	63
[L-(−)carnitine] [DL-malic acid]	Insulin	Mouse	7	15
[EDMPC][Lin]	Ovalbumin	Mouse Pig	15.16	64
[TIPA][OA]	Phenol red	Rat	18.01	25

Table 5
Drug solubility in ILs[27, 28].

Cation	Anion	Molar proportion	Drug model	Solubility (mg/mL)	References
Propyl-Ethyl	Ferulate	1:1	Luteolin	42.6	65
Propyl-Ethyl	Coumarinylmethyl	1:1	Luteolin	27.6	65
Propyl-Ethyl	Benzoate	1:1	Luteolin	11	65
Choline	Oleate	1:1	Paclitaxel	6	66
Choline	Glycine	1:1	Acyclovir	250 ± 18	30
Choline	serine	1:1	Acyclovir	135 ± 12	30
Menthol	Capric acid	5:5a	Risperidone	334	67
Menthol	Capric acid	7:3a	Risperidone	168	67
L- (−)-carnitine	DL-malic acid	1:1	Rosiglitazone	10	15
L- (−)-carnitine	DL-malic acid	1:1	Bezafibrate	11.25	15
Choline	Geranic acid	1:1	Ketoconazole	8.7	68
DC-7	NTf2	1:1	Amphotericin B	0.8	69
Choline	Hexanoate	1:1	Amphotericin B	7	69

➢ **Functional Groups**:

Reducing Toxicity: The presence of polar functional groups like ether, ester, and hydroxyl groups can reduce the toxicity of ILs by making them more hydrophilic and less likely to disrupt cell membranes.[82]

Increasing Toxicity: Conversely, hydrophobic aromatic groups can enhance toxicity. These groups increase the likelihood of ILs interacting disruptively with cell membranes, leading to cellular damage.[83]

➢ **Interconnected Properties for TDDS Applications**

When designing ILs for TDDS, three key properties must be considered: melting point, skin permeability, and toxicity. These properties are interrelated and influenced by the structure of both cations and anions:

➢ **Melting Point**:

The melting point of ILs is primarily determined by the strength of

Table 6
Regulating drug-polymer miscibility utilizing API-ILs.[27].

Cation	Anion	Molar Ratio	Polymer
Lidocaine	Ibuprofen	1:1	PVDF [Polyvinylidene fluoride]
Lidocaine	Naproxen	1:1	PVDF
Choline	Citrate	1:1	Gelatin
Naproxen	Triamylamine	1:1	PSA [Pressure-Sensitive adhesive]
Cholinium	Ibuprofenate	1:1.05	BC [Bacterial Cellulose]
Cholinium	Ketoprofenate	1:1.05	BC
Lidocaine	Diclofenac	1:1	Eudragit NE 30 D

Table 7
Regulating drug release behaviour utilizing API-ILs[28].

Cation	Anion	Molar ratio	Drug cumulative release (%)
Brilliant Blue	Atenolol	1:1	100
P6,6,6,14	Gliclazide	1:1	88.17 ± 3.59
Triethylamine	Ketoprofen	1:1	about 70
Lidocaine	Ibuprofen	1:1	about 90
	Naproxen	1:1	about 85
	Diclofenac	1:1	about 75
C4MIm	-	1:1	about 79
Choline	Mefenamic acid	1:1	100
Lidocaine	Ibuprofen	1:1	>90

interactions between their cations and anions. Weaker interactions result in lower lattice energy and thus lower melting points, which are desirable for applications that require liquid forms at room temperature.

➢ **Skin Permeability**:

The ability of ILs to penetrate the skin is influenced by their balance between hydrophilicity and hydrophobicity and their interaction strength with skin lipids. ILs with longer alkyl chains or those capable of forming strong dipole-dipole interactions with skin components tend to exhibit higher permeability.[29]

➢ **Toxicity**:

The toxicity of ILs is linked to their interaction with biological membranes. ILs with long hydrophobic alkyl chains or aromatic groups are more likely to integrate into and destabilize cellular structures, increasing their toxic potential.

➢ **Structural Considerations for IL Performance**

To optimize ILs for TDDS and other applications, understanding how their structure affects their properties is crucial:

➢ **Cation and Anion Interactions:** Dipole-dipole interactions, hydrogen bonds, and van der Waals forces are examples of important interactions between cations and anions. In order to maximize skin permeability and reduce toxicity, weaker total interactions must be matched with lower lattice energy and melting temperatures.[61]

➢ **Polarizability and Alkyl Chain Length:**

Polarizability, influenced by the length of alkyl chains, affects how ILs interact with the skin and their melting points. Longer alkyl chains result in lower melting points due to less efficient packing but enhance skin permeability and potentially increase toxicity.

➢ **Functional Groups and Polar Surface Area**:

The presence of functional groups such as hydroxyl groups increases the polar surface area and can form hydrogen bonds, reducing the ability to form ionic interactions and thereby decreasing toxicity. However, these groups also influence other properties like melting points and skin permeability.

➢ **Future Directions in IL Design**

To create effective and safe ILs for applications like TDDS, future research should focus on:

➢ **Balancing Alkyl Chain Length**:

Finding the optimal balance in alkyl chain length is essential to maintain sufficient skin permeability without significantly increasing toxicity.

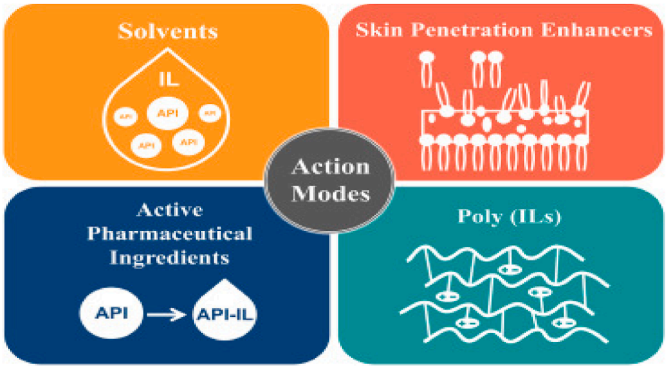
➢ **Incorporating Beneficial Functional Groups**:

Adding polar functional groups that enhance hydrophilicity and reduce toxicity, while maintaining effective skin permeability, is crucial.

➢ **Enhancing Noncovalent Interactions**:
Strengthening noncovalent interactions (such as hydrogen bonds and dipole-dipole interactions) between ILs and skin components to improve performance while minimizing adverse effects.[79]

3. Roles and mechanisms of ILS in TDDS

In the pharmaceutical industry, ILs have attracted a lot of interest, especially in relation to TDDS. Four primary categories can be used to classify their functions in TDDS:



➢ **Enhancers of Skin Penetration:**

ILs can improve a drug's ability to pass through the epidermal barrier and enter the bloodstream. They accomplish this by changing the stratum corneum's intercellular gaps and lipid bilayer structure, which improves medication penetration.[29]

➢ **Solvents**:

ILs serve as effective solvents for both hydrophilic and hydrophobic drugs, providing a versatile medium for drug formulation. Their ability to dissolve a wide range of compounds makes them valuable for preparing drug formulations suitable for TDDS applications.[61]

➢ **API-ILs**:

Some ILs themselves can act as APIs in TDDS formulations. These API-ILs are designed to possess therapeutic properties and can be directly incorporated into transdermal patches or formulations for controlled drug release.[84]

➢ **Poly (ILs)**:

Poly (ionic liquids) or Poly (ILs) are macromolecular structures derived from IL monomers. These polymers exhibit unique properties, such as tunable ionic conductivity, mechanical flexibility, and stimuli responsiveness, making them promising candidates for use in TDDS applications. Poly (ILs) can be employed as drug carriers, matrices for sustained drug release, or components of transdermal patches.[85]

3.1. ILs as Novel Skin Penetration Enhancers

The skin acts as a barrier, preventing the entry of harmful substances and the loss of essential ones from the body.[86] However, this barrier, especially the stratum corneum (SC), poses challenges for drug penetration. Chemical penetration enhancers (CPEs) offer a straightforward solution to overcome this barrier, and among them, ILs have emerged as promising candidates due to their unique properties [54,87–89].

3.1.1. High skin penetration enhancement ability

ILs known for their high skin penetration enhancement often contain imidazole, amino acid esters, and choline derivatives [52,57,90]. Amino acid esters and choline-based ILs are particularly noteworthy due to their excellent biodegradability and effectiveness in transdermal delivery, especially for large biomacromolecules [91–94]. Current research is also investigating other ILs, such as cyclic onium salts and combinations of menthol and capric acid, for their potential to enhance skin penetration.[95]

3.1.2. Mechanisms of enhanced transdermal transport

ILs enhance transdermal drug transport through both cellular and intercellular pathways.[96] Hydrophilic ILs primarily promote paracellular transport by fluidizing protein and lipid regions, while hydrophobic ILs facilitate transcellular transport by providing channels.[52,97] For example, ILs like 1-butyl-3-methylimidazolium bromide affect lipid mobility and keratin, crucial factors for transdermal penetration.[98]

3.1.3. Interaction forces and safety considerations

Enhancing drug transdermal distribution, especially in the hydrophobic area of the skin, requires strong contact forces, especially hydrogen bonds.[56] ILs influence the structure of skin constituents and facilitate medication penetration. Because of its strong covalent bonds with skin components, novel ILs, like those that contain amino acids and citric acid, have demonstrated encouraging outcomes in increasing skin permeability.[18] Because of their sufficient polar contact and hydrogen bonding with the skin, these ILs are safer and more effective than traditional CPEs.[26]

3.2. ILs enhancing solubility for drug delivery

ILs have emerged as promising solvents for enhancing the solubility of drugs, overcoming limitations posed by the poor solubility of many pharmaceutical compounds. Cosmo-RS calculations have been instrumental in selecting ILs based on their ability to accept hydrogen bonds, a crucial factor in their effectiveness [99–101].

The ability to solubilize bioactive substances like luteolin (LUT) through a variety of interactions, including as hydrogen bonds, π-π interactions, and cation-π interactions, is demonstrated by ILs, especially those based on the proline ethyl ester phenolate. Similar to this, a variety of interactions greatly improve medication solubility in nonaqueous micelle systems made possible by surface-active ILs, including SAIL [Cho][Ole] [102–104].

Studies have shown that different ILs exhibit varying solubility enhancement ratios for specific drugs. For instance, cholinium-based on ILs with different anions demonstrate distinct solubility enhancement effects for drugs like naproxen and ibuprofen. Additionally, ILs containing menthol and capsaicin can enhance the solubility of hydrophobic drugs like risperidone, with the degree of enhancement linked to capsaicin content[105–108].

Further investigations into drug solubility in ILs with varied compositions have elucidated the influence of factors such as alkyl chain length, branching, and the presence of functional groups like hydroxyl and carboxyl groups. These factors can affect drug solubility differently depending on the specific IL system[109–112].

As novel solvents, ILs play a pivotal role in improving drug solubility by strengthening interactions between drugs and excipients. However, given the reversible nature of interactions between IL ions and the need for safety considerations, careful attention must be paid to IL dosage to ensure therapeutic efficacy while minimizing potential adverse effects.[100]

3.2.1. ILs enhancing solubility for drug delivery

Weakly acidic or alkaline drugs often exhibit poor water solubility, posing a significant challenge in developing new drug formulations. ILs offer a promising solution by increasing the solubility of insoluble small molecules and biomolecules, thereby enhancing their potential for drug delivery.[101]

3.2.2. Broad applications in solubility enhancement

ILs are utilized to enhance the solubility of hydrophilic, lipophilic, and amphiphilic drugs by reducing the interfacial tension between drugs and the solvent medium. Their superior amphiphilic properties make ILs valuable for improving the stability of lipid formulations, thereby expanding their application in drug delivery systems.[65]

3.2.3. Diverse formulations for enhanced delivery

Researchers have developed various IL-assisted delivery systems to address solubility challenges across different drug classes:

ILs-in-Oil Microemulsion: Islam et al. utilized choline-fatty acids in ILs-in-oil microemulsions for transdermal insulin delivery, demonstrating enhanced solubility and delivery efficacy.[66]

ILs in Cancer Immunotherapy: ILs containing choline and propionic acid were used to form complexes with ovalbumin (OVA), improving its dispersibility in isopropyl myristate (IPM) for effective cancer immunotherapy.[30]

ILs as Surfactants in Nano-dispersions: ILs as surfactants increased the stability, drug-loading capacity, and encapsulation efficiency in ILs-in-oil nano-dispersions, reported by Uddinet et al.

Hydrophobic Dicationic Cholinium-based ILs: Esson et al. synthesized novel ILs mimicking the amphiphilicity of amphotericin B (AmB), enhancing its solubility and delivery potential.

ILs in Ternary Systems: ILs were incorporated into effective ternary systems, improving the solubility of acyclovir (ACV) and water-soluble drugs, as demonstrated in various studies.[67]

3.2.4. Mechanisms of solubility enhancement

ILs enhance solubility through interactions with solutes. These interactions involve various mechanisms, including hydrogen bonding, ion-dipole interactions, and van der Waals forces, effectively increasing the solubility of drugs in IL-based formulations.[68]

3.3. ILs as innovative APIs

The utilization of ILs as novel APIs involves the amalgamation of an API with a counterion or even the combination of two distinct APIs. These API-ILs find wide-ranging applications in various drug delivery systems including transdermal, oral, and injectable formulations [113–115]. Therefore, the meticulous selection of appropriate counterions becomes paramount [116–118]. API-ILs play a crucial role in modulating drug skin permeability, drug-polymer compatibility, release kinetics, and pharmacokinetic profiles of drugs [119–122]. Furthermore, certain ILs exhibit inherent biological activities that synergistically augment the therapeutic efficacy of the encapsulated APIs [123–125].

3.3.1. Controlling skin permeability

The transformation of insoluble APIs into API-ILs has demonstrated enhancements in their penetration levels. For instance, Furukawa et al. devised API-ILs comprising non-steroidal anti-inflammatory drugs with proline ethyl ester as the counterion, resulting in enhanced transdermal drug penetration [126–128,27]. Similarly, Moshikur et al. employed n-methyl-2-pyrrolidone (NMP) as a biocompatible counterion to formulate API-ILs, which exhibited improved physico-thermal stability and enhanced skin penetration. These NMP-ILs facilitated a 2.6-fold increase in drug accumulation in the target tissue. Moreover, the incorporation of piperine in a 1:1 M ratio enhanced the skin penetration of ketoprofen.[129,130]

3.3.2. Regulating drug-polymer miscibility

Regulating drug-polymer miscibility is essential for crafting sustained and controlled release formulations. For example, choline citrate, a bio-based IL, has been shown to stabilize homogeneous gelatin-lignin UV-shielding films, boasting excellent antimicrobial and mechanical properties.[131] Moreover, API-ILs are utilized to augment drug-loading in polymers. Carboxylic pressure-sensitive adhesives effectively deter API-ILs recrystallization and bolster drug loading by establishing robust ionic hydrogen bonds with PSA-COOˆ- and conventional hydrogen bonds with the carbonyl group of PSA, thus synergistically enhancing drug capacity.[132]

In addition, dual biofunctional ILs, with both analgesic and anti-inflammatory properties, have been synthesized and seamlessly blended with hydrophobic polyvinylidene fluoride membranes for drug delivery systems.[120] Similarly, the conversion of low water-soluble APIs into choline-based ILs allows for their integration into bacterial cellulose membranes, thus improving rehydration capability compared to pure bacterial cellulose. Novel drug delivery systems based on grafted-Poly (L-lactide) nanoparticles loaded with API-ILs have also exhibited high encapsulation efficiency. These investigations exemplify how API-ILs regulate drug-polymer miscibility, thereby facilitating the advancement of novel drug delivery systems.

3.3.3. Regulating drug release behavior

API-ILs (Active Pharmaceutical Ingredient-Ionic Liquids) are pivotal in modulating drug release behavior across diverse delivery systems. Interactions between the drugs and polymers, comprising ionic bonds, hydrogen bonds, and van der Waals forces, exert a profound influence on the drug release profile. The characteristics and intensity of these interactions are contingent upon the types of donors and acceptors engaged. Through the formation of API-ILs, these interactions between the drug and polymer can be tailored, thereby eliciting alterations in both the quantity and rate of drug release.[133]

3.3.3.1. Key findings and examples

3.3.3.1.1. pH-dependent release. ❖ **Brilliant Blue Encapsulation:** Lozoya-Agullo et al. devised ILs combined with brilliant blue dye and encapsulated them in polymer nanoparticles (NPs). *In vitro* release studies revealed that these NPs exhibited a pH-dependent release profile, offering a controlled and adaptable release mechanism across different pH conditions.[134]

3.3.3.1.2. Sustained drug release. ❖**Gliclazide API-ILs:** Zhou et al. transformed gliclazide into API-ILs using tributyl (tetradecyl) phosphonium. The resultant transdermal patches achieved sustained drug release, with 88.17% of the drug being released over three days during *in vitro* tests. This underscores the potential of API-ILs in facilitating prolonged drug delivery.[119]

❖ **Donepezil API-ILs:** Wu et al. engineered a controlled-release transdermal patch utilizing donepezil API-ILs. The heightened molecular mobility of the API-ILs within the patch facilitated an improved drug release profile.

3.3.3.1.3. Interaction with polymers. ❖ **Dual-Drug API-ILs**: Yang et al. studied API-ILs containing two active ingredients within different pressure-sensitive adhesives (PSAs). They found that the release rates of the two drugs were significantly different across the four PSAs tested. This asynchronous release was attributed to the PSAs' participation in inter-ionic interactions with the API-ILs, which effectively reduced the drug release rates.[135]

❖ **ILs in Drug-Polymer Systems**: The transformation of drugs into API-ILs modifies the interactions with the polymers, such as forming stronger ionic or hydrogen bonds. For instance, in systems where ILs interact with polymers like PSA-COOˆ-, these interactions can inhibit recrystallization and enhance drug loading, as well as control the release rate of the drug from the formulation.[49]

3.3.3.1.4. Enhanced drug release. ❖ **Atenolol and Brilliant Blue**: ILs containing atenolol and brilliant blue demonstrated nearly 100% drug release when encapsulated in suitable polymer systems, showing the efficiency of ILs in achieving complete drug release in specific applications.[134]

❖ **Lidocaine API-ILs**: Lidocaine combined with various counterions like ibuprofen, naproxen, and diclofenac, achieved high cumulative release percentages, highlighting the flexibility of API-ILs in enhancing drug release across different delivery matrices.[129]

API-ILs are thus instrumental in tailoring drug release profiles by manipulating the interactions between drugs and the polymers, enabling the development of advanced and efficient drug delivery systems.

3.3.4. Regulating drug pharmacokinetic behaviour with API-ILs

API-ILs (Active Pharmaceutical Ingredient-Ionic Liquids) significantly influence the pharmacokinetic behavior of drugs by enhancing absorption, preventing degradation, slowing elimination, and improving targeted distribution. This can lead to more effective and efficient drug delivery system.[136]

3.3.4.1. Enhanced absorption and protection. CAGE Study: API-ILs like CAGE (Choline and Geranate IL)[137] have shown high delivery efficacy by inhibiting proteolytic enzymes that typically degrade drugs, thereby protecting the drug and enhancing absorption. Theophylline Stability: Research by Mohamed et al. on theophylline ILs with various amine counterions demonstrated enhanced stability and increased uptake in lung cells, suggesting that poly amines as counterions can significantly enhance drug accumulation in cells [138–142].

3.3.4.2. Regulated elimination and targeted distribution. API-ILs can modulate how quickly a drug is eliminated from the body, potentially leading to prolonged therapeutic effects. They can also be engineered to enhance drug targeting to specific tissues or cells, thereby improving efficacy and reducing side effects.[143]

3.3.4.3. Comprehensive API-ILs design. Designing effective API-ILs involves a thorough investigation of their behavior throughout the entire TDDS process. This includes understanding changes in drug pharmacological action when formulated as API-ILs, which is crucial for their clinical application.[144]

3.4. Novel Polymers as poly (ILs)

Introduction to Poly (ILs): Poly (ILs) are innovative polymers derived from ionic liquids, combining the beneficial properties of ILs—such as low volatility, thermal stability, and electrochemical stability with the mechanical strength of traditional polymers. These materials are used to create advanced drug delivery systems and intelligent devices.[145]

3.4.1. Applications and examples

3.4.1.1. Smart and durable materials. **Gel Ionic Conductors:** Poly (ILs)

such as PMMA-r-PBA combined with ILs like [EMI][TFSI] create highly stretchable and robust gel conductors used in human motion sensors. These materials can withstand significant deformation without losing functionality.

Anti-Freeze Hydrogels: Poly-ILs-based amphoteric hydrogels prevent freezing and degradation at low temperatures, making them suitable for use as sophisticated artificial skin with multifunctional and adaptive properties.[146]

3.4.1.2. Controlled drug release and antibacterial properties. **Nanocarriers:** Poly (tetra butyl phosphonium styrene sulfonate) exhibits dual responsiveness to pH and temperature, making it an effective shell for drug nanocarriers with controlled release properties.[147]

Antibacterial TDDS: Cationic Poly (ILs) with intrinsic antibacterial activity can be integrated into drug delivery systems to enhance therapeutic effects and protect against infections.[148]

3.4.1.3. Specialized applications. **Microneedle Patches:** Imidazolium-based poly (ILs) microneedle patches, loaded with salicylic acid, are designed for acne treatment due to their combined antibacterial and anti-inflammatory properties.[149]

Hydrogel Wound Dressings: Deferoxamine and halogen-free imidazolium poly (ILs) are used in hydrogel wound dressings. These dressings degrade in the presence of hyaluronidase, releasing their active components gradually to promote wound healing.[150]

3.4.2. Challenges and Future Directions

Despite their promising applications, poly (ILs) face several challenges:

Complex Synthesis and Purification: The processes for creating poly (ILs) can be complicated, which limits their widespread adoption.

Monomer Availability: There is a limited range of IL monomers available, which constrains the variety of poly (ILs) that can be synthesized.

Monomer Residue Issues: Residual monomers from the synthesis process can pose problems, requiring careful optimization of production methods.

3.4.3. Future Directions

Screening and Optimization: Ongoing research aims to identify suitable ILs and refine the synthesis processes for poly (ILs) to overcome these challenges and expand their applications in TDDS and other advanced fields.

In summary, API-ILs and poly (ILs) represent significant advancements in drug delivery and material science. They offer novel strategies for improving drug pharmacokinetics and creating versatile, durable polymers for various applications.

4. Conclusions and challenges

ILs in TDDS: ILs have demonstrated immense potential in advancing the field of TDDS. They serve multiple roles, enhancing drug delivery and providing innovative solutions for medical materials.

4.1. Key roles of ILs

1. **Novel Skin Penetration Enhancers:** ILs can enhance the transdermal absorption of drugs by disrupting the skin barrier, thus facilitating the delivery of APIs through the skin.
2. **Novel Solvents:** They improve the solubility of drugs, especially those with poor water solubility, making it easier to formulate and deliver these compounds effectively.
3. **Novel APIs:** ILs can be used as APIs themselves or in combination with other APIs, regulating drug properties and enhancing pharmacokinetic profiles.
4. **Novel Polymers:** Poly (ILs), synthesized from ILs, offer innovative solutions for creating smart medical materials, such as advanced drug delivery systems and responsive biomaterials.

Mechanistic Insights: Understanding the mechanisms of the ILs is crucial for their effective application. Research shows that the functionality of ILs is deeply tied to their structure, including ion types, proportions, and functional groups. These structural attributes influence IL behavior through various molecular interactions.

4.2. Challenges in IL development and application

1. **Quantitative Structure-Activity Relationship (QSAR) Models:** There is a need to develop robust QSAR models to design biocompatible ILs with tailored functions. These models would provide foundational principles for predicting and optimizing IL performance.
2. **Action Mechanisms:** More detailed studies are needed to uncover the precise mechanisms by which ILs exert their effects. This includes understanding the interactions between cations and anions at a molecular level, which influence the overall function of ILs.
3. **Long-Term Stability:** Investigating the long-term stability of ILs is critical. The stability, governed by the reversible nature of non-covalent bonds between ions, affects their safety and efficacy in medical applications.
4. ***In Vivo* Behaviour:** Understanding the pharmacokinetics of ILs within the body is vital to address potential safety concerns. This requires comprehensive studies on how ILs behave and are metabolized *in vivo*.
5. **Biocompatibility and Biodegradability of Poly (ILs):** While poly (ILs) combine the benefits of ILs and polymers, their biocompatibility and biodegradability need thorough exploration. Addressing these issues is essential for their safe and effective use in medical applications.

CRediT authorship contribution statement

Parwinder Kaur: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Amanpreet Kaur:** Investigation. **Rimpi:** Formal analysis.

Data availability statement

The data supporting the findings of this study are included within the manuscript. Further inquiries can be directed to the corresponding author upon reasonable request.

Declaration of interests

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PARWINDER KAUR reports was provided by research scholar. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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