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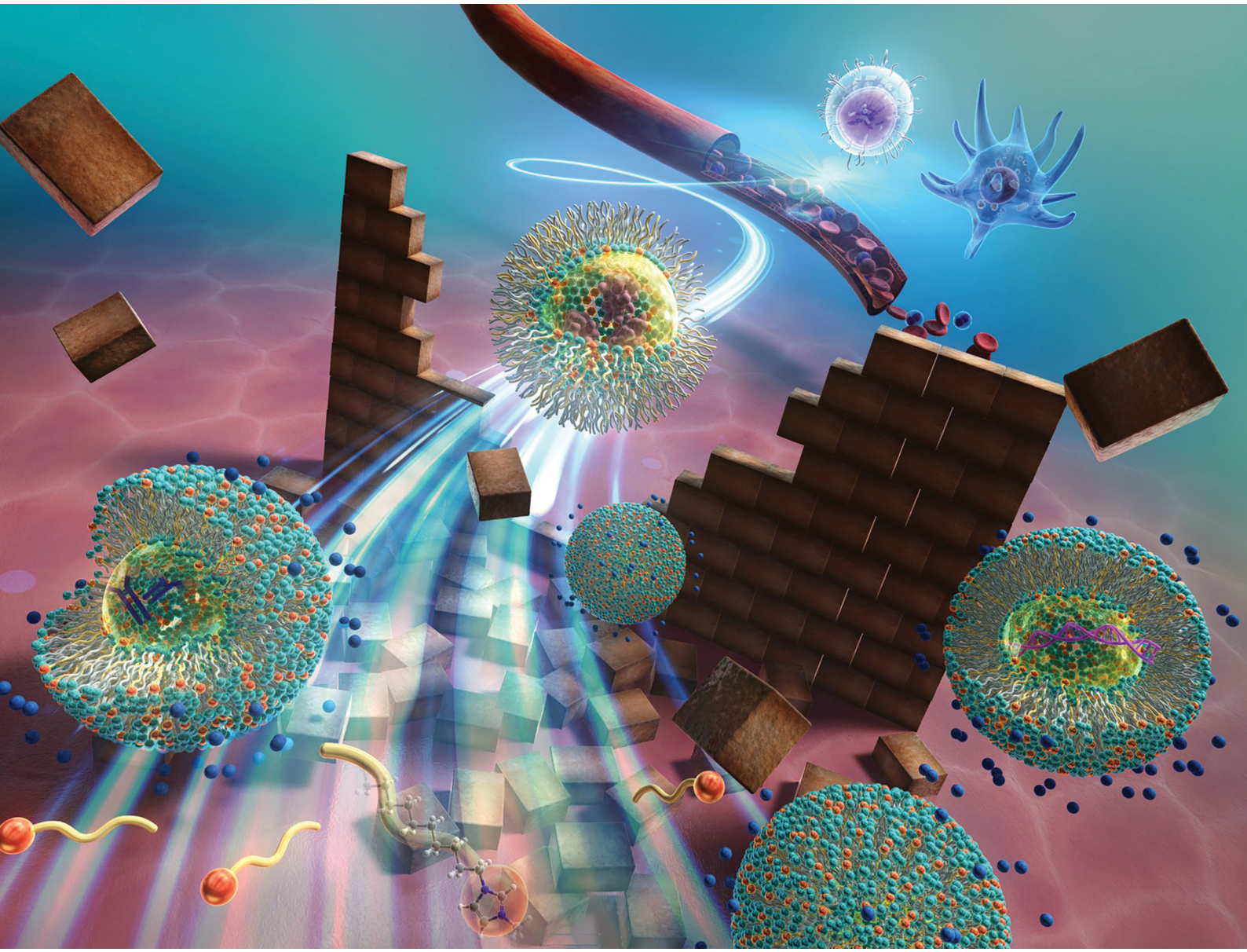

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FEATURE ARTICLE

Fahmida Habib Nabila, Masahiro Goto *et al.*

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Ionic liquid-based transdermal drug delivery systems for biopharmaceuticals

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The non-invasive transdermal delivery of biopharmaceuticals, including proteins, peptides, and nucleic acids, remains a considerable challenge because of the formidable barrier function of the stratum corneum. Ionic liquids (ILs) composed of tunable cations and anions have emerged as useful multifunctional materials in transdermal drug delivery systems (TDDS) because of their excellent physicochemical properties. By acting simultaneously as solvents and permeation enhancers, ILs can considerably improve the solubility and stability of labile biomolecules and facilitate their transport across the skin. Recent studies have demonstrated the successful integration of ILs into nanocarrier systems, including ethosomes, transethosomes, IL-in-oil micro-/nano-emulsion formulations, and solid-in-oil dispersions, enabling the effective transdermal delivery of insulin, siRNA, mRNA, and other biologics. Compared with conventional solvent-based transdermal systems, biocompatible IL-based formulations can confer high stability and enhanced drug bioavailability. This review surveys the most recent advances in IL-TDDS, with particular focus on lipid- and choline-derived IL-enabled TDDS that have demonstrated prolonged glycemic control in diabetic models and potent anti-tumor responses in nucleic-acid immunotherapy.

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1. Introduction

The success of modern pharmacotherapy strategies is increasingly dependent on formulations that can increase the bioavailability of a potential pharmaceutical without compromising safety or patient adherence.[1–3] Global demographic shifts, including population growth, population aging, and escalating rates of autoimmune and chronic diseases, are further amplifying the need for medicines that are simultaneously potent and user-friendly.[4] Although the current market is still dominated by conventional, low-molecular-weight synthetic drugs,[5] the newer class of biopharmaceuticals, which includes therapeutic proteins, peptides, nucleic acids, and other biologically derived entities, has gained remarkable momentum since their debut in the 1980s.[6,7] Biopharmaceuticals, also known as biologics, now account for roughly one-third of all pipeline drugs and represent the fastest-growing sector of the pharmaceutical industry, propelled by their ability to modulate previously "undruggable" targets with high specificity.[5,8] Biopharmaceuticals can offer precise target specificity and reduced systemic toxicity.[9,10] However, the clinical impact is frequently hampered by the poor permeability, high molecular weight, and structural fragility of biopharmaceuticals.[11] Unlike small-molecule or synthetic drugs, biopharmaceuticals are typically derived from biological sources and possess complex structures, making them highly susceptible to denaturation and degradation (Fig. 1).[8] Ensuring the long-term stability and bioactivity of biopharmaceuticals is critical, often requiring the incorporation of stabilizing excipients or the use of costly preservation techniques.[12] Additionally, the low *in vivo* bioavailability of biopharmaceuticals remains a considerable challenge, as low bioavailability can compromise the therapeutic efficacy and disrupt the desired pharmacokinetics.[13] These limitations have hindered the development of safe, effective, and commercially viable biopharmaceutical therapies.[14]

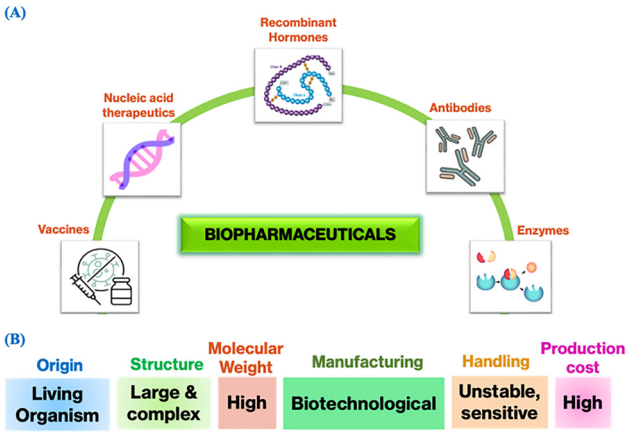

Fig. 1 Biopharmaceuticals: (A) types and (B) properties.

Ionic liquids (ILs), which are organic salts that remain liquid at near ambient temperature, have become of sustained interest in drug development because ILs unite designer-level tunability with exceptional solvent power.[15,16] Structurally, ILs consist of bulky, often asymmetric, cations paired with diverse anions; this asymmetry disrupts crystal packing, lowers lattice energy, and maintains the material in a liquid state.[17,18] Through the strategic selection of cation–anion pairs, the polarity, viscosity, hydrophobicity, hydrogen-bonding capacity, and thermal stability can be finely tuned, enabling custom solutions for drug solubilization, pharmacokinetic modulation, and molecular targeting.[19,20] This versatility has enabled ILs to play an extensive array of pharmaceutical roles, from co-solvents for small molecules to stabilizers, permeation enhancers, and even as active carrier phases for macromolecular therapeutics.[21,22] Recent literature examples have underscored how ILs can mitigate long-standing formulation bottlenecks.[23] *In vitro* and *in silico* studies have shown that biocompatible cholinium ILs elevated the melting point of insulin by ≈13 °C and that of the monoclonal antibody trastuzumab by >20 °C, which markedly delayed unfolding and aggregation.[24] Mounting evidence has indicated that ILs can dissolve, extract, and refold labile proteins while preserving the biological activity, provided the ion pair is chosen to avoid chaotropic or cytotoxic effects.[25] This protection extends beyond proteins: ILs have stabilized plasmid DNA, and siRNA, often by forming a nano-layer that shielded labile bonds and prevented protease or nuclease actions.[26–31]

Beyond bulk stabilization, ILs are reshaping drug-delivery paradigms. Third-generation (biodegradable) cholinium- and lipid-derived ILs embedded in microemulsions (MEs), ethosomes (ETs), and transethosomes (TETs) have been used to encapsulate high-molecular-weight drugs with near-quantitative efficiency, enabling sustained release and transient disruption of the stratum corneum (SC) without lasting damage.[27,28,32] Recently, our group has reported dimyristoyl-phosphatidylcholine IL ETs that achieved ∼99% insulin encapsulation, month-long stability at both 4 and 25 °C, and a two-fold increase in skin flux compared

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with conventional vesicles.[32] Such advances illustrate how ILs function dually as microenvironment modulators that suppress aggregation and as permeation enhancers that enable non-invasive routes of administration, thereby widening the therapeutic window for fragile biologics while obviating the need for needle-based administration.[19,22,33]

Transdermal drug delivery (TDD) offers a non-invasive administration route that bypasses first-pass metabolism, enables sustained release, and supports patient self-administration—properties that are especially valuable in chronic care.[34,35] The principal obstacle for TDD is the SC: a ~10 μm-thick, lipid-rich barrier that favors small, lipophilic molecules and excludes hydrophilic or high-molecular-weight therapeutics.[10,36] Even when drugs can traverse the SC, the action of epidermal and dermal enzymes, and slow uptake can limit the therapeutic efficacy.[37] Engineered ILs can transiently fluidize SC lipids, enhance drug loading, and act as reservoirs for controlled release while maintaining safety, particularly when biodegradable ions are employed.[22,38] Collectively, these properties enable ILs to function as a multifunctional toolkit for biopharmaceutical formulation, combining molecular stabilization, solvent versatility, and transdermal delivery capability in a single, highly tunable platform.

This review presents a focused overview of IL-based transdermal drug delivery systems (TDDS), specifically for biopharmaceuticals, as shown in Fig. 2. While many published reviews have explored the biological activity,[39–43] design principles,[44] mechanisms,[44,45] toxicological profiles,[17,45–47] and general pharmaceutical applications[44,45,48–51] of ILs, this review focuses on emerging non-invasive delivery platforms that exploit IL tunability to conquer the triad of stability, permeability, and patient compliance. Special emphasis is placed on choline- and fatty-acid/lipid-derived ILs integrated into advanced nanostructured carriers, which collectively herald a new generation of needle-free, patient-centric biotherapeutics.

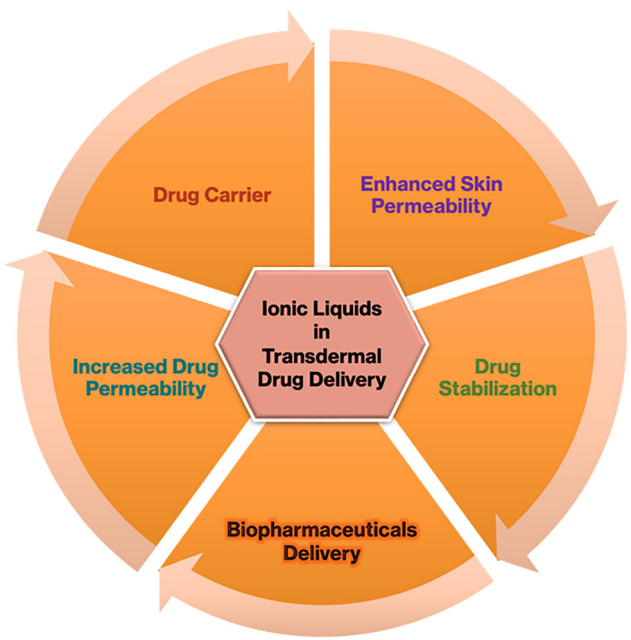

Fig. 2 Schematic diagram of the application of ILs in transdermal delivery.

2. Importance of transdermal drug delivery

Since the first US Food and Drug Administration (FDA) approval of a transdermal scopolamine patch in 1979,[52] TDDS have evolved from niche applications into a robust segment of the global pharmaceutical market. In 2023, the market for TDDS was valued at approximately USD 62 billion and was projected to grow at a compound annual growth rate of ~12%, to reach an estimated USD 137 billion by 2030.[53] This surge is driven by the rising prevalence of chronic disease, patient preference for non-invasive therapies, and expanding research into smart and responsive delivery technologies.[53] Compared with oral or parenteral routes, TDDS offer many clinical and practical advantages, including avoidance of first-pass metabolism, sustained and controlled drug release, improved patient compliance, painless administration, and a lower risk of systemic side effects.[54] However, most TDDS currently on the market are limited to delivering small, lipophilic drugs with molecular weights under 500 Da and log P values typically ranging from 1 to 3 because of the selective permeability of the SC.[55] Commercially available transdermal therapeutics include hormones (*e.g.*, estradiol and testosterone), analgesics (*e.g.*, fentanyl and buprenorphine), cardiovascular agents (*e.g.*, nitroglycerin and clonidine), central nervous system drugs (*e.g.*, rivastigmine, selegiline, and rotigotine), and smoking cessation aids (*e.g.*, nicotine).[53] Despite clinical successes, these systems still have issues, such as limited drug loading capacity (<10 mg per day), site-specific variability in skin permeability, the potential for skin irritation, and poor adhesion under conditions of sweat, motion, or prolonged use.[56] Table 1 summarizes some of the currently marketed formulations for TDDS.

2.1. ILs in transdermal drug delivery

ILs have emerged as a transformative class of permeation enhancers because they offer a tunable balance of lipophilicity, hydrogen-bonding ability, and solvent power that addresses each step of the transdermal transport cascade.[57] Mechanistic studies using attenuated-total-reflectance Fourier Transform Infrared Spectroscopy (FTIR) and confocal Raman microscopy have shown that selected IL ion pairs, particularly choline/geranate, choline/oleate, and imidazolium-based fatty esters, inserted into the SC lipid lamellae, fluidizing orthorhombic and hexagonal phases without extracting ceramides or cholesterol, thereby opening transient nano-channels that could accommodate macromolecules up to 70 kDa.[58–60] Unlike classical enhancers (*e.g.*, ethanol and DMSO) that rapidly dehydrate the SC and may trigger irritation, third-generation biodegradable ILs maintain skin hydration and have exhibited irritation indices comparable to placebo gels in murine, porcine, and human *ex vivo* models.[27,61,62]

2.1.1. ILs as drug-solubility enhancers. Poor aqueous solubility remains one of the most problematic issues in the design

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Table 1 Examples of some currently marketed drugs delivered *via* the transdermal route

Therapeutic class	Drug name	Molecular weight (Da)	Primary indication	Limitations	Ref.
Hormonal	Estradiol	272.4	Menopausal symptoms	Skin irritation, variable absorption with site; low drug loading	66
Analgesic	Buprenorphine	467.6	Moderate to severe pain	Application site reactions; delayed onset	67
Cardiovascular	Clonidine	230.1	Hypertension	Dry skin; dose limitation; delayed onset	68
Parkinson's	Selegiline	187.2	Major depressive disorder	Insomnia, irritation, dietary restrictions	69
Smoking cessation	Nicotine	162.2	Nicotine dependence	Skin irritation; variable absorption	70

of TDDS. Conventional organic solubilizers (*e.g.*, PEG 400, ethanol, and DMSO) can improve payload dissolution but introduce issues of volatility, skin irritation, and regulatory limits on residual solvents.[27,61] ILs can dramatically improve drug solubility. For example, the solubility of both biologics and small drugs, such as acyclovir, increases when transitioning from aqueous buffer to choline-based fatty acid IL-mediated MEs and biphasic systems. This increased solubility has enabled high drug-to-patch load without crystallization.[63,64]

Spectroscopic and molecular-dynamics evidence has suggested that this dramatic solubility enhancement was driven by several cooperative and non-covalent interactions facilitated by the IL environment.[65] First, hydrogen-bond donation and acceptance interactions dominate when carbonyl-rich anions such as bis-(trifluoromethanesulfonyl)-amide are paired with imidazolium cations.

For the poorly soluble cardiovascular lead compound, LASSBio-294, carbonyl oxygens on the anion form strong H-bonds with the drug N–H groups, while cation π-faces engage with the aromatic core of the active pharmaceutical ingredient (API), which together increased the solubility by more than two orders of magnitude (Fig. 3A). Second, π–π and van der Waals stacking interactions become dominant for hydrophobic molecules, such as danazol and thymoquinone. The long-alkyl imidazolium cations align parallel to the aromatic rings of the drug, disrupt self-aggregation, and increase the dispersion forces that stabilize the dissolved state (Fig. 3B).[71] Third, multipoint hydrogen bonding is pivotal in cholinium systems. All three oxygen atoms of the geranate anion in choline geranate (CAGE) simultaneously bind to the carbonyl and methoxy oxygens of nobiletin, yielding a 450-fold solubility increase, relative to water, enabling the formulation of high-loading transdermal gels.[72] Finally, molecular-dynamics simulations have revealed that many IL/water mixtures segregate into bicontinuous morphologies with percolating polar channels intertwined with non-polar domains. Hydrophilic drug moieties reside in the polar network while hydrophobic fragments partition into contiguous apolar regions, creating a versatile "solvent sponge" that can accommodate structurally diverse APIs.[73]

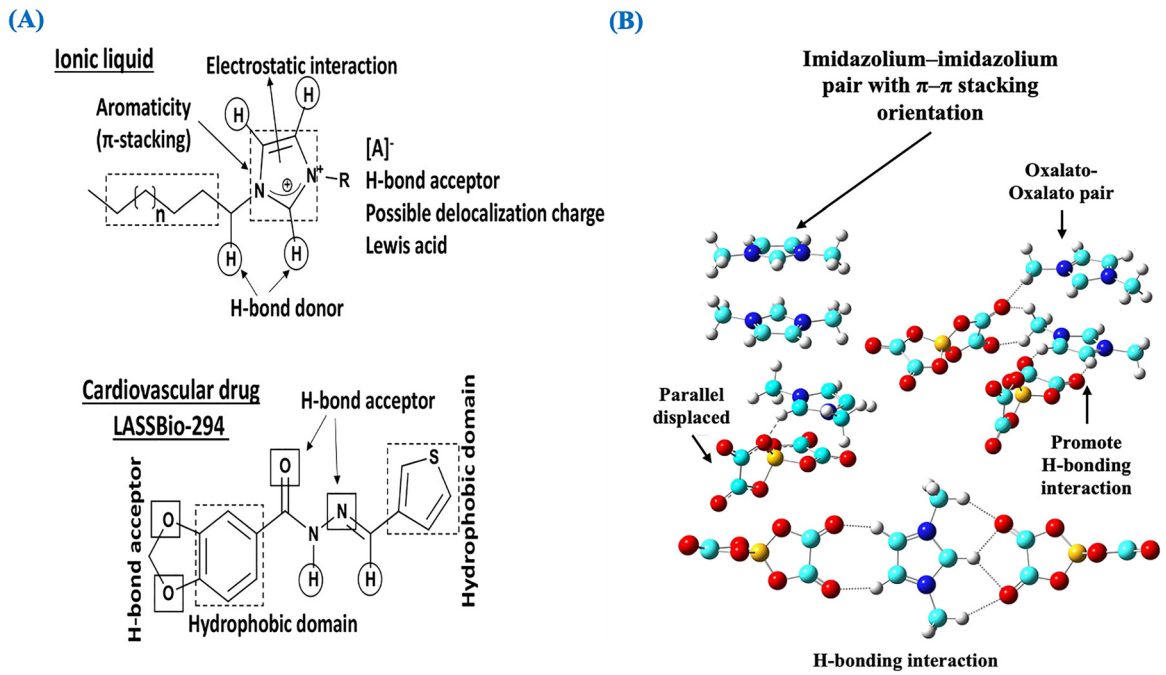

Fig. 3 (A) Schematic diagram of hypothetical interactions between imidazolium-based ILs and LASSBio-294, reproduced with permission from ref. 51. (B) Representative molecular distributions among close-contact ionic groups showing π–π stacking orientation, reproduced with permission from ref. 71. Copyright © 2017, American Chemical Society.

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In studies highlighting the potency of ILs as solubilizers, acyclovir and paclitaxel were dissolved 625- and 5585-fold, respectively, in cholinium glycinate than in water[74,75] and the solubility of insulin reached >50 mg mL^{-1} in CAGE/propyleneglycol deep eutectic media, which was >250-fold higher than the aqueous solubility, without loss of bioactivity.[76,77] Importantly, these solubility increases can translate directly into higher patch loading, thinner reservoirs, and lower risk of recrystallization during storage.

2.1.2. ILs as drug carriers. A key property of ILs is the ability to slot into almost any transdermal carrier architecture, each role exploiting a different facet of IL chemistry.[80] Because ion-pair structures can be "dial-tuned," ILs can be incorporated into many carrier formats, from neat pretreatment fluids to complex nanovesicles, while simultaneously improving the solubility, stability, and skin flux of the encapsulated drugs. For example, replacing conventional surfactants with IL surfactants expanded the ME regions two-fold and increased celecoxib and acyclovir skin flux by 4–6× with negligible irritation.[53] The types of formulations discussed in this review are shown in Fig. 4 and key examples of IL formulations of biopharmaceuticals are summarized in Table 2. The above-mentioned findings demonstrated that ILs are not confined to a single formulation niche; rather, ILs are a versatile, plug-and-play class of excipients, capable of functioning as solvents, surfactants, oil phases, solid carriers, nanovesicles, and even polymeric materials. By harnessing the tunable hydrogen-bonding and π–π stacking capabilities of ILs, molecular-level interactions can be consistently translated into substantial improvements in drug solubility, loading capacity, and transdermal permeability.[22]

3. Importance of ILs in the transdermal delivery of biopharmaceuticals

Over the past two decades, ILs have progressed from laboratory curiosities to multifunctional excipients that can address, within a single formulation, three issues that have traditionally limited transdermal biopharmaceuticals: poor solubility; molecular fragility; and low skin permeability.[22] The modular architecture of ILs, in which bulky, asymmetric cations are paired with a virtually unlimited library of anions, allows independent tuning of the polarity, hydrogen-bonding strength, lipophilicity, viscosity, and redox and thermal stability.[81] This "designer-solvent" capability means a single IL formulation can replace

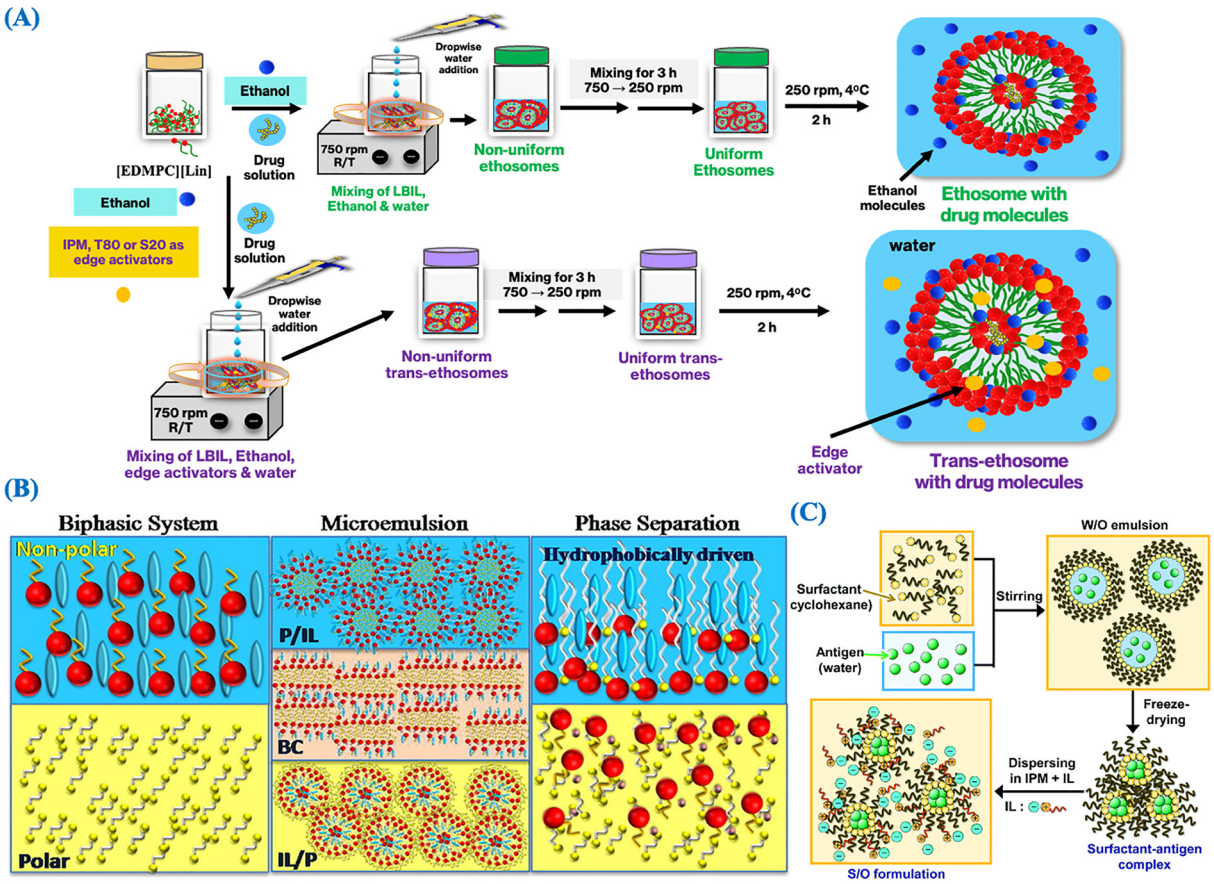

Fig. 4 Different types of IL-mediated formulations. (A) IL-mediated nanovesicular ETs. Figure reproduced with permission from ref. 32. Copyright 2024. (B) IL-mediated MEs, P indicates polar. Figure reproduced with permission from ref. 78. Copyright 2018. (C) IL-mediated solid in oil (S/O) dispersion, figure reproduced with permission from ref. 79. Copyright 2015.

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Table 2 Formulation of IL-enabled transdermal systems

Formulation strategy	Model drug(s)	IL composition & role	Carrier architecture	Performance	Ref.
IL pretreatment	Insulin	Step 1: cholinium citrate (hydration); step 2: CAGE (permeation)	Thin film applied before patch	Normalised blood glucose in diabetic rats within 8 h; ethanol gel ineffective	58 and 60
IL-in-oil and IL/W ME	Celecoxib, Acyclovir	Imidazolium and cholinium IL surfactant replaces oil phase and solvent respectively	ME or microemulgel and ME in pressure sensitive patch	ME region ↑ 2×; drug loading ↑ 4–6×; porcine-skin flux ↑ 6× with no irritation	16 and 83
IL-surfactant hybrid micelles	Dencichine	[HOEIM]Cl and [BMIM][$C_{12}SO_3$] in aqueous and surfactant phase	Mixed micellar ME	*In vivo* flux ↑ 10×; haemostatic efficacy retained; no erythema	84
IL/W or W/IL micro-/nano-emulsion	Artemisinin	[HOEmim]Cl in aqueous phase + lidocaine:ibuprofen as oil	IL/DE-based ME	Skin transport ↑ 3× *vs.* IPM ME; intact histology	85
Solid-in-oil dispersion	ASO	[EDMPC][Lin], [EDMPC][Ole], and [EDMPC][Ste] stabilize ASO	S/O nanoparticles	ASO delivery ↑; maintains secondary structure	86
IL-modified nanovesicles	Insulin	[EDMPC][Lin] within lipid bilayer	Deformable vesicles	>99% EE; insulin flux ↑ 2× *vs.* EtOH ethosome; 70% gene knock-down *in vivo*	27 and 32
IL-polymer micelles	Paclitaxel	Cholinium linoleate as hydrotropic core	PEG-PLA micelles	≥40 mg mL^{-1} loading; cadaver-skin flux ↑ 3× *vs.* Cremophor EL	87

[HOEIM]/[HOEmim] Cl: 1-hydroxyethyl-3-methylimidazolium chloride, [BMIM][$C_{12}SO_3$]: 1-butyl-3-methylimidazolium dodecanesulfate, W: water, IPM: isopropyl myristate, *vs.*: *versus*, EDMPC: ethyl 1,2-dimyristoyl-*sn-glycero*-3-phosphatidylcholine, Lin: linoleic acid, Ole: oleic acid, Ste: stearic acid, ASO: anti-sense oligonucleotide, EE: encapsulation efficiency, EtOH: ethanol.

the use of several buffers, surfactants, and permeation enhancers, which often show conflicting requirements and toxicities.[8,82]

3.1. Stabilization of biopharmaceuticals by ILs

The structural fragility of biopharmaceuticals, including proteins, peptides, nucleic acids, and viral vectors, poses considerable challenges for TDD. These types of molecules are highly susceptible to degradation through aggregation, denaturation, hydrolysis, and oxidation during processing, storage, and delivery, especially under non-refrigerated conditions.[8] Traditional stabilizers, such as sugars, polyols, and surfactants, offer limited protection and often fail to preserve bioactivity over extended periods. ILs, particularly those designed from naturally derived cations (*e.g.*, choline, lipids, and amino acids) and biocompatible anions (organic acids and carboxylates), overcome these limitations by creating multivalent hydrogen-bond and electrostatic networks around the biomolecule while simultaneously offering a hydrophobic shield against solvent exposure.[14,89] For example, cholinium isoleucinate and other hydrophilic ILs preserved B-form DNA for months at room temperature (20–25 °C) by electrostatically screening phosphate repulsion, whereas hydrophobic imidazolium ILs can be selected to denature duplexes for strand-separation workflows.[90,91] Amino-acid IL coatings mitigated capsid oxidation in the adeno-associated virus and stabilized lyophilized mRNA-lipid nanoparticle (LNP) vaccines for ≥6 weeks at 25 °C, dramatically reducing the cold-chain requirements.[88] A comparison of IL-enabled TDD platforms with conventional solvent-based approaches for biopharmaceuticals is summarized in Table 3.

3.2. ILs in the TDD of biopharmaceuticals

Recent research has indicated that ILs are positioned to be transformative excipients for the transdermal delivery of biopharmaceuticals.[24,94–96] A landmark example is the work of Mitragotri *et al.* in 2018, in which use of the deep-eutectic IL, CAGE, markedly enhanced insulin permeation across excised skin.[60] Mitragotri and co-workers then reported transmucosal insulin delivery using CAGE and taurine/carnitine ILs as a form of biodegradable polymeric patch. *In vivo* studies in diabetic rat models demonstrated significant reductions in blood glucose levels using such patches, which were comparable to subcutaneous insulin injections (Fig. 5A and B).[76] Recently, Vieira *et al.* have synthesized a family of fluorinated, surface-active ILs (SAILs) by pairing perfluorobutanesulfonate anions with imidazolium, pyridinium, or cholinium cations.[92] These SAILs self-assembled in aqueous and buffered media to encapsulate lysozymes. These complexes remained intact at 4 °C for 12 h but released the protein completely with full enzymatic activity within 12 h at 37 °C, indicating a temperature-responsive delivery profile ideal for controlled dosing (Fig. 5C).[92] Beyond proteins, Dharamdasani *et al.* have employed a hydrophobic IL ''robe'' in combination with CAGE to transport anti-GAPDH (glyceraldehyde-3-phosphate dehydrogenase) siRNA through porcine and murine skin, achieving potent gene silencing without skin irritation (Fig. 5D).[93]

The following sections (and Table 4) detail additional recent examples of choline- and lipid-based ILs that highlight the growing importance of ILs in transdermal biopharmaceutical delivery.

3.2.1. Transdermal insulin delivery using IL-based formulations. In recent years, considerable attention has been devoted to the IL-mediated transdermal delivery of therapeutic proteins, particularly insulin, because of the growing need for non-invasive alternatives to subcutaneous injections in diabetes management.[27] IL-based nanocarriers have enabled non-invasive means of glucose control, reducing the reliance on injections.[27] Choline–oleate and imidazolium-based ILs have shown high permeation rates, enzyme stability, and sustained release in diabetic models.[22]

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Table 3 IL *vs.* conventional TDDS of biopharmaceuticals

Parameter	Conventional TDD systems	IL-based TDD systems	Ref.
Drug type compatibility	Primarily small, lipophilic molecules (<500 Da)	Capable of delivering large, hydrophilic biomolecules (proteins, peptides, nucleic acids)	82
Permeation	Relies on solvent (*e.g.*, ethanol), surfactants (*e.g.*, Tween-80), or chemical enhancers	ILs disrupt SC lipid order *via* H-bonding & π–π stacking, enhancing skin penetration	71
Solubility	Limited solubilization capacity for poorly soluble drugs	ILs improve solubility *via* ionic interactions, hydrogen bonding, and domain restructuring	8
Formulation flexibility	Gels, creams, patches with limited versatility	Neat ILs, IL-in-oil MEs, IL-based nanovesicles (ETs, TETs), IL-micelles	28 and 32
Stability of biologics	Prone to enzymatic degradation and aggregation	ILs enhance the stability of sensitive macromolecules by preventing aggregation and improving thermal stability	24
Delivery efficiency	Low for high MW drugs; minimal systemic absorption	High permeation rates demonstrated for insulin, siRNA, mRNA, ASOs	27 and 86
Toxicity concerns	Lower toxicity with approved excipients	Requires careful selection of biocompatible, biodegradable ILs (*e.g.*, choline-based)	49 and 51
Cold chain dependency	High for peptides and nucleic acids	ILs reduce or eliminate cold chain needs by enhancing thermal stability (*e.g.*, mRNA-LNPs stable at 25 °C)	88
Mechanism of action	Passive diffusion or SC hydration	Reversible disruption of SC structure, creation of intercellular channels, polar–nonpolar domain alignment	27 and 86
Clinical translation	Multiple FDA-approved systems (*e.g.*, nicotine, estradiol patches)	Mostly in preclinical or early-phase research; regulatory approval pending	64

LNP: lipid nanoparticle.

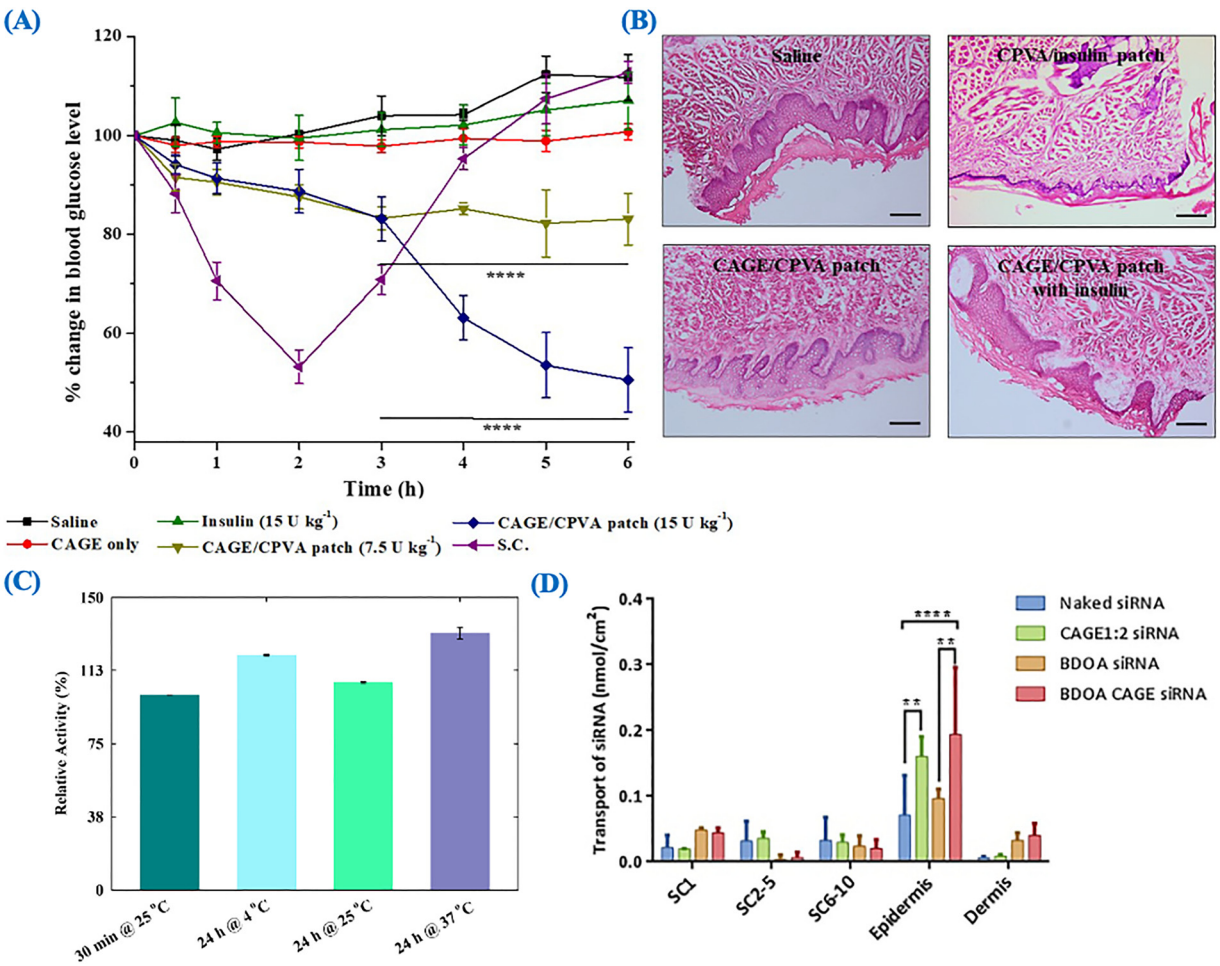

Fig. 5 (A) *In vivo* pharmacodynamic efficacy of CAGE/insulin administered in the buccal cavity of rats. (B) Hematoxylin and eosin (H&E) staining of rat buccal mucosa (scale bar = 200 μm). Figure reproduced with permission from ref. 76. (C) Lysozyme relative activity under different incubation conditions. Figure reproduced with permission from ref. 92. (D) Penetration of siRNA-ILs: porcine skin quantification using tape-stripping indicated improved permeation of robed-siRNA in presence of an IL (CAGE) into the epidermis. Figure reproduced with permission from ref. 93.

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Table 4 Summary of IL-mediated TDD of biopharmaceuticals

Biopharmaceuticals	IL-based carrier	Key ILs	Significant findings	Ref.
Insulin (5.8 kDa)	IL-in-oil ME (SAIL-stabilised)	[Chol][C18:2] (surface-active IL) + [Chol][C3] polar core	Diabetic mice: 56% glucose drop with 50 IU kg^{-1} patch; serum $t^{\frac{1}{2}} \approx$ 24 h *vs.* 1.3 h (sub-Q); formulation room-temp-stable 3 months	28
Insulin	IL-mediated ETs ($\approx$160 nm deformable vesicles)	Dimyristoyl-phosphatidylcholine lipid IL	>99% EE; mouse-skin flux sufficient to cut blood glucose by 62% and keep normoglycaemia >15 h (SC injection held $\leq$2 h)	32
Insulin	IL-mediated TETs (deformable vesicles)	Dimyristoyl-phosphatidylcholine lipid IL	Mouse-skin flux sufficient to cut blood glucose by 34% and keep normoglycaemia >15 h (SC injection held $\leq$2 h), $\geq$80% cell viability	27
OVA (44 kDa)	IL in oil	Cholinium–fatty-acid ILs (*e.g.*, [Cho][C18:1])	Peptide flux ↑28×, ↑10× OVA-specific IgG titres, significant tumor growth suppression *in vivo*, no dermal irritation	97
Trabederson (ASO) (20-mer)	IL-S/O	Lipidic IL surfactant shell	Porcine skin flux ↑ ~10×; potent TGF-β knock-down; no toxicity	86
OVA	IL-S/O nanodispersion patch with PSA	[Chol][C18:1] lipid IL	Yucatan pig skin: 5.5-fold higher OVA delivery *vs.* aqueous; mice: 10-fold IgG↑, robust $CD8^+$ response, no dermal damage	36

In 2021, Islam *et al.* reported a fully biocompatible ME that employed choline–fatty-acid, surface-active ILs ([Chol][Ste], [Chol][Ole], and [Chol][Lin]) as surfactants, choline propionate as the polar IL core, and IPM as the continuous oil phase (Fig. 6A).[28] Use of the IL in oil (IL/O) ME expanded the ternary ME region by two-fold relative to Tween-80 systems, solubilized insulin at a therapeutically high loading, and could deliver a low dose (50 IU kg^{-1}) of insulin transdermally to diabetic mice, lowering blood glucose levels by 56% and sustaining circulating insulin for >24 h (half-life $\approx$ 24 h *vs.* 1.3 h for sub-Q injection) (Fig. 6C and D). No cytotoxicity (<10% loss in human adult keratinocyte-derived immortalized cell line (HaCaT) viability) or histopathological changes were observed, and the formulation remained stable at room temperature for three months (Fig. 6B).[28]

In 2024, Nabila *et al.* reported a more advanced "IL-mediated ET" built from dimyristoyl-phosphatidylcholine paired with linoleate-based lipid ILs, which encapsulated >99% of human insulin in deformable vesicles $\approx$160 nm in diameter.[32] In the same year, IL-mediated ET and TET1 formulations were reported by the same group. When 30 IU kg^{-1} of the ET formulation was applied to diabetic mouse skin, blood-glucose levels fell by 62% and remained below baseline for >15 h, whereas subcutaneous injection maintained glycemic control for only 2 h (Fig. 6E). TET1 reduced glucose levels by 34% for >15 h in the same mouse model. Confocal microscopy (Fig. 6F) and ATR-FTIR showed that the IL disrupted orthorhombic SC lipids, creating intercellular nano-channels while preserving epidermal viability. Skin-irritation tests using a 3-D human epidermis model indicated $\geq$80% cell viability (Fig. 6G), underscoring the biocompatibility of the IL–lipid hybrid.[27]

Mechanistic commonalities across the three systems (ME, ETs, and TETs) include (i) IL-driven disruption and fluidization of SC lipids without ceramide extraction, confirmed by FTIR lipid-order markers; and (ii) multipoint hydrogen bonding between choline-carboxylate ILs/lipid-based ILs and insulin that maintained the molecular dispersion of the peptide and prevented aggregation. Collectively, these studies demonstrated that rationally chosen, biocompatible ILs can be paired with ETs, TETs, and MEs to achieve long-acting, needle-free insulin delivery, meeting key therapeutic benchmarks for glucose control while avoiding cold-chain and injection-related burdens.

3.2.2. Transdermal nucleic acid and vaccine delivery using ILs. The delivery of nucleic acids, such as siRNA and mRNA, is hindered by their size, charge, and instability. ILs can shield nucleic acids from degradation, facilitate skin penetration, and allow co-delivery with peptides or adjuvants.[98] Lipid–IL hybrid nanocarriers have shown successful gene knockdown *in vitro*, highlighting the potential of ILs in RNA therapeutics. Recently, Goto and co-workers have reported that hydrophobic, lipid-derived IL surfactants can transform antisense oligonucleotides (ASOs) into a solid-in-oil (S/O) dispersion capable of non-invasive skin penetration (Fig. 7A, B and E).[86] In this formulation, each ASO strand is coated with amphiphilic IL ions, which (i) mask the polyanionic phosphate backbone, (ii) confer hydrophobicity that favors partitioning into the SC lipids, and (iii) act as built-in permeation enhancers. Compared with conventional S/O carriers, the IL-S/O increased the transdermal flux of fluorescently labeled ASOs by an order of magnitude in excised porcine skin (Fig. 7C) and, crucially, drove cytoplasmic uptake in keratinocytes without endosomal entrapment.[86] *In vitro*, the formulation achieved potent knockdown of Transforming Growth Factor beta (TGF-β) mRNA, confirming that the IL coating did not compromise the antisense activity. In tumor-bearing mice, a once-daily topical application produced an anti-tumor effect statistically indistinguishable from that of subcutaneous ASO injections (Fig. 7C), yet with no injection-site reactions or systemic toxicity.[86] These findings underscore the dual role of biocompatible IL surfactants as both molecular shields and skin-barrier modulators, opening a path toward needle-free RNA and DNA therapeutics.

ILs are also emerging as potent enablers for the delivery of vaccines and antibodies, leveraging the IL multifunctionality to stabilize antigens and enhance the dermal uptake.[94] In 2020, Tahara *et al.* reported the use of biocompatible cholinium–fatty-acid ILs (*e.g.*, [Cho][C18:1]) to solubilize ovalbumin (OVA) in oil-based penetration enhancers. Compared with aqueous formulations, the IL-enhanced system increased peptide flux

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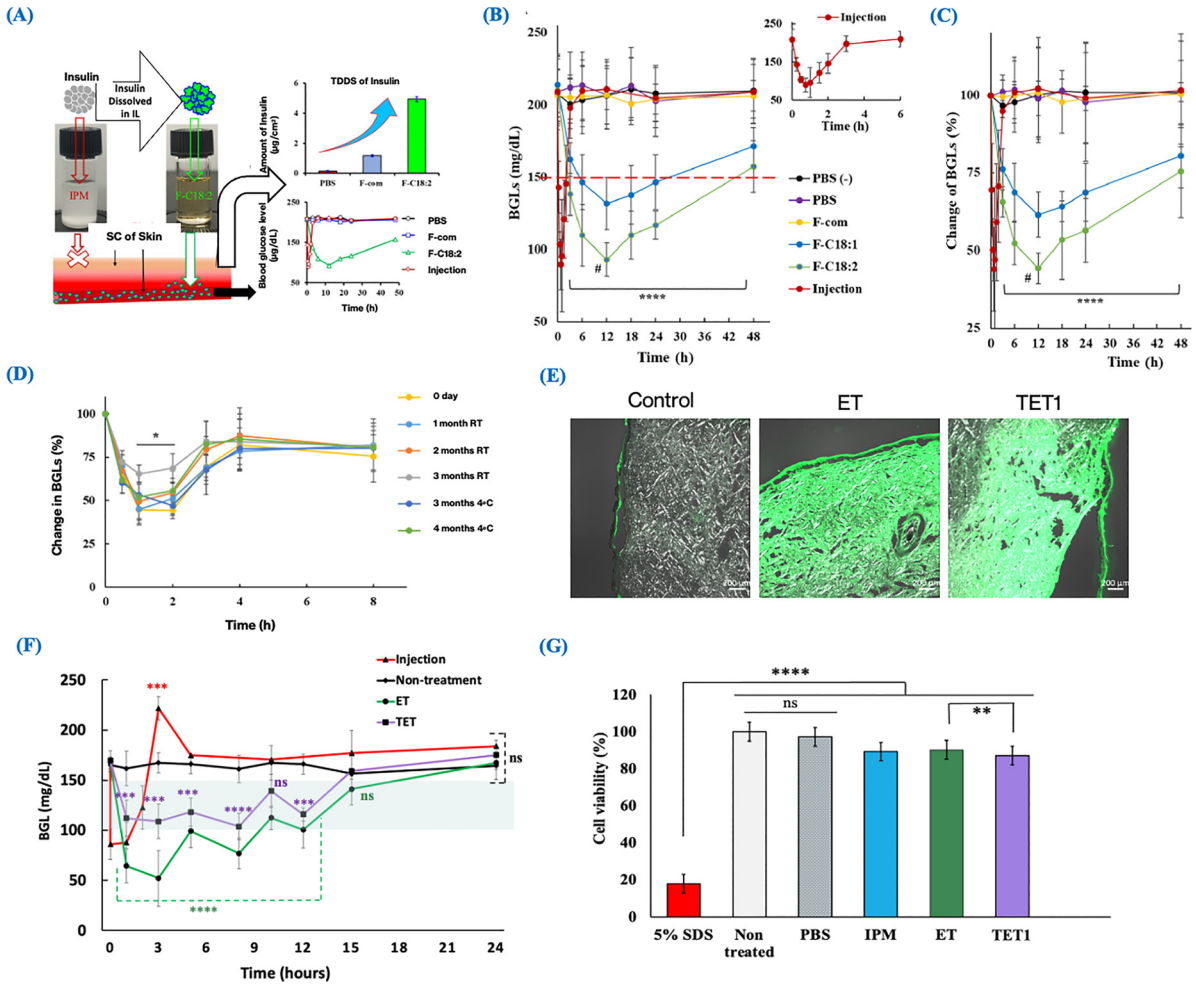

Fig. 6 (A) Cholinium IL-based ME increased the solubility and permeability of insulin. (B) Changes in mouse blood glucose levels over time and (C) blood glucose-lowering potency of different formulations compared with baseline levels. (D) Assessment of the biological activity of insulin stored with ME formulations (MEFs) for different periods at RT and 4 °C; effect of SAIL-based MEFs in lowering blood glucose levels (BGLs) in diabetic mice following transdermal delivery. Figure reproduced with permission from ref. 28. (E) Skin permeability of FITC-Insulin (FITC-Ins) using ET and TET1, Confocal Laser Scanning Microscopy (CLSM) images of skin cross sections of Yucatan micropig (YMP) skin treated with FITC-Ins in ET and TET1 formulations along with control FITC-Ins solution for 24 h. (F) Changes in diabetic mice BGLs over time after transdermal insulin delivery with ET and TET1 nanovesicles. (G) Biocompatibility of ET and TET1 formulations compared with positive and negative controls using artificial human epidermal tissue. Figure reproduced with permission from ref. 27.

across excised skin 28-fold, and elicited a tenfold increase in OVA-specific IgG titers and significant tumor growth suppression *in vivo*, with no dermal irritation detected *via ex vivo* assays (Fig. 7G).[97] In a follow-up study in 2021, Chowdhury *et al.* formulated an S/O IL dispersion combining an IL-coated OVA antigen with the Toll-like receptor 7 (TLR7) agonist resiquimod.[90] When applied as a patch, this system enabled transdermal delivery of both antigen and adjuvant, generating robust cytotoxic T-cell responses and cancer protection in murine models. Mechanistically these effects were attributed to the dual role of the IL in charge shielding and lipid-phase fluidization, which facilitated skin permeability and intracellular uptake.[99] In further innovation by Islam *et al.* in 2024, an IL-based immunization patch combining an IL-S/O nanoparticle dispersion with pressure-sensitive adhesives was developed. In pig-skin assays and a C57BL/6 mouse model, this patch delivered 5.5-fold more OVA and generated 10-fold higher IgG levels, than aqueous controls, without evidence of histopathological skin damage.[36]

The studies described in the above sections clearly showcase ILs as versatile excipients that can simultaneously solubilize biologics, interact with skin lipids to enhance transdermal permeability, and preserve the integrity of the biologics. Beyond proteins, peptides and nucleic acids, recent advances have extended the application of ILs to the TDD of large polysaccharides.[100] Notably, Wu *et al.* have systematically evaluated a series of eight choline-based ILs, comprising cholinium paired with various amino-acid and organic-acid anions, for the transdermal administration of hyaluronic acid, a high-molecular-weight biopolymer widely used in skin hydration and regenerative medicine. Specific ILs, including [choline][lactate] and [choline][pyrrolidone carboxylate], significantly enhanced HA permeation through the SC by modulating lipid packing and increasing skin hydration. These ILs not only

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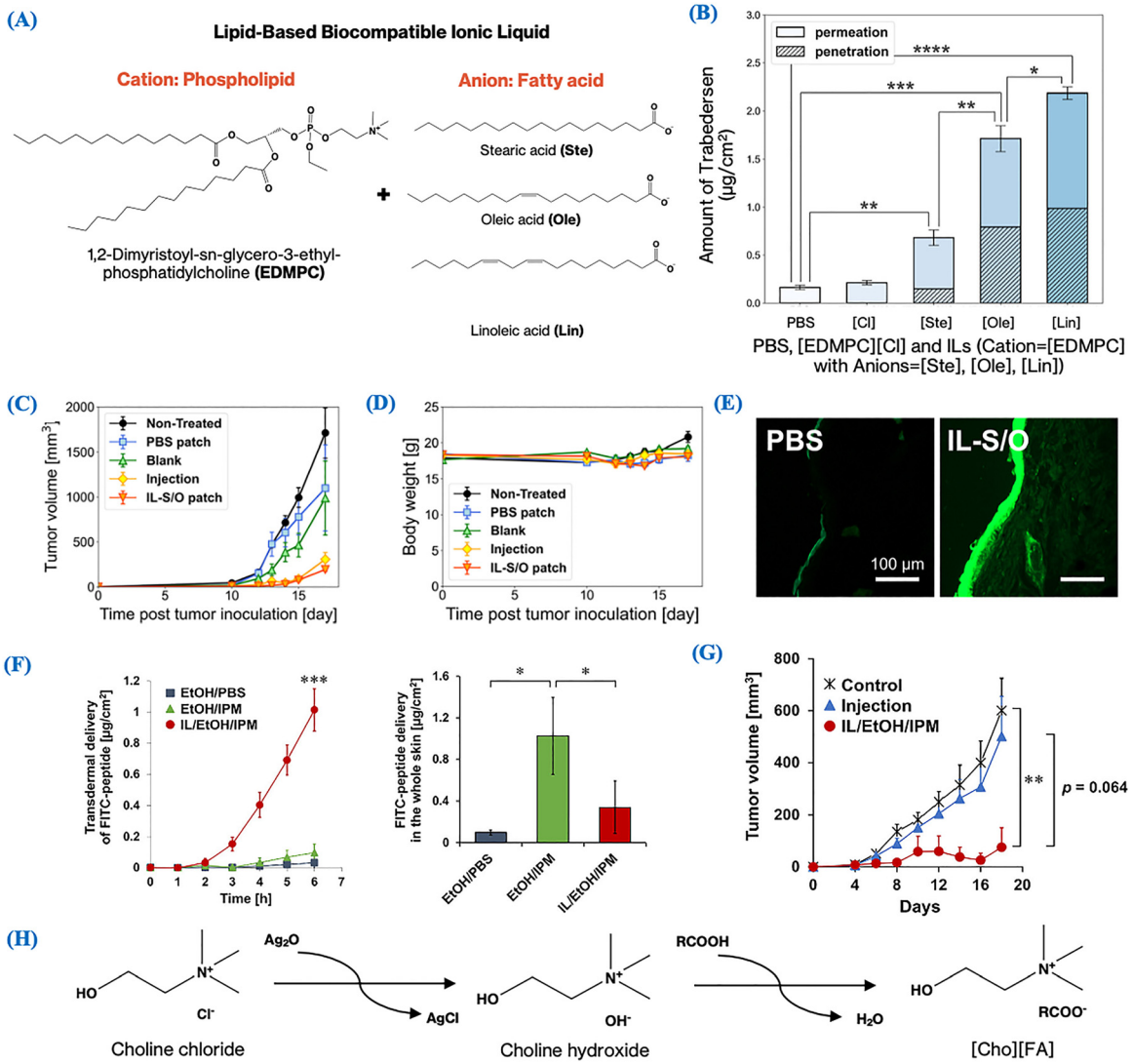

Fig. 7 (A) Chemical structures of cation and anions of lipid-based ILs. (B) Amount of trabedersen that permeated into the mouse skin and penetrated to the receiver phase. (C) and (D) Antitumor effect of trabedersen against B16F10 melanoma, (C) change in tumor volume and (D) change in body weight. (E) CLSM images of the skin cross sections of mouse skin treated with 6-carboxyfluorescein (FAM)-trabedersen in PBS or [EDMPC][Lin]-S/O. Scale bars: 100 μm. Figure reproduced with permission from ref. 86. (F) Transdermal and topical delivery of FITC-peptide in EtOH/isopropyl myristate (IPM), EtOH/PBS, and IL/EtOH/IPM through the mouse skin. (G) Effect of transcutaneous cancer vaccination *via* the IL/EtOH/IPM system. (H) Synthetic scheme for [Cho][FA]. [Cho][FA] was synthesized through the metathesis reaction of choline chloride with Ag_2O to prepare choline hydroxide, followed by the acid–base neutralization reaction of the fatty acid and choline hydroxide. Figure reproduced with permission from ref. 97.

improved skin moisture retention but also exhibited excellent biocompatibility, causing no detectable irritation or cytotoxicity in *in vitro* and *in vivo* assays.[101]

Overall, the ability of IL-mediated systems to deliver biologics through intact skin and elicit strong systemic immune responses underscores the considerable potential of ILs in transdermal biopharmaceutical delivery applications.

4. Conclusion and future outlooks

This review highlights the pivotal role of ILs, particularly those based on lipids and choline, in advancing TDDS for biopharmaceuticals. Compared with conventional organic solvents and penetration enhancers, ILs offer distinct advantages, including structural tunability, intrinsic biocompatibility, and dual functionality as both solubilizing agents and permeation enhancers. Hydrogen-bonding networks and ionic complexes formed between ILs and biomolecules, including proteins, peptides, and nucleotides, help to stabilize these therapeutic agents by shielding the agents from enzymatic degradation, thus allowing room-temperature formulations. These combined effects should facilitate the reduction of cold-chain dependency and the expansion of global access to biologics. Preclinical and *in vivo* studies using IL-incorporated vesicular systems have demonstrated enhanced permeability, stability,

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and therapeutic outcomes for challenging macromolecular drugs such as insulin. This needle-free approach to systemic drug delivery is particularly valuable for chronic disease management, where patient adherence and comfort and the stability of biologics remain persistent hurdles.

Despite promising progress in preclinical studies, the clinical translation of IL-based TDDS demands a multifaceted strategy to address several persistent challenges. First, regulatory pathways for IL-containing pharmaceutical products are not yet well established, and existing guidelines for excipients may not fully address the unique physicochemical and toxicological properties of ILs. Second, formulation scale-up poses difficulties, as the stability, purity, and reproducibility of IL-based systems can be sensitive to manufacturing conditions, requiring rigorous process optimization and quality control. Finally, there is a scarcity of long-term safety data in humans, particularly regarding potential systemic accumulation and chronic exposure effects. Addressing these challenges through harmonized regulatory standards, scalable manufacturing strategies, and comprehensive preclinical-to-clinical safety evaluations will be essential to advance IL-based TDDS toward clinical translation. A priority in this strategy is the rational expansion of IL chemical libraries through data-driven design, where computational modeling, high-throughput experimental screening, and machine learning can converge to identify ion-pair combinations optimized for skin permeability, toxicity thresholds, and drug compatibility. Such rationalization is essential to navigate the vast and largely unexplored chemical space of ILs, allowing the systematic tailoring of physicochemical and biological properties for specific therapeutic contexts. Particular emphasis should be placed on the synthesis of next-generation, biodegradable ILs derived from amino acids, sugars, and natural lipids to improve safety profiles and align with environmental sustainability goals. Equally crucial is a deeper mechanistic understanding of the IL-skin and IL-biologic interactions at a molecular level. To this end, future research must integrate tools, including molecular dynamics simulations, small angle scattering, and advanced vibrational spectroscopy, to elucidate how ILs perturb lipid packing, alter hydration shells, and stabilize drug conformations within complex biological matrices. Insights from these studies will be instrumental in refining the structure–activity relationships that underpin the efficacy and safety of IL-enhanced formulations.

From a translational perspective, the sustainable and scalable synthesis of ILs is another pressing requirement. Current synthetic methods often involve environmentally hazardous reagents or generate waste streams incompatible with green chemistry standards. Therefore, the development of eco-benign and economically viable synthetic routes, such as solvent-free protocols, enzymatic catalysis, and flow chemistry, will be essential for ensuring the regulatory compliance and commercial feasibility of the use of ILs in DDS. Concurrently, rigorous preclinical and clinical evaluations must be conducted to establish the pharmacokinetics, dermal toxicology, immunogenicity, and therapeutic efficacy of IL formulations across diverse animal models and patient populations. Collaborating early with regulatory agencies, such as the US FDA and European Medicines Agency (EMA), can also streamline classification, standardization, and approval pathways for IL-based drug products. Looking ahead, the convergence of ILs with emerging technologies, such as smart, stimuli-responsive delivery platforms, holds immense promise. These systems could enable biomarker-triggered or environmentally responsive drug release (*e.g.*, pH-, glucose-, and temperature-sensitive mechanisms), allowing for dynamic, feedback-controlled therapies that are personalized to individual patient needs. Such integration should not only improve therapeutic precision and minimize adverse effects but also redefine dosing paradigms and improve patient quality of life. Additionally, ILs are well suited for enabling combination drug strategies, in which multiple biopharmaceuticals with differing solubility or stability profiles can be co-formulated and delivered in a synchronized manner.

In summary, ILs offer a coherent, tunable platform that can simultaneously overcome the solubility, stability, and permeability barriers that have historically limited the transdermal delivery of biopharmaceuticals. Concerted interdisciplinary efforts spanning synthetic chemistry, computational modeling, formulation science, toxicology, and clinical medicine will be essential to translate this promise into approved therapies. With continued innovation in formulation design, mechanistic elucidation, green manufacturing, and regulatory harmonization, IL-based systems are poised, not only to broaden the therapeutic landscape for biopharmaceuticals, but also to redefine the future of patient-centric, non-invasive drug delivery on a global scale.

Conflicts of interest

There are no conflicts to declare.

Data availability

As this article is a feature article, the data supporting this article can be found in the original articles discussing each topic.

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