

Formulation approaches and strategies for transdermal delivery of insulin: special emphasis on microneedle-based systems

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ABSTRACT

The prevalence of diabetes is increasing and expected to become a major global health burden. Various pharmaceutical approaches have been used to manage diabetes and reduce the associated risks. Subcutaneous insulin injection remains the primary treatment due to the physicochemical properties of insulin, which limit oral absorption. The gastrointestinal tract presents further challenges, including enzymatic degradation and harsh environmental conditions, resulting in oral insulin bioavailability < 1%. As a result, alternative delivery routes, such as transdermal delivery, have been extensively explored. However, this approach is also challenging due to the structural barriers of the skin, which hinder drug absorption. The high molecular weight of insulin further limits permeation across the skin. To address these limitations, various formulation and delivery strategies have been investigated to improve transdermal drug delivery of insulin and are the subject of this review. Approaches, including penetration enhancers, lipid-based carriers, microemulsion, polymeric systems, and physical enhancement technologies, have demonstrated potential for enhancing skin permeability. However, the potential adverse effects and patient discomfort associated with these conventional methods highlights the need for more user-friendly alternatives. Microneedles have emerged as a promising transdermal delivery system, offering a painless, simple, and user-friendly approach to overcome challenges, thus improving adherence and treatment efficacy.

Keywords: Transdermal delivery systems, Diabetes mellitus formulations, Insulin, Skin penetration enhancers, Liposomes, Niosomes, Transferosomes, Microemulsions, Microneedles

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that is characterised by elevated blood glucose levels (BGLs). Poor control of BGLs can lead to severe damage to the heart, blood vessels, eyes, kidneys, and nerves, and may result in amputation or death. Diabetes mellitus can be classified into two primary types (type 1 and 2). Type 1 diabetes occurs when the pancreas fails to secrete insulin, while type 2 diabetes, which is the more common form (especially among adults), arises when the body becomes resistant to insulin or does not produce an adequate amount of insulin [1-5]. In addition, gestational diabetes may present in pregnant women with

increased BGLs. Type 1 diabetes, which can present at any age, is characterised by a total lack of insulin due to autoimmune destruction of insulin-producing β -cells in the pancreas. This condition is thought to result from a combination of genetic susceptibility and environmental triggers [6]. Type 2 diabetes, in contrast, is characterised by a more multifactorial and complex aetiology. Factors influencing both insulin secretion and action contribute to pathogenesis of type 2 diabetes. Decreased insulin secretion may arise from dysfunction or a reduction in the mass of β -cells, leading to diminished insulin signalling in target tissues. Insulin resistance hinders the effect of insulin on key tissues, leading to higher levels of fatty acids and glucose in the systemic circulation, which

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further exacerbates insulin secretion deficits and insulin resistance. Despite the current state of knowledge regarding the pathogenesis of diabetic complications, most diabetic patients struggle to achieve optimal glycaemic control in clinical trials and in real-world clinical practice [6]. Approximately 463 million adults worldwide have diabetes mellitus according to the 2019 report from the International Diabetes Federation and it is predicted that by 2045 700 million adults will be diagnosed with diabetes [1].

Insulin, the most effective compound for reducing BGLs was discovered in 1922 [7]. Human insulin, a peptide hormone, is synthesised by the β -cells in the pancreatic islets of Langerhans in response to elevated BGLs [3, 8]. Insulin has a critical role in regulation of carbohydrate and lipid metabolism and is stored in the pancreas in an inactive hexameric form, consisting of a dimer composed of an A- and B-chain [3]. The inactive hexamer form protects insulin from the highly reactive nature while keeping insulin readily available. The monomer, which is the active form, has a diffusion rate that is inversely proportional to particle size [3, 9]. The two polypeptide chains are collectively comprised of 51 amino acids with 16 different types. The A chain contains 21 amino acids with an internal disulfide bond, while the B chain has 30 amino acids. The two chains are linked by two disulfide bonds, as shown in Figure 1 [8, 9].

Insulin, a hydrophilic protein with a high molecular weight of 5808 g/mol, is commonly administered intradermally via subcutaneous injection to treat diabetes [10, 11]. Administering insulin exogenously is vital in the management of type 1 diabetes and advanced diabetes type 2 diabetes in advanced stages [9]. Insulin therapy aims to prevent further complications by controlling BGLs [12]. Diabetic patients are often required

to self-administer insulin subcutaneously several times a day, which involves training and rigorous self-management to support frequent dose adjustments based on glucose monitoring [5, 13]. Thus, the need for regular dosing can impact medication adherence among diabetic patients. Multiple daily insulin injections are often painful, may traumatise the skin, and can lead to microbial contamination, nerve injury, or local tissue necrosis, making it challenging for patients to maintain consistent adherence [6, 14, 15]. Technical constraints can impede the utilisation of continuous subcutaneous insulin infusion devices [16]. Research indicates that approximately 25% of insulin-dependent individuals experience anxiety related to self-injection, contributing to inconsistent adherence [13, 17]. This reluctance, compounded by the fear of hypoglycaemia, constitutes a major obstacle to achieving optimal glycaemic control [5]. Furthermore, one study reported that nearly 65% of individuals with type 1 or 2 diabetes lacked confidence in independently managing their disease [13].

To address the aforementioned challenges, a range of needle-free insulin delivery systems, including oral, pulmonary, nasal, and transdermal routes, have been investigated for routine insulin administration [18]. Nevertheless, the relatively high molecular weight of insulin poses a significant barrier to efficient transport across biological membranes [10]. Moreover, insulin is highly susceptible to enzymatic degradation by gastrointestinal proteases, aminopeptidases, and other metabolic enzymes, which significantly reduce the *in vivo* half-life of insulin [19]. These limitations necessitate the development of innovative and advanced delivery strategies that not only improve the pharmacokinetic profile of insulin but also enhance insulin safety and therapeutic efficacy.

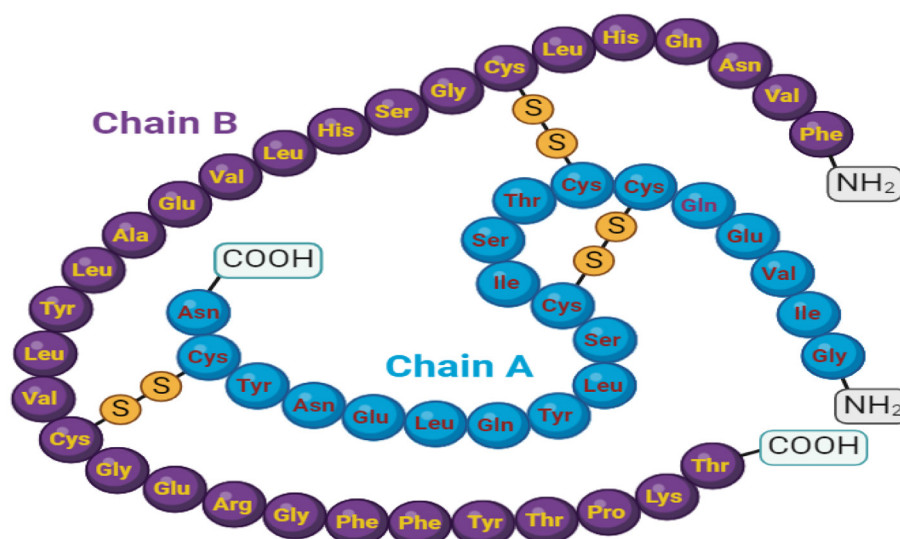


Figure 1 | Structural representation of insulin (created with BioRender.com).

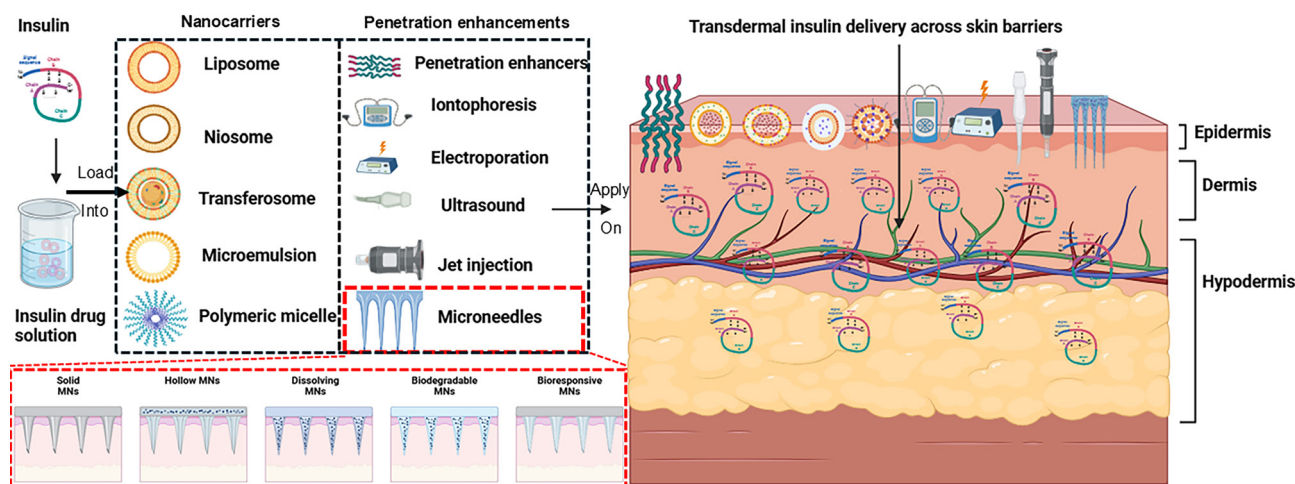


Figure 2 | The schematic illustration of formulation strategies and penetration enhancement approaches for transdermal insulin delivery systems (created with Biorender.com).

As illustrated in the schematic diagram in **Figure 2**, this review focuses on the development of transdermal insulin delivery systems with particular attention to strategies that facilitate the transport of insulin across the skin barrier. Special emphasis is placed on the physicochemical characteristics of insulin and the application of technologies, such as microneedles, which have shown promise in improving transdermal absorption. Limitations and challenges in moving towards clinical implementation of transdermal insulin delivery will also be identified.

2. CHALLENGES IN TRANSDERMAL INSULIN DELIVERY

The transdermal route for insulin administration, specifically via penetration through the stratum corneum (SC), has been the subject of considerable research and shows promising potential [7]. However, the formidable barrier function of the skin presents substantial obstacles that must be surmounted to facilitate effective systemic absorption of insulin [13, 14, 16, 18, 20]. The primary aim of a transdermal drug delivery system is to enable the drug to successfully traverse the SC and reach the target site in therapeutically relevant concentrations [4]. There are three main pathways through which a drug can penetrate the SC, as illustrated in **Figure 3** and include [3]: 1) **intracellular**, the drug enters through keratinocytes and intercellular lipids; 2) **intercellular**, the drug passes through the tight junctions between keratinocyte; and 3) **trans-appendageal**, the drug is absorbed through hair follicles and other skin appendages.

The intracellular pathway is suitable for small hydrophilic compounds, while the intercellular route is ideal for the transport of lipophilic drugs [3]. Most drugs are transported across the skin via the intercellular route, moving between cells as the follicular pathway and

other skin appendages account for approximately 1% of the total skin area [21]. The permeation of a drug across the SC follows Fick's law of diffusion and can be represented by equation 1 [22]:

$$\frac{dm}{dt} = J = \frac{DC_0P}{h}, \quad (1)$$

where (J) is the steady-state flux, (D) is the diffusion coefficient of the drug molecule, (h) is the thickness of the membrane, (P) represents the partition coefficient between the vehicle and the SC, and C_0 is the concentration of the applied drug, which is assumed to remain constant [23].

Consequently, drugs exhibiting the optimal physicochemical properties outlined in **Table 1** are capable of undergoing passive diffusion across the skin with relative ease [3, 23, 24].

Because insulin primarily relies on passive diffusion for absorption but lacks the requisite physicochemical properties for efficient transdermal penetration as outlined in the **Table 2**, development of novel strategies to enhance permeability across the SC is imperative. A well-designed transdermal delivery system capable of overcoming these barriers offers a promising, minimally invasive alternative to conventional subcutaneous injections, potentially mitigating the discomfort and patient resistance associated with traditional insulin administration. Furthermore, such systems may enable sustained insulin release, thereby maintaining therapeutic plasma concentrations over extended periods and reducing frequency of dosing [3, 15]. This approach could contribute to improved glycaemic control by enhancing patient adherence. Effective transdermal delivery of insulin requires adequate solubility in both hydrophilic and lipophilic environments [3]. To address these challenges, a variety of strategies have been investigated. These strategies include the

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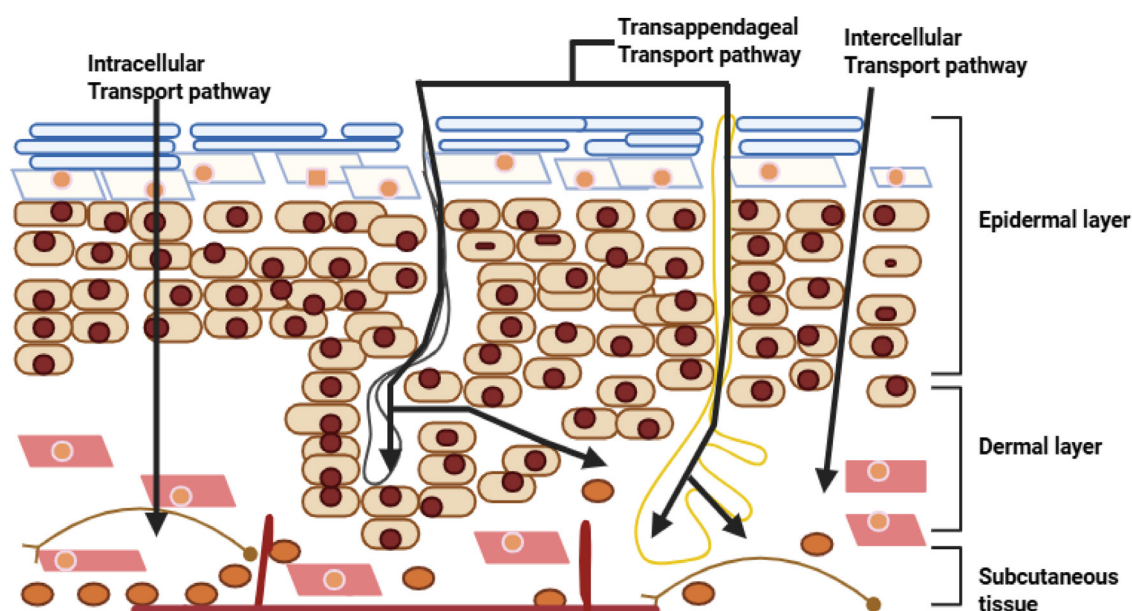


Figure 3 | Intracellular, trans-appendageal, and interstitial transdermal drug delivery pathways through the SC (created with Biorender.com).

Table 1 | Ideal drug properties for passive transdermal delivery [23, 24].

Drug properties	Ideal range
Potency dose	< 10 mg/day
Molecular weight	< 500 g/mol
Melting point	< 250°C
Log P	1–3

application of chemical enhancers, formulation-based approaches, such as lipid vesicles, microemulsions, and polymeric systems [28]. Additionally, physical enhancement methods, such as iontophoresis, electroporation, ultrasound, and jet injection have been investigated. More recently, integrated approaches combining

formulation strategies with physical enhancement technologies, particularly microneedle-assisted systems, have emerged as advanced solutions aimed at overcoming the limitations of conventional transdermal insulin delivery methods [15].

3. CHEMICAL ENHANCERS FOR SKIN PENETRATION

Skin penetration enhancers act on the skin surface to increase permeability by reversibly altering the physicochemical properties of the SC, thereby reducing diffusional resistance and enhancing transdermal delivery of therapeutics [21, 29]. These chemical agents function by directly disrupting or fluidising the lipid bilayers of the SC or indirectly modifying the formulation to improve drug solubility and distribution across the skin, as shown in Figure 4 [23]. Chemical enhancers are simple in design,

Table 2 | Physicochemical properties of insulin.

Properties	Chain A	Chain B	Chain A + B (insulin molecule)	References
Log P	–3.69	–2.03	–4.87	[25]
Pka	4.06		3.6	[25]
Molecular weight (g/mol)	~2380	~3430	5808	[3, 26]
Denaturation temperature/ Melting point (°C)			~35, more stable at temperature < 37	[25, 27]
Stability			Most stable at pH 3–4, prone to aggregation at pH ~5.3	[25, 27]
Solubility			Water soluble with increase solubility under ionization state (pH 2–3)	[25, 27]

easy to manufacture, and cost-effective. However, application of chemical enhancers may occasionally result in adverse effects, such as skin irritation and inflammation. Examples of drugs formulated with chemical enhancers are presented in Table 3. Studies have also been conducted using chemical agents in combination with complementary formulations approaches, including liposomes [33] and microemulsions [33-35], as well

as physical methods, such as iontophoresis, to further augment skin permeability and enhance transdermal drug delivery [36, 37]. Certain skin penetration enhancers have shown efficacy in the transdermal delivery of proteins and peptides, including insulin [4, 7, 21, 38]. In a study conducted by Yerramsetty and colleagues [39], 43 different chemical penetration agents were initially screened and 22 were

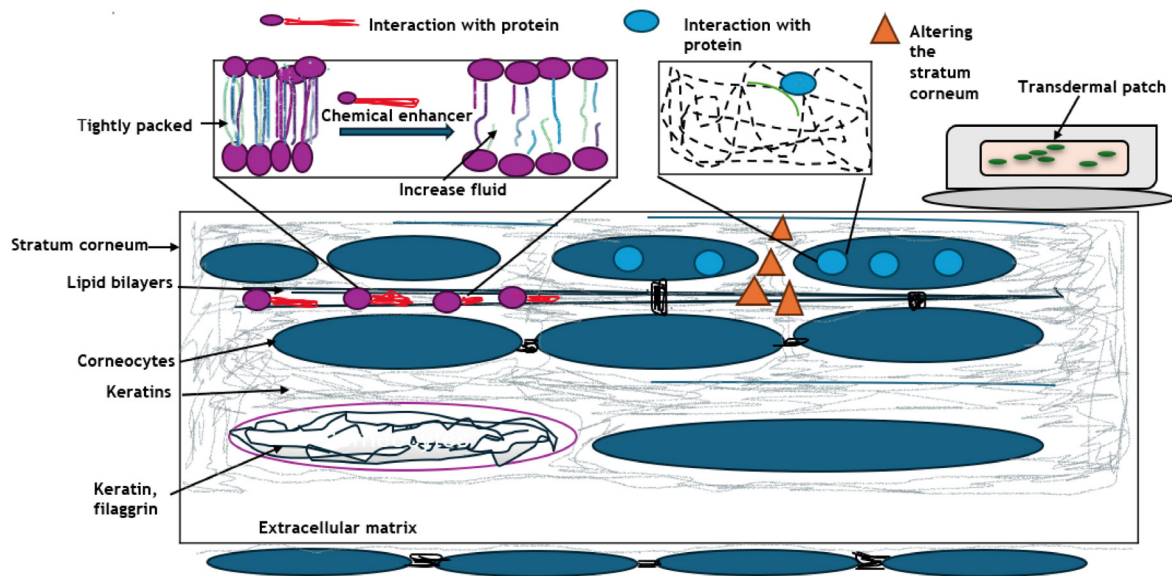


Figure 4 | Mechanism of action of chemical penetration enhancers across the SC (Created by Microsoft 360).

Table 3 | Commonly used skin permeation enhancers.

Chemical enhancers	Examples	Examples of drugs formulated	References
Fatty acids	Oleic acid, lauric acid, myristic acid, capric acid	Alfluzosin, ketotifen, 5-fluorouracil	[30]
Alcohols	Ethanol, dodecanol, propylene glycol, diethylene glycol	Norethindrone, scopolamine, estradiol	[23]
Esters	Glycerol monolaurate, ethyl oleate, isopropyl myristate, oleyl oleate	Serotonin	[23]
Azone	1-dodecylazacycloheptan-2-one or laurocapran	Amlodipine	[30]
Terpenes	dimethyl isosorbide	5-fluorouracil	[30]
Oxazolidinones	4-decyloxazolidin-2-one	retinoic acid and diclofenac sodium	[30]
Pyrrolidones	N-methyl-2-pyrrolidone	Mannitol, 5-fluorouracil, progesterone, hydrocortisone	[30]
Peptides	Trypsin, ACSSSPSKHCG (TD-1), maganin	Insulin	[23, 31, 32]
Sugar and vitamin derivatives	Sorbitan monooleate, ascorbyl palmitate, D- α -tocopherol	Estrogen	[23]
Amino acid derivatives	Dodecyl 2-dimethylaminopropionate (DDAIP), dodecyl N-acetylproline (Pro2), N-lauroylsarcosine, dodecyl 6-dimethylaminohexanoate (DDAK)	Meloxicam	[23]
Other solvents	Dimethylsulfoxide (DMSO), N-methylpyrrolidone, diethyleneglycol monoethyl ether, propylene glycol	Betamethasone, nicotine	[23, 30]

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selected for further testing based on optimal penetration properties and minimal skin irritation [39]. Iodine and bio-penetrating peptides have been reported to transport insulin effectively across the skin barrier. For example, Sintov and Wormser showed enhanced insulin delivery with iodine, which was achieved by inactivating endogenous sulfhydryl molecules, such as glutathione and gamma-glutamyl cysteine, thus limiting the formation of disulfide bonds and maintaining insulin potency in the systemic circulation [40]. Similarly, trypsin has been shown to induce a conformational change in SC proteins by shifting the secondary structure from alpha-helices to beta sheets, which subsequently led to a reduction in the electrical resistance of the skin. This process resulted to a 5.2-fold enhancement in insulin uptake at pH 3 [31]. A class of membrane-permeable peptides, exemplified by the sequence, ACSSPSKHCG (TD-1), has been identified as a promising means to facilitate transdermal insulin delivery [10, 32]. These bio-penetrating peptides, typically composed of 5–30 amino acid residues, have demonstrated safety and efficacy, and the ability to enhance drug permeation is not limited by the molecular weight of the drug. In one study, TD-1 peptides were shown to transiently disrupt the skin barrier, enabling insulin transport into hair follicles to depths exceeding 600 μm . These peptides facilitate insulin uptake through *in vivo* phage display, thereby enhancing systemic absorption [32]. The TD-1 peptide mediates the effect in an energy-dependent manner, modifying the structural properties of the skin, especially the dermis, by binding to the C-terminal region of the Na^+/K^+ -ATPase β subunit in epidermal cells. This interaction increases the permeability of insulin across the skin [41]. This delivery method achieved a significant reduction in BGLs (~40% of baseline values) in diabetic rat models that was sustained for up to 11 h. In contrast, insulin administered via subcutaneous injection demonstrated efficacy for < 5 h, emphasising the prolonged therapeutic effect of the peptide-enhanced transdermal system [32]. This finding prompted further research into a broader range of peptide-based penetration enhancers, which demonstrated enhanced transdermal activity in *in vitro* and *in vivo* models. Specifically, studies using Caco-2 cell monolayers reported improved permeability, while *in vivo* experiments in diabetic rats showed a reduction in BGLs by approximately 26% with the effect sustained up to 8 h [42]. Similarly, improved transdermal permeability of hydrophilic macromolecules was observed in diabetic rats *in vivo*, further supporting the potential of this approach [10]. However, the translation of these results to human use is uncertain. The quantity of insulin required for effective treatment in humans significantly exceeds that required in animal models and anatomic differences, such as the substantially higher hair follicle density in rats (estimated to be approximately 20-fold greater than in humans) may contribute to the observed permeability differences [10]. Therefore, it is unclear whether the peptide-mediated enhancement of

transdermal delivery is sufficient to support the effective delivery of proteins and peptides, including human insulin. Further concerns, including the risk of therapeutics diffusing away from the SC and the potential for irritation or damage to deeper skin tissues caused by penetration enhancers, must be addressed. These limitations underscore the need for further research to assess the long-term safety, efficacy, and clinical applicability of peptide-based transdermal delivery systems.

4. FORMULATION APPROACHES TO ENHANCE TRANSDERMAL INSULIN DELIVERY

Formulation approaches, such as lipid vesicles, micro-emulsions, and polymeric systems, have been studied for transdermal drug delivery.

4.1 Lipid based nano-carriers

4.1.1 Liposomes. Liposomes (Figure 5) are biodegradable and biocompatible vesicular carriers composed of natural or synthetic phospholipids [43]. The liposomal amphiphilic molecules can form bilayer structures consisting of lipid and aqueous compartments, owing to the hydrophobic tails and hydrophilic heads [44]. These vesicles exhibit a spherical morphology with particle sizes ranging from approximately 20 nm–100 μm [8, 45]. The penetration capacity is largely influenced by particle size, with smaller particles demonstrating higher penetration ability [46, 47]. Liposomes predominantly facilitate drug penetration through the SC but exhibit limited ability to navigate deeper skin layers, such as the viable epidermis and dermis. Consequently, liposomal formulations often accumulate within the epidermis with minimal distribution to the underlying dermal tissue or systemic circulation [24, 47]. Liposomal formulations exhibit several limitations in transdermal drug delivery due to physicochemical properties, such as chemical composition, particle size, and surface characteristics [24, 47]. These constraints often result in reduced stability, variable drug encapsulation efficiency, and elevated production costs. Despite these obstacles, liposomal formulations containing therapeutic agents, such as

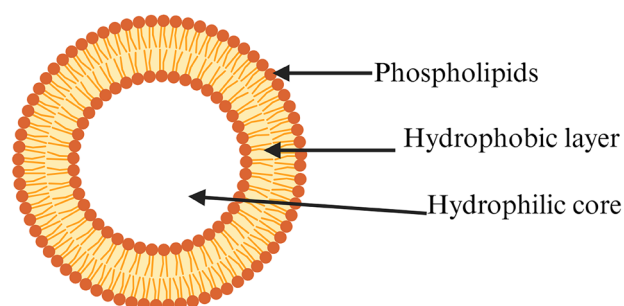


Figure 5 | The liposome structure showing lipid and aqueous bilayers (created with Biorender.com).

amphotericin B, ketoprofen, tetracaine, cyclosporin-A, melanin, lidocaine, bupivacaine, and dithranol, have received approval for transdermal application [44]. To enhance the transdermal delivery of therapeutic molecules such as insulin, advanced delivery systems including niosomes and transferosomes have been developed to improve skin penetration and facilitate more effective drug transport across the SC.

4.1.2 Niosomes. Niosomes (Figure 6) are submicron-sized drug delivery vesicles that are formed via the self-assembly of non-ionic surfactants and/or cholesterol to form a bilayer structure that can encapsulate lipophilic and hydrophilic molecules [48, 49]. Additives, such as fatty alcohols or dicetyl phosphate, are also used in the preparation of niosomes. For example, cholesterol is added to improve permeability, rigidity, and fluidity, thus avoiding niosome aggregation [24, 48]. Niosomes are prepared with similar methods to liposomes and are non-toxic, biocompatible, and non-immunogenic, but differ in particle size with niosomes ranging from 10 nm–10 μ m [50, 51]. Niosomes have demonstrated the ability to enhance transdermal drug delivery by interacting with the intercellular lipids of the SC to improve drug penetration [24, 52]. Unlike liposomes, niosomes offer a more cost-effective and structurally stable alternative to liposomes, making niosomes a preferred choice in pharmaceutical drug delivery systems [53]. Studies have been conducted on the application of niosomes in dermal drug delivery for treating various skin disorders [54, 55]. For example, in the management of psoriasis, dithranol-loaded niosomes demonstrated superior skin penetration compared to conventional cream formulations, suggesting enhanced therapeutic potential [56]. Paolino et al. developed a niosomal formulation for the transdermal delivery of 5-fluorouracil to treat skin cancer, where the enhanced intracellular transport capability improved the anti-cancer efficacy of the encapsulated drug [57]. Niosomes have also been widely used in the cosmetic industry. Various studies have explored the use of niosomes in encapsulating anti-aging and skin-brightening agents within niosomal vesicles

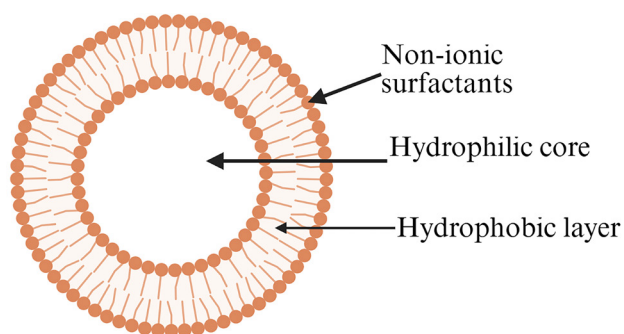


Figure 6 | The structure of niosome indicating lipophilic and aqueous compartments (created with Biorender.com).

[58–60]. Other examples of drugs formulated with niosomes for transdermal delivery include aceclofenac [61], diclofenac diethylammonium [62], vinpocetine [63], and lopinavir [64]. The outcome of these studies indicated efficient penetration of the SC with enhanced efficacy [61–64]. Niosomes possess ideal characteristics that could be further optimised to improve transdermal delivery of proteins and peptides, including insulin. Insulin-loaded niosomes have been prepared for oral, parenteral, and vaginal routes, and have shown therapeutic efficacy in reducing BGLs with good stability [65–67].

4.1.3 Transferosomes. Transferosomes, another lipid-based nano-carrier (Figure 7), are ultra-deformable lipid vesicles that can penetrate the skin barrier by squeezing through narrow spaces in the skin and provides targeted transdermal drug delivery [47]. Transferosomes are vesicular carriers primarily composed of phospholipids, with 10–25% surfactant and 3–10% ethanol [21]. The surfactant functions as an “edge activator,” providing the transferosomes with ultra-deformability and enabling transferosomes to pass through channels in the SC that are < 0.1 the transferosome diameter [21]. Addition of ethanol increases the fluidity of the phospholipid bilayers and enhances permeability of transferosomes into the deeper layers of the skin [68]. Transferosomes exhibit the ability to penetrate deeper layers of the skin after topical application compared to liposomes and deliver higher drug concentrations [47]. Transferosomes are more stable, biodegradable, and suitable for transporting hydrophilic and lipophilic molecules, as well as low and high molecular weight compounds [43]. While conventional liposomes encounter difficulty traversing pores < 50 nm in diameter, transferosomes possess the ability to deform and spontaneously penetrate the SC, despite the larger size, often reaching up to 500 nm in diameter. This enhanced deformability enables transferosomes to navigate through narrow intercellular pathways and facilitates more efficient transdermal delivery. The enhanced penetration is driven by a

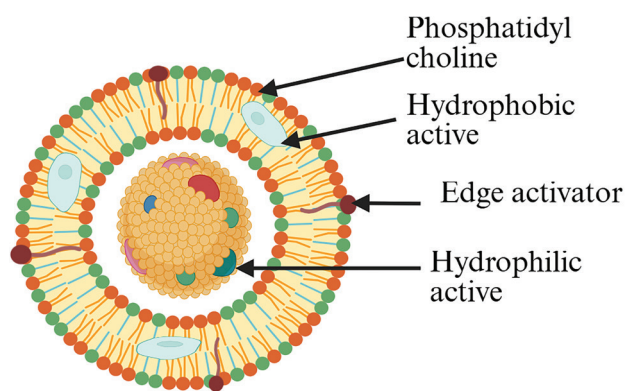


Figure 7 | The transferosome structure and composition (created with Biorender.com).

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transdermal gradient created by the difference in water content between the dehydrated surface of the skin (~20% water) and the highly aqueous viable epidermis [~100% water]. Transferosomes exhibit a propensity to migrate into deeper skin layers to prevent dehydration resulting from trans-epidermal water loss on non-occluded skin surfaces. In contrast, conventional liposomes typically remain localized on the skin surface, where they are prone to dehydration and subsequent fusion due to evaporation [21, 47]. Consequently, transferosomes enhance transdermal drug delivery, with one study reporting 50–80% of transferosome-associated insulin successfully penetrated the skin [21]. Transferosome-based gels, containing highly deformable, insulin-loaded vesicles demonstrated effective transdermal permeability *in vitro* using porcine skin models in an unrelated study. *In vivo* studies of the optimised transferosome gel showed a prolonged hypoglycaemic effect lasting 24 h in alloxan-induced diabetic rats following transdermal administration [69]. Moreover, *in vivo* analysis using a transferosomal hydrogel in diabetic rats revealed sustained hypoglycaemic effects, featuring the potential utility of transferosomes for transdermal insulin delivery [70]. Despite these promising outcomes, certain limitations persist, including high formulation costs and the potential for minimal oxidative degradation, which may impact long-term stability and efficacy [43].

4.2 Microemulsions

Microemulsions are clear, stable, isotropic blends of oil, water, and a surfactant that is often combined with a co-surfactant [71]. Microemulsions are classified into three main types (oil-in-water [O/W], water-in-oil [W/O], and bicontinuous; Figure 8). O/W microemulsions are formed from oil droplets dispersed in a continuous aqueous phase, while W/O emulsions are formed with water droplets dispersed in a continuous oil phase [72]. Bicontinuous

emulsions are characterised by an interpenetrating network of continuous phase that is neither water nor oil [72]. Microemulsions are thermodynamically stable and the composition aids the reduction of interfacial tension to facilitate self-assembly of dispersed phases [73]. The ideal range of droplet sizes for microemulsions systems ranges between 10 and 200 nm. This size is beneficial for stability and drug solubility, thereby promoting enhanced transdermal delivery of drugs. Microemulsions offer several benefits, including ease of preparation and cost-effectiveness with an improved drug release profile and enhanced bioavailability relative to conventional delivery systems [74, 75]. Microemulsions promote absorption by enhancing skin penetration for topical drug applications [33, 76, 77]. Saturated and unsaturated fatty acids are often used as components of the oil phase and function as penetration enhancers with oleic acid being the most popular penetration enhancer [33]. Microemulsions are considered an optimal vehicle for transdermal insulin delivery. However, these microemulsions have limitations. One significant drawback is the requirement for elevated temperatures during preparation, which may compromise the stability of thermolabile molecules, such as insulin [78]. Exposure to high temperatures (60–70°C) may lead to insulin degradation, ultimately reducing potency and therapeutic efficacy if not carefully formulated [78]. Several studies have reported an enhanced penetration effect with microemulsion formulations for protein delivery [34, 79–83]. For example, an insulin-loaded microemulsion formulation containing oleic acid (10%), DMSO (2%), and a 50% surfactant phase demonstrated excellent *in vitro* permeation flux of insulin [83]. However, the study concluded that additional *in vivo* investigations are needed to assess the long-term efficacy and sustainability of the formulation. In another study, King et al. investigated a biphasic lipid vesicle-based transdermal insulin delivery system. An O/W emulsion was incorporated into

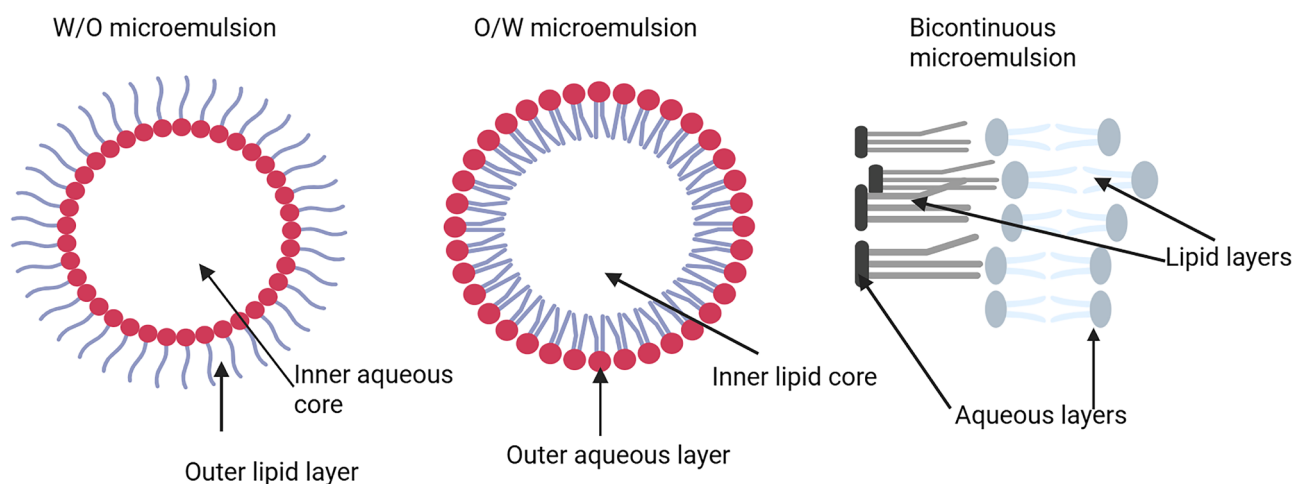


Figure 8 | Microemulsions, water in oil (w/o), oil in water (o/w), and bicontinuous (created with Biorender.com).

patches and demonstrated a hypoglycaemic effect lasting up to 77 h in rats, indicating a sustained insulin release profile [80]. A follow-up study showed dose-dependent blood glucose reduction with varying insulin concentrations (1–10 mg) over 73 h, with insulin accumulation in inguinal lymph nodes acting as a reservoir for controlled systemic release [84]. These studies suggested that microemulsions possess the capacity to effectively penetrate the skin, thereby enhancing permeability and promoting the transdermal transport of insulin against the concentration gradient. The potential mechanisms through which microemulsions facilitate transdermal drug delivery involve direct interaction with the skin barrier or formulation-based modifications that enhance permeation. These mechanisms have been discussed in detail elsewhere [33].

4.3 Polymeric systems

Polymeric systems, such as nanogels, are composed of cross-linked networks formed from ionic and non-ionic polymers (Figure 9), enabling polymeric systems to encapsulate a wide range of therapeutic agents, including biomolecules, such as insulin and low molecular weight compounds [85, 86]. Polymeric materials used in drug delivery systems are composed of natural or synthetic materials. Common natural biopolymers that have been used in insulin delivery include chitosan, gelatin, dextrin, and hyaluronic acid (HA), while synthetic biodegradable and biocompatible polymers include carboxymethylcellulose (CMC), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), poly(D,L-lactic acid) (PLA), poly(glycolic acid) (PGA), poly(D,L-lactic-co-glycolic acid) [PLGA], poly(ϵ -caprolactone) [PCL], polyethylene glycol [PEG] [86, 87], and poloxamers [36, 88] and non-biodegradable polymers, such as poly(methyl methacrylate) [PMMA] and poly(methylvinylether-maleic anhydride) [PMVE/MA] [89]. Polymeric particles demonstrate superior encapsulation efficiency and improved storage

stability for insulin in comparison to lipid-based carriers [8, 86]. However, long-term toxicity is a limitation [86], thus careful selection and optimisation of polymer composition and concentration are essential when designing polymer-based formulations for insulin delivery.

Insulin release from polymeric vesicles can occur through several mechanisms, including biodegradable polymeric nanoparticles that release insulin as the polymer matrix degrades [90–94], insulin-loaded hydrogels that swell and release insulin in a controlled manner when applied to the skin [95–100], thermo-responsive hydrogels that release insulin in response to temperature changes [101]. In addition, glucose-responsive hydrogels that release insulin based on fluctuations in blood glucose levels [102].

Several studies have explored the use of polymeric nanoparticles in combination with microneedle systems for the transdermal delivery of insulin, as summarised in Table 4.

Examples of formulations that facilitate transdermal delivery of insulin across the skin barriers are illustrated in Figure 10.

5. PHYSICAL ENHANCEMENT METHODS

Physical enhancement methods (Figure 11) for transdermal insulin delivery encompass techniques, such as iontophoresis and electroporation, which utilise electrical currents to enhance drug permeability. Other physical methods, including ultrasound and jet injection, employ mechanical force to increase permeability through the SC without causing significant damage to the skin. Another technique is the microneedle-based transdermal drug delivery system. A range of microneedle (MN) systems has been developed, each varying in composition and mechanism of action [4, 15, 89]. These systems will be discussed in detail in the subsequent sections.

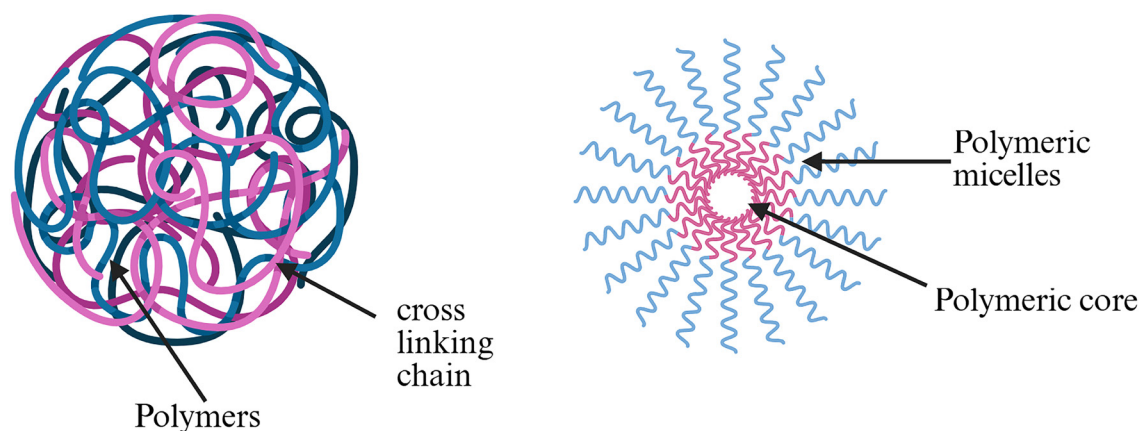


Figure 9 | Polymeric vesicles (created with Biorender.com).

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Table 4 | List of microneedle-based polymer preparations for transdermal insulin delivery.

Polymers	Preparation	Model	Study outcome (insulin release rate and/or BGL lowering effect)	References
Chitosan/PVP/HPMC	Patch	<i>In vitro</i> study	83% permeation rate for 8 h	[103]
Polystyrene-block-poly (acrylic acid) (PS-PAA)	Bullet-shaped swellable MN patch	Diabetic Sprague-Dawley (SD) rats	~60% prolonged <i>in vitro</i> insulin release over 12 h, <i>in vivo</i> BGL decreased gradually to 31.33 ± 11.5 mg/dL at 4 h	[95]
Gelatin/CMC	Dissolving MN patch	Diabetic mice	Maximum BGL decreased at 70% insulin release	[104]
Gelatin/CMC	Two-layer dissolving MN patch	Diabetic mice	RPA: 95.6%, RBA: 85.7%	[105]
Gelatin/starch	Dissolving MN patch	Diabetic SD rats	RPA: $92.2 \pm 3.5\%$, RBA: $92.3 \pm 7.2\%$	[90]
Gelatin/hydroxyapatite	Bioceramic composite MN patch	Diabetic Sprague-Dawley (SD) rats	BGL < 200 mg/dL kept longer for up to 5 h with doses of 5, 10, and 20 IU	[99]
Gelation/calcium sulfate hemihydrate ($\text{CaSO}_4 \cdot 0.5\text{H}_2\text{O}$)	Biodegradable composite MN patch	Diabetic SD rats	> 90% biological activity detected and reduced to 20% at high temperatures (> 45°C). BGL maintained at normoglycemic state (200 mg/dL) up to 4.8 h	[100]
PVA	Phase-transition MN patch	Diabetic pigs	RBA: > 20%, indicated potential for sustained release	[98]
PVA	Multilayered PVA pedicle dissolving MN patch	Diabetic obese mice	RPA: 82%, RBA: 78%	[93]
PVA/Sucrose	Dissolving MN patch	Diabetic mice	BGLs reduced to ~15% (3.5 mmol/L with a 0.2 U/patch insulin in 1.5 h	[106]
PGA	pH sensitive MN patch	Diabetic rats	BGL declined by ~86.2% and minimum BGL appeared 2 h post-treatment	[107]
PLGA/HA	Electrospun dissolving MNs	Male C57BL/6 mice	Complete dissolution and insulin release with BGL reduction within 5 h	[108]
Alginate/maltose	Calcium ion cross linked MN patch	Diabetic SD rats	RPA: $94.1 \pm 5.6\%$, RBA: $93.7 \pm 4.7\%$	[96]
PMVE/MA	Electrically assisted dissolving MN patch	<i>In vitro</i> study	Cumulative amount of insulin permeated at 6 h were 150 μg (3.25%), 227 μg (4.85%), and 462 μg (9.87%) for 3 different formulations	[109]
CMC/HA/PVP	Dissolving MN patch	Streptozotocin (STZ)-induced diabetic mice	RBA - $96.6 \pm 2.4\%$	[110]
PVP- CaCO_3 - (PVP as surfactant)	Composite dissolving MN patch	STZ-induced diabetic rats	RPA: 98.2%, RBA: 96.6%	[94]
PVP	Two-layer dissolving MN patch	Diabetic mice	Cumulative permeation > 30% in 6 h and reached 80% in 60 h RPA: 108.74%	[111]
Poly- γ -glutamic acid (γ -PGA)/PVA/PVP	Supporting structure design dissolving MN patch	Diabetic rats	Both RPA and PBA ranges from 90–97%	[92]
HA - hypoxia sensitive	Glucose-sensitive vesicles - dissolving MN patch	Diabetic mice	Glucose triggered insulin release observed	[102]

Abbreviations: RPA, relative pharmacologic availability; h, hour(s); RBA, relative bioavailability.

5.1 Iontophoresis

The iontophoresis technique involves application of a mild electrical current to facilitate efficient transport of macromolecules and/or charged molecules across

the skin barrier [112]. Specifically, two electrodes (positively and negatively charged) are positioned on the skin to generate an electrical force between the skin surface and the capillaries under the skin, thereby

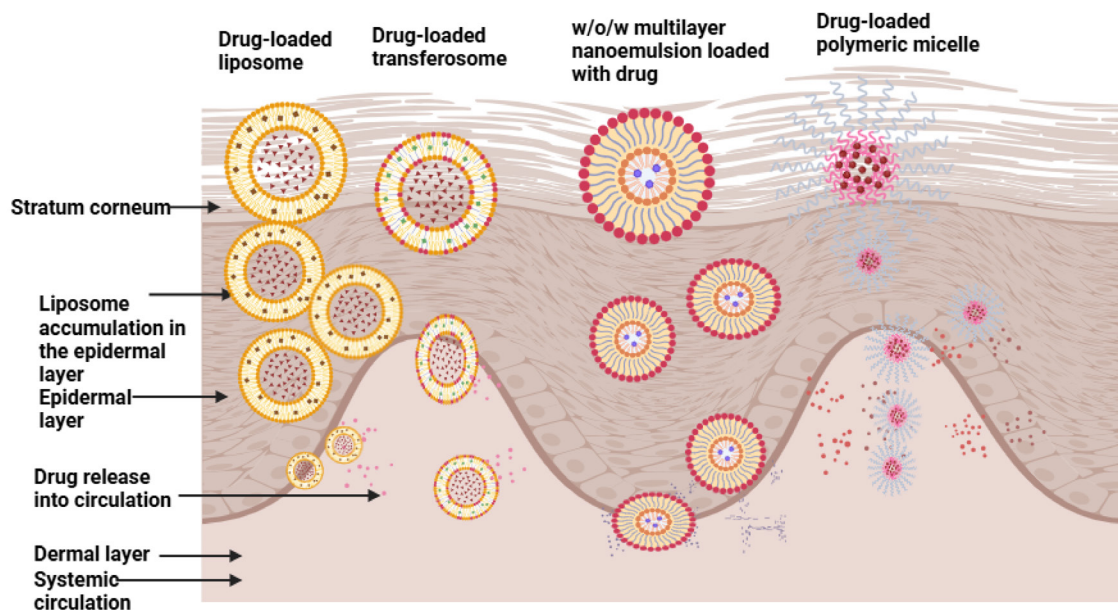


Figure 10 | Schematic representation of formulation approaches enhancing transdermal drug delivery (created with [BioRender.com](#)).

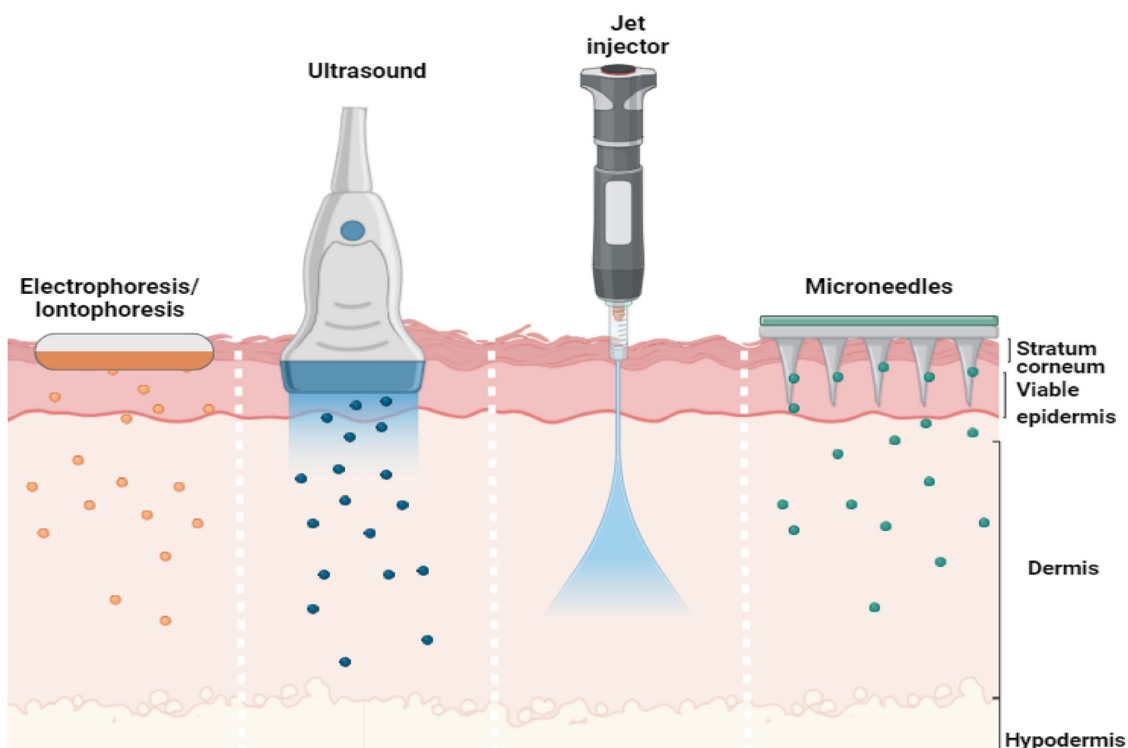


Figure 11 | Diagram showing various transdermal physical enhancement strategies with differing mechanisms (created with [BioRender.com](#)).

attracting positively and negatively charged molecules to the capillaries and through the skin, respectively [112]. The primary advantage of this technique lies in

the ability to facilitate transdermal penetration and delivery of moderately sized, charged molecules across the skin.

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Numerous studies using iontophoresis to facilitate transdermal delivery of insulin have been published [36, 37, 113–117]. Even these studies revealed the potential of iontophoresis to improve insulin permeation across the SC, they present several limitations and dissimilarities in study outcomes. Several studies have reported moderate transdermal insulin fluxes when using iontophoresis alone [118–120]. In one study, for example, electroosmosis and electromigration were identified as the main influencing mechanisms to push the charged molecule through the skin to reach the absorption site [118]. Another study reported that the transported amount of insulin was proportional to the intensity of electrical current and the duration of treatment [119]. Nonetheless, the applicability is limited to ionizable compounds and the overall transfer efficiency remains relatively low [typically < 10%] [43]. Notably, the skin exhibits permselectivity toward cations under the influence of an electric current due to the negative charge in physiological conditions [120]. Therefore, the transdermal delivery of insulin at therapeutic levels is hindered by the negative charge of human insulin under physiological conditions [121]. Additionally, the high molecular weight of insulin inherently hinders passive diffusion, even when assisted by an electric current. Therefore, high voltages or longer application times are required, which can lead to skin irritation and patient discomfort [116]. Studies have reported that adjusting the insulin solution concentration and pH can promote transport across the SC [113, 114]. To enhance the transdermal delivery efficiency of insulin, iontophoresis has been integrated with liposomes, chemical enhancers, and polymer-based systems [36, 37, 115, 122]. For example, charged liposomes have been shown to protect insulin from enzymatic degradation under iontophoresis and facilitated increased efficiency in the transdermal transport of insulin [115]. However, such combinations introduce concerns related to potential electrochemical skin toxicity and formulation stability, which are often not widely addressed in initial studies.

Comparative *in vivo* studies revealed that while iontophoresis can reduce BGLs, the hypoglycaemic effects are often transient and less pronounced than the hypoglycaemic effects achieved via subcutaneous injections [119, 122]. Some studies have reported sustained BGL reductions following optimised iontophoretic delivery. For example, insulin in a poloxamer gel delivered via iontophoresis alone or in combination with a chemical enhancer demonstrated a 36–40% reduction in BGLs in diabetic rats [36]. But these outcomes are highly dependent on variables, such as current density, formulation composition, skin pretreatment, and species-specific skin properties. For example, rat skin is thinner and more permeable than human skin and may lead to a miscalculation of the clinical efficacy observed in humans.

Advances in iontophoretic technology, such as incorporation of hydrogel formulations into iontophoretic

patches, have addressed some of the challenges by offering better skin conformity, reduced skin irritation, and improved transdermal delivery, due to the electroconductive properties [117, 122]. Nevertheless, concerns regarding electrochemical damage persists, particularly with prolonged use and needs to be thoroughly examined in clinical settings. In conclusion, iontophoresis does not disrupt the structure of the skin, unlike chemical penetration enhancers, and presents a promising technique for transdermal insulin delivery. The critical evaluation of existing studies indicates that clinical translation of iontophoresis is hampered by the relatively low current intensity generated, which impedes the efficient transport of insulin through the SC [112, 118, 119]. The formulation challenges and the potential for discomfort and skin irritation are deterrents to increasing the current intensity to enhance insulin delivery. Future studies should focus on optimising formulation-device integration, reducing harmful effects, and conducting large-scale, long-term clinical trials to establish safety and efficacy in humans.

5.2 Electroporation

Unlike iontophoresis, electroporation requires short, high voltage to create micro-channels in the lipid bilayer of the SC [123]. The temporary pores created by the high voltage facilitate the transport of therapeutics across the skin barrier [123, 124]. Various studies have been conducted to explore the potential of electroporation in the transdermal delivery of insulin. For example, Chen et al. demonstrated improved insulin permeation across porcine skin with a good safety profile using a combination of electroporation and microneedles. Despite these developments, the long-term stability and repeatability was not assessed and the sample size and study duration in the study is not adequate [123]. Another study evaluated the effectiveness of low-voltage electroporation with microsecond pulses to deliver insulin in rabbits via a wearable patch, considering factors, such as drug concentration, number of generated electrical pulses, and field strengths with and without chemical enhancers [125]. While this study demonstrated enhanced encapsulation and bioavailability with a significant reduction (> 50%) in BGLs and safe alternative to injections, electroporation lacks direct comparisons with other transdermal enhancement methods. The study mainly focused on acute glycaemic control, long-term effects, including repeated dose and potential skin irritation, were not fully evaluated. In addition, the effect of electric pulses on insulin stability was not assessed. Repeated electroporation may denature insulin and affect the therapeutic efficacy. Electroporation in combination with polymeric nanoparticles revealed a 4-fold increase in insulin concentration in the rat skin with reduced skin irritation [126]. Importantly, one of the earlier studies demonstrated that ionic lipids in combination with electrophoresis had an enhancing effect on drug molecules of larger molecular weight (10 kDa)

in combination with electroporation. This finding is due to the increase in size and more prolonged period of pores opening created by electrophoresis in the presence of the lipid bilayer [127]. Like previous studies, this study did not address long-term safety and effects on skin with repeated electroporation. Further studies indicated the enhancement effect of parameters, such as pH and temperature, in electrophoresis transdermal delivery of insulin [121, 124]. Based on research to date, it is evident that electroporation with the use of high electric current provides enhanced transdermal insulin transport than iontophoresis [121, 125]. However, energy requirements and skin safety were not fully examined and the device was not optimised for human translation [121, 125]. The high electrical current that penetrates deeper tissues may lead to pain and irritation of the muscle. Further studies with a focus on optimising device design and long-term safety of repeated electroporation are required to establish safety profile and enable clinical application.

5.3 Ultrasound

Ultrasound technology has been used in medical applications since the 20th century, especially in diagnostic imaging, ablating tissues, kidney stone treatment, and the enhancement of transdermal drug delivery [128, 129]. When applied to the skin, ultrasound induces transient disruptions in the SC, thereby increasing skin permeability and facilitating the transport of therapeutic agents. This concept is known as sonophoresis [129]. The ultrasonic conditions utilised in sonophoresis vary between frequencies ranging from 0.02–16 MHz [128].

In recent years several studies have investigated the potential of ultrasound in transdermal drug delivery. One such study demonstrated a rapid, reproducible, and irreversible insulin transport associated with ultrasound pulse and energy dose, which aligned with a cavitation-related mechanism in rats and newborn pigs at 20 Hz low-frequency sonophoresis (LFS) [129]. Although the study revealed the feasibility of ultrasound in transdermal delivery of insulin, the study focused on short-term effects and did not evaluate the cumulative effect of repeated ultrasound, thus limiting insight into chronic usability. Smith et al. [130] observed a reduction in BGLs of 262 ± 40 mg/dL within 90 min in rats compared to a lower reduction (-190 ± 96 mg/dL) in rats receiving a subcutaneous injection of the same insulin dosage (0.15, 0.2, and 0.25 U/kg) with LFS frequencies adjustable between 1 and 100 kHz. However, this approach was limited by low bioavailability, requiring high insulin doses to achieve therapeutic efficacy. Consequently, integration with other strategies, such as permeation enhancers, carrier systems, or a responsive delivery platform, may be required to enhance clinical effectiveness. Studies conducted in pigs with LFS for 60 min (20 kHz, 100 mW/cm², 20% duty cycle) with ultrasound treatments (3 × 3, 30 kHz, 100 mW/

cm²) integrated with a glucose-sensing closed-loop system (2 × 2, 20 kHz, 100 mW/cm²) demonstrated a BGL reduction of 72 ± 5 mg/dL 60 min post-treatment and 91 ± 23 mg/dL at 90 min. These results support the potential clinical feasibility of using combined cymbal ultrasound arrays for non-invasive glucose sensing and insulin delivery [131, 132]. Like other studies, the long-term effects of repeated pulsed use was not evaluated. Di et al. reported normalized BGLs (< 200 mg/dL) within 10 min and sustained reductions within 1 h in diabetic rats with focused ultrasound (FUS) treatment [950 kHz, 4.31 W] [133, 134]. Use of the nanoparticle-assisted technique was reported with improved stability and drug localisation. Nonetheless, the insulin dose required was higher than subcutaneous injections, which may suggest suboptimal delivery efficiency. Studies involving pancreatic β -cells indicated significant insulin release (approximately 150 ng/10⁶ cells) with cell viability preserved. This finding highlighted the role of calcium in ultrasound-induced insulin secretion, featuring the potential of ultrasound in facilitating insulin release from pancreatic cells [135, 136]. Although the study detailed the mechanistic investigation and revealed enhanced skin permeability, the study lacked *in vivo* efficacy data and did not examine insulin activity post-ultrasound exposure. Additional, data on device wearability and skin adherence was limited and the study focused mainly on safety rather than device optimisation for transdermal delivery.

Although ultrasound-assisted transdermal insulin delivery has shown promising potential, mainly with low frequency, targeted wearable devices and in combination with nanoparticles, most studies are preclinical, in which device usability, human skin variability, and insulin stability could not be fully evaluated. Moreover, device optimisation, cost efficiency, and long-term adverse effects for repeated use should be addressed before clinical use.

5.4 Jet injection

Jet injection is another needle-free technique that utilises high-speed liquid to exert force on the skin surface, creating microchannels that facilitate drug penetration and permeability. Research by Engwerda and colleagues demonstrated rapid insulin action and enhanced postprandial glucose control in diabetic patients [137, 138]. The key advantage of this study was that a direct comparison of pharmacodynamic data was evaluated in human subjects, despite limited duration of study and lack of long-term safety data. Another study demonstrated effective insulin absorption without skin damage when using microjet injections in a rat model [137, 138]. Nevertheless, this study also lacked long-term safety data and the investigation was conducted in an animal model, which may have a different effect on human skin. Notably, the level of insulin delivered by jet injection more closely mimics endogenous insulin secretion by the pancreas compared to conventional subcutaneous

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injections primarily because the jet injection covers a larger surface area of the skin [139]. Although jet injection systems offer notable advantages, concerns have been raised regarding the high-pressure spray used during administration, which may result in adverse effects, such as skin bruising, pain, and bleeding [140]. These complications have been cited as limiting factors for the widespread adoption of jet injection in transdermal drug delivery [140]. In response to these challenges, a study developed a miniaturized, high-precision microjet injection system, which demonstrated effective insulin permeation through the skin without causing deep tissue penetration in a rat model [141]. Therefore, to support the clinical translation of jet injection technology, optimisation of device size, performance, and cost is essential to ensure efficacy and patient safety.

6. MICRONEEDLE (MN) TRANSDERMAL DELIVERY

MN transdermal systems were introduced to overcome the challenges encountered with previously described skin penetration methods [4, 7]. These systems consist of micron-sized arrays of needles, typically ranging from 25–2000 μm in length, designed to penetrate the SC and facilitate drug delivery into the epidermal and dermal layers upon application to the skin surface [4, 142]. MNs create transient microchannels with minimal or no pain, which rapidly reseal following needle removal, thereby minimizing the risk of prolonged skin injury [4, 15, 89]. MN differ in material composition, physicochemical properties, manufacturing methods, and functionalities

[7, 15, 89]. MN have been widely used for transdermal delivery of both small lipophilic compounds [143–145] and larger macromolecules, including proteins and peptides, and have been further advanced through the development of bioresponsive MN systems [4, 10, 102].

Generally, MNs are classified into several types depending on the structure and mode of delivery, as shown in Figure 12. These types include solid, hollow, dissolvable, and biodegradable MNs [87], and more recently bioresponsive MNs have been fabricated [146]. A successful MN device application should possess the following characteristics [89, 147]: (i) fabrication without affecting the integrity of the drug; (ii) good mechanical strength without damaging the skin during insertion; (iii) high drug encapsulation with the reduced waste of drug concentration; (iv) good stability; and (v) ability to facilitate predictable sustained, effective, and safe drug release.

Most polymeric MNs have challenges with respect to mechanical strength and structural stability, which can hinder effective skin penetration and limit rapid release of encapsulated drugs [147]. The following sections provide a comprehensive review of the various types of MNs with particular emphasis on application in the transdermal delivery of insulin.

6.1 Fabrication methods for MNs

MNs are fabricated using a range of materials and manufacturing techniques that are selected based on the intended application [89]. The materials and fabrication methods used, along with the associated limitations,

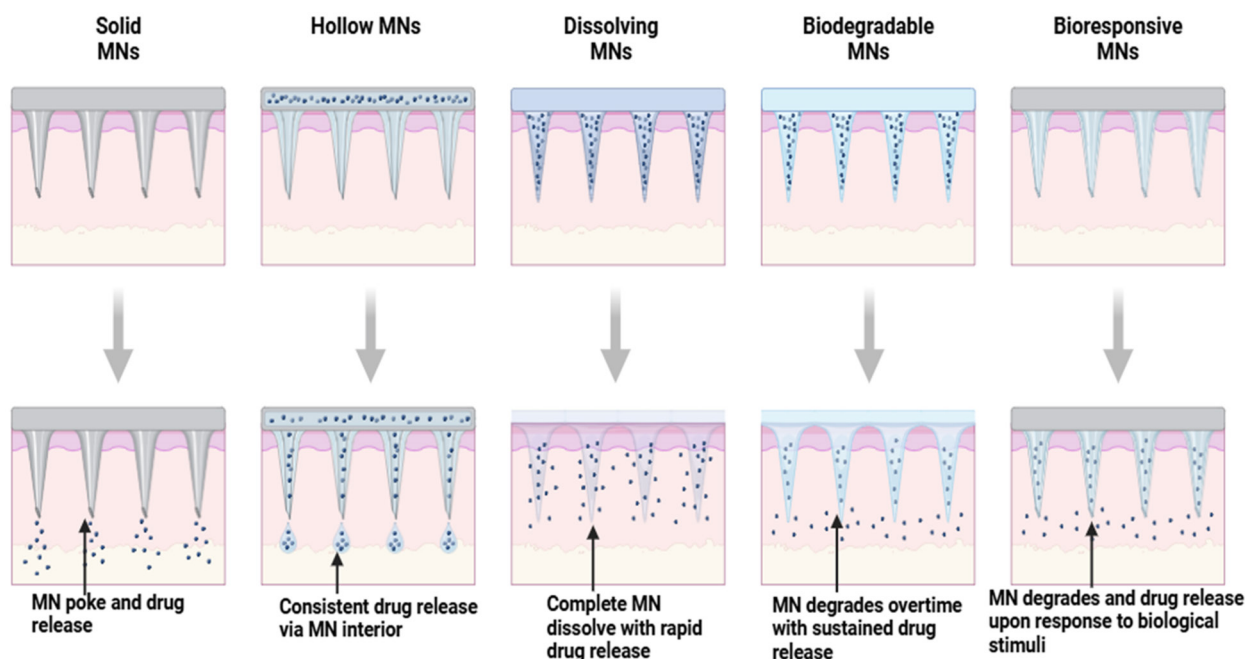


Figure 12 | Schematic illustration of various MNs and the mechanism of delivery (created with BioRender.com).

Table 5 | Fabrication methods, composition and limitations of MNs for transdermal insulin delivery.

MN type	Materials used	Fabrication methods	Limitations	References
Solid	Silicon, metals (such as stainless steel, nickel tantalum, titanium, palladium and ceramics), non-biodegradable polymers (such as PMMA and PMVE/MA). Biodegradable polymer (such as maltose and UV-curable [SU-8])	Microfabrication technology known as micromachining or micro-electromechanical systems (MEMS).	Costly, require specialized handling, involve complex process, potential for needle breakage, drug delivery inefficiency, e.g., total drug amount and drug release difficult to control	[89, 148-153]
		MEMS include thin film deposition, photolithography imaging and selective etching, such as isotropic, anisotropic, isotropic dry and wet etching, acid etching		[148, 151, 154-167]
		Electroplating, photochemical etching, and laser ablation		[89, 163-167]
		Magnetorheological drawing lithography		[168]
Hollow	Carbohydrates, ceramic, glass, metals, polymers, and silicon	MEMs technology: e.g., laser micromachining, deep reactive ion etching (DRIE), deep X-ray photolithography, integrated lithographic molding, wet chemical etching, drawing lithography and metal electroplating, isotropic and wet etching, digital micromirror stereolithography, lithographic and electroplating methods, copper etching and nickel plating	Complex and costly process, reduced mechanical strength, requires additional support	[89, 169-183]
Dissolving	Biodegradable polymers, such as sucrose, maltose, trehalose, CMC, gelatin, HA, PVP, PVA, PLGA, PGA, PMVE-MA, and PVPMAA	Mold-based techniques, e.g., solvent casting, drawing lithography, droplet-born air blowing, laser machining, hot embossing, microinjection molding, and ultrasound welding	Incomplete drug loading may be the limitation	[89, 109, 184-188]
Biodegradable	Biodegradable polymers, such as CMC, gelatin, HA, PVP, PVA, PLGA, PLA, PGA, PCL, PMVE-MA, PVPMAA, PS-PPA, and HPMC	Mold-based techniques, e.g., solvent casting, drawing lithography, droplet-born air blowing, laser machining, hot embossing, microinjection molding, and ultrasound welding	Slow drug release, cannot meet immediate needs and long-term safety issues	[89, 95, 184-188]

are summarised in [Table 5](#). Comprehensive procedural descriptions, including step-by-step methodologies for the fabrication of various types of MNs, are provided in detail elsewhere [\[89\]](#).

6.2 Solid MNs

Solid MNs deliver drugs by creating micro-pores on the skin to facilitate insulin delivery with subsequent application of the patch or topical formulation. Solid MNs are often referred to as “poke with patch” [\[15, 89\]](#).

Various studies over the past decade have reported insulin delivery via solid MNs [\[15\]](#). For example, Martanto et al. evaluated the feasibility of stainless steel solid MNs and demonstrated an 80% reduction in BGLs in diabetic rats after 4 h of MN administration, highlighting the hypoglycaemic effect of insulin delivered through this method [\[189\]](#). This study confirmed a proof of concept for transdermal insulin delivery using solid MNs and provided a baseline for MN optimisation.

However, variability in insulin delivery and insertion depth due to manual application requires improvement. Additionally, a rapid decrease in BGLs was observed in just 1 h after application of solid MNs in combination with topical insulin. While this finding suggested the potential for incorporating hydrogels with MNs for enhanced delivery, the study lacked safety information on prolonged and repeated use [\[190\]](#). Comparison of the different MN lengths (250, 500, and 1000 μm) in rat models indicated that MNs $\leq 500 \mu\text{m}$ were safe and effective in transdermal insulin delivery. Another study reported that an extended reduction in BGLs could be achieved by increasing the treated area with MNs, likely due to the larger surface area available for absorption [\[191\]](#). There was a strong focus on biocompatibility and safety issues and provided consisted results due to precise MN geometry but lacked comparison with subcutaneous injections in terms of long-term glucose regulation.

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A 700-fold increase in insulin absorption from nanovesicles was reported when iontophoresis was combined with MNs compared to passive transport of insulin [192]. BGLs were reduced to 33.3% and 28.3% of the initial values at 4 and 6 h, respectively. The synergistic effect was observed with MNs in combination with nanoparticles and improved glucose regulation was achieved, despite limited *in vivo* data on sustained glucose regulation. Several studies support solid MNs as a feasible system for improving transdermal insulin delivery. However, concerns remain regarding the consistency, uniformity, reproducibility, and stability of solid MNs in delivering optimal insulin concentrations in a consistent manner. Therefore, successful clinical application requires integration with controlled-release systems, economical, and simplified MN designs and in-depth, long-term, safety and efficacy studies.

6.3 Hollow MNs

Hollow MNs have been designed in such a way to allow the transport of therapeutics into the skin via the needle interior [4, 15, 89]. Unlike solid MNs, which can deliver only low and varying quantity of drugs, hollow MNs provide consistent flow of high quantities of therapeutics [89].

Several studies have demonstrated improved transdermal insulin delivery facilitated by hollow MNs. For example, a diabetic rat model showed a sustained reduction in the BGL (up to 70% over 5 h) with minimal skin trauma. While this study ascertained feasibility in transdermal insulin delivery using hollow MNs, *in vivo* pharmacokinetic or pharmacodynamic data were lacking, thus therapeutic efficacy was not validated [193]. The same research group further developed and fabricated metal hollow MNs and demonstrated sufficient mechanical strength, which facilitated rapid insulin absorption and action. However, long-term stability and insulin degradation were not investigated [169]. Other researchers explored silicon hollow MNs for insulin delivery with desirable MN properties, including sufficient mechanical strength, minimal skin irritation, as well as fast acting and controlled on-demand insulin release. However, long-term biocompatibility still requires investigation [194]. Another study highlighted ideal controlled-release properties with precise dosing and effective glycaemic control in diabetic mice. The device design was sophisticated and external infusion was required, which may complicate the application in clinical settings [6, 195]. Kochba et al. determined the efficacy of hollow MNs in adults with type 1 diabetes and demonstrated immediate insulin absorption and prompt reduction in BGLs. The results demonstrated clinical validity but the study was constrained by a limited sample size and short duration. Therefore, further investigations with larger cohorts and extended follow-up periods are warranted to substantiate these findings [196]. In 2022 a research team developed a thermosensitive hydrogel hollow MNs that demonstrated bioresponsive controlled insulin

release and effective hypoglycaemic outcomes. While this study may require a complex and high-cost fabrication process, the viability of hollow MNs with next-generation smart insulin delivery systems was presented [101]. Even though consistent outcomes, rapid insulin release, minimal skin damage, and increased tolerability were observed across all studies, further clinical research is required to evaluate the long-term safety and efficacy for repeated-use of hollow MNs.

6.4 Dissolving MNs

Dissolving MNs comprise soluble and biocompatible polymers that can encapsulate a drug. When inserted into the skin, dissolving MNs completely dissolve to release contents into the systemic circulation [4, 15]. The use of biocompatible polymers offers the advantage of avoiding residual drugs and biohazardous waste because these polymers undergo complete dissolution, while releasing drug into the absorption site. MNs made of sugar polymers, such as sucrose [197], maltose [198], and trehalose [199], have been reported as rapidly dissolving. However, fabricating MNs with these sugars has traditionally required extreme temperatures (> 100°C) to cause rubber-to-glass transitions, which could destroy the bioactivity of biomolecules, such as insulin [200]. Moreover, sugar-based polymers are suboptimal for the management of diabetes because complete dissolution in the systemic circulation may lead to elevated BGLs. Therefore, alternative polymeric materials should be considered for the transdermal delivery of insulin to avoid compromising glycaemic control. To address the challenge of high-temperature fabrication, the following new fabrication methods for dissolving MNs have been reported: (i) low-temperature processing [197]; and (ii) using other water-soluble polymers to form MNs, such as CMC [105, 199], gelatine [105], HA [102], PVP [111], PVA, PLGA, PGA, PMVE-MA, and poly (vinylpyrrolidone-co-methacrylic acid) [PVPMAA] [89, 201]. Of note, the selection of material composition for MN arrays has a critical role in determining the release kinetics of the encapsulated drug [4, 15, 86]. The drug release profiles can be modulated by altering the material composition or by utilising different MN fabrication methods [4, 15, 86]. Moreover, the duration of drug release is governed by the dissolution rate of the polymeric matrix, which can be tailored from min-to-h to meet specific therapeutic needs [4, 15]. Several studies have explored the use of dissolvable MN arrays for the transdermal delivery of insulin. In one such investigation, MNs composed of a gelatin/starch composite demonstrated favourable mechanical strength and achieved a skin penetration depth of approximately 200 µm in porcine and rat skin models [90]. Rapid and efficient insulin release was observed within 5 min with an enhanced hypoglycaemic effect (> 90%) in diabetic rats. The stability of insulin was also preserved after 1 month of storage at 25°C or 37°C, indicating the potential of starch/gelatin-dissolving MNs to be a promising delivery option for biomolecules with reasonable

stability. Similarly, Liu et al. designed HA-based MNs via a micromolding technique which demonstrated insulin bioactivity retained > 90% following 1 month of storage across a range of temperatures [−40°C, 4°C, 20°C, and 40°C] [91]. However, there was a degree of drug wastage attributed to incomplete insertion of the HA MNs, which is primarily due to the elastic nature of the skin [91]. To circumvent this limitation, researchers proceeded by developing fully insertable MNs with extended structures attached that could offset the skin elasticity properties during the administration of therapeutics [92]. While this is an innovative design and may improve a complete insertion challenge, the fabrication process is complex and may limit scalability. Moreover, Liu and colleagues designed robust mechanical strength multilayered dissolving MNs supported by additional structures that were able to dissolve fully to release the loaded insulin and maximum serum concentration was reached after 2 h [93]. With such a design, the mechanical strength for the tips and base of the MNs could be optimised with condensation of the drug concentration during multilayered fabrication. However, commercial viability may still be a challenge. Further research has explored bi-layered MN fabrication utilising varying ratios of PVP polymers (PVP10 and PVP360). Indeed, a PVP 1:3 ratio showed an enhanced *in vivo* insulin uptake compared to other PVP ratios [105, 111]. The study revealed suboptimal skin fitting properties when using a PVP composition alone for the MN backing layer. Thus, CMC, a hydrophilic polymer, was incorporated to enhance flexibility. The combined PVP360/CMC formulation demonstrated superior skin adaptability compared to pure PVP360, which improved the suitability for transdermal applications. Furthermore, Liu et al. fabricated composite insulin-loaded CaCO₃ microparticle MNs integrated with a PVP matrix to further harness the mechanical properties of the MNs [94]. The results demonstrated increased mechanical strength and toughness and reduced solubility compared to pure PVP MNs. While these properties are suitable for skin penetration, which could provide efficient drug release behaviour, drug loss during MN fabrication is a limitation. To overcome drug loss during the MN fabrication, Kim and colleagues developed a droplet-born air blowing (DAB) technique by applying biopolymer droplets on the flat base surface of the MNs, followed by addition of drug-loaded droplets onto the MN tips [110]. During the DAB fabrication method, the size and quantity of the loaded insulin concentration were adjusted with the application of pressure and air-blowing droplets. This fabrication method has demonstrated effective insulin delivery, with a reduction in BGLs in diabetic mice and improved bioavailability (> 95%), despite lengthy fabrication steps [110].

Recently, Yang et al. designed an electrospun pillar array-assisted MN to enable rapid MN insertion into the skin to overcome incomplete drug delivery [108]. The effectiveness of this method was investigated using porcine skin and the *in vivo* hypoglycaemic effect was

examined in a healthy mouse model. Drug-loading efficacy was improved but the complexity and cost of materials were few limitations. Furthermore, Garland et al. conducted investigations into the synergistic effects of dissolving MNs in combination with other enhancement technologies. The Garland et al. study demonstrated that coupling iontophoresis with insulin-loaded dissolving poly (methylvinyl ether-co-maleic acid [PMVE/MA]) resulted in a > 2-fold increase in insulin permeation across the skin of the neonatal porcine compared to MNs alone [109]. However, no *in vivo* data were available. Nevertheless, this finding could support the feasibility of combination approaches with other physical enhancement methods to improve insulin transdermal delivery.

Overall, dissolvable MNs provide a convenient and user-friendly approach for transdermal insulin delivery with ongoing research in bioresponsive materials, drug loading methods, and manufacturing scalability. Nevertheless, clinical validation and regulatory promptness remain key obstacles for widespread adoption.

6.5 Biodegradable MNs

MNs with controlled degradation are ideal for maintaining continuous drug concentrations and achieving the desired therapeutic outcome for protein drugs, like insulin [202]. Unlike dissolving MNs, biodegradable MNs do not dissolve easily but degrade over an extended period to release drug and provide a sustained therapeutic concentration [95, 100, 203].

Polymers with extensive crosslinking and higher molecular weights have been shown to provide superior mechanical strength and enable sustained drug release [204–206]. In this scenario, insulin is gradually released from the hydrogel forming biodegradable MNs through passive diffusion during the process of degradation. In addition, MN swelling can further enhance diffusion of the drug from the polymer matrix. For example, Yang and colleagues developed a double-layer MN patch consisting of swellable MN tips made from PS-PAA and a non-swellable polystyrene (PS) base layer [95]. The MN system demonstrated enhanced mechanical strength (~1.6 N/cm² on rat skin) with *in vitro* studies indicating approximately 60% insulin release over a 12-h period, while maintaining ~70% structural integrity. *In vivo* pilot studies revealed a sustained release profile without burst release, which is advantageous for maintaining stable BGLs. Despite these promising mechanical and release properties, the limited release efficiency suggests that a substantial proportion of the insulin remains unreleased, potentially compromising therapeutic efficacy. Moreover, the system lacks a glucose-responsive mechanism to modulate insulin release in response to glycaemic fluctuations. Furthermore, the complexity of the double-layered design may pose challenges for large-scale manufacturing and consistent quality control, potentially limiting the commercial viability. Another study revealed a sustained reduction in

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BGLs in diabetic rats administered insulin-loaded biodegradable MNs fabricated from calcium ion crosslinked alginate/maltose [96]. The incorporation of maltose enhanced the mechanical strength of the alginate MNs, enabling successful skin penetration without fracture. Both maltose and alginate are FDA-approved, economical, easy to fabricate, and scalable, supporting the potential for commercial production. The MN system demonstrated rapid swelling within 5 min, followed by complete dissolution within 40 min, sustaining the pharmacologic action of insulin longer than an equivalent subcutaneous dose. However, insulin bioavailability was lower compared to injection, indicating potential losses during transdermal transport. Importantly, no local skin irritation, inflammation, or tissue damage was observed, confirming favorable biocompatibility. Despite these advantages, the transient glucose-lowering effect due to rapid polymer dissolution suggests the need for frequent reapplication to maintain glycaemic control. Furthermore, the absence of a glucose-responsive release mechanism limits the ability of the system to adapt to dynamic BGLs, posing a risk of hypoglycaemia with improper dosing. In another design, Di and co-workers developed a stretchable MN patch triggered by tensile strain [97]. Insulin-loaded microgel depots incorporated within an elastomeric patch were designed to release insulin upon mechanical stretching, facilitating diffusion into a cross-linked HA MN matrix for transdermal delivery. The use of HA provided biocompatibility, flexibility, and patient comfort. *In vivo* studies in streptozotocin-induced diabetic mice demonstrated that a single application effectively reduced BGLs within 30 min, comparable to subcutaneous injection. Additionally, the patch enabled on-demand insulin release through repeated mechanical stretching, offering a novel approach for dynamic dosing. No significant biocompatibility concerns were reported, indicating good local tolerability. However, the system evaluation was limited to short-term use with insufficient data on long-term safety, repeated applications, or dose consistency. The reliance on voluntary or involuntary body movements for activation may pose challenges in achieving consistent dosing and could hinder patient adherence. Furthermore, the complex fabrication process, particularly ensuring uniformity and reproducibility of mechanical responsiveness, may limit scalability and increase manufacturing costs. Further research by Yang et al. explored a phase-transition MN patch made of PVA for transdermal insulin administration [98]. When the MN was inserted into the skin, the microcrystalline crosslinking caused the MN to swell rather than dissolve, which resulted in a continuous release of insulin from the MN patch. The phase-transition occurs immediately upon skin insertion, allowing the MNs to maintain mechanical strength during penetration, then soften to facilitate drug release. The MNs exhibited sufficient insertion force and penetrated rat and porcine skin without breakage. The MN patches effectively

reduced BGLs within 30 min in streptozotocin-induced diabetic rats, achieving a sustained hypoglycaemic effect for up to 8 h. Studies conducted in a model of diabetic pigs revealed transdermal bioavailability that was > 20%. Pigs treated with insulin patches continuously for 2 months had lower glycated haemoglobin levels than pigs treated with an insulin pen, suggesting that the insulin patches had a superior ability to regulate BGLs [15]. This dual-functional phase-transition MN system demonstrates an initial rigidity to facilitate efficient skin insertion, followed by post-insertion softening that promotes drug diffusion. This structural transformation enhances delivery efficiency and patient safety. The system exhibits a high insulin loading capacity with minimal drug wastage, rapid onset of action, and sustained insulin release, which contribute to improved glycaemic control. The user-friendly design supports self-administration and enhances patient compliance. Furthermore, the mold-based fabrication process presents a viable pathway for large-scale manufacturing. Nevertheless, the system lacks responsiveness to fluctuating BGLs, which may lead to suboptimal dosing, including risks of hypo- or hyper-glycaemia. The current research primarily addresses short-term glycaemic management; long-term efficacy, immunogenicity, and safety data remain insufficient. Additionally, the phase-transition behaviour may be influenced by individual variations in skin hydration, potentially affecting release kinetics and interpatient consistency. Integrating this phase-transition platform with a biosensing-controlled release mechanism may enhance therapeutic precision and adaptability in future applications.

Recent advances have highlighted bioceramics as a promising platform for the transdermal delivery of biomolecules [99]. This is largely due to robust mechanical strength and favorable biocompatibility. Additionally, bioceramics have a flexible porous structure and the electrostatic interaction between the biomolecules and the ceramic surface. Yu et al. (2017) pioneered the development of organic-inorganic bioceramics composite MNs composed of biodegradable hydroxyapatite and gelatin for sustained transdermal delivery of insulin [99]. MNs fabricated from cross-linked gelatin and incorporating hydroxyapatite demonstrated sufficient mechanical strength to penetrate the skin surface in *in vivo* studies conducted on diabetic rats, induced a hypoglycaemic response, and facilitated prolonged insulin release into the bloodstream, outperforming the traditional subcutaneous injections. However, the insulin release profile was governed by passive diffusion, lacking glucose-responsive regulation, which may limit the ability to adapt to fluctuating BGLs. Additionally, the potential long-term immunogenicity associated with hydroxyapatite has not been thoroughly investigated, representing a possible limitation for long-term clinical application. The same research group subsequently developed gelatin/calcium sulfate composite MNs, which demonstrated effective skin penetration

and sustained insulin release. These MNs demonstrated superior performance in diabetic mouse models compared to subcutaneous injections by prolonging the glucose-lowering effect. This enhanced therapeutic outcome was attributed to the increased matrix density conferred by the degradable composite formulation. [100]. However, the mechanical rigidity of the MNs may present challenges in achieving consistent insertion through the thicker and more resilient human skin. Furthermore, the study did not include comparisons with rapid-acting insulin formulations, limiting evaluation of the system efficacy in managing postprandial glycaemic fluctuations.

Generally, the complexity in device design, lack of long-term biocompatibility data, limited duration of action, moderate bioavailability observed in some studies, and lack of glucose responsivity and scalability are some of the issues that need to be addressed in future studies. Integrating glucose-responsive elements or combining with controlled-release matrices may enhance the clinical applicability for chronic diabetes management.

6.6 Bioresponsive MN system

More recently, bioresponsive systems have been developed to address challenges and ensure safe, consistent, and effective insulin delivery with minimal treatment intervals [8, 207-220]. Bioresponsive MN patches

typically incorporate encapsulated insulin along with glucose-sensitive elements, such as glucose oxidase (GO_x), to form a glucose-sensitive system capable of responding to elevated BGLs upon administration [217, 218].

Biologically responsive stimuli are generated by the GO_x reaction [102] and provide indirect indicators of elevated glucose levels, such as hypoxia, increased hydrogen peroxide (H_2O_2) concentrations, and an acidic pH environment. These signals subsequently activate disassembly of the insulin-loaded MN patch, prompting the release of insulin [217, 218].

Numerous studies have demonstrated the efficacy of bioresponsive smart insulin MN systems in achieving BGL reduction and regulation in diabetic mice and rat models as summarised in Table 6.

6.6.1 Stability and scalability challenges of bioresponsive MNs. Although biologically responsive stimuli have demonstrated improved therapeutic outcomes based on BGL regulation, several critical factors must be considered when designing bioresponsive MN systems for long-term use and scalability. These considerations necessitate the characterisation of the physicochemical properties of the bioresponsive stimuli, including the following: GO_x and phenylboronic acid (PBA) are susceptible to degradation and loss of functional activity over prolonged periods, particularly under physiological

Table 6 | Overview and key observations of various studies that have investigated bioresponsive MN systems.

Bioresponsive MNs	Materials for preparation	Model	Observations	References
Hypoxia-sensitive	Cross-linked HA matrix	Diabetic mice	BGLs rapidly reduced to ~200 mg/dL within 0.5 h and normal glycaemic level maintained up to 4 h	[102]
H_2O_2 -sensitive	1. PEG and Phenylboronic (PBE) ester-conjugated polyserin	Diabetic mice	Indicated self-regulating BGLs	[207, 208]
	2. Mesoporous silica nanoparticles	Diabetic rats	Host-complex dissociation and insulin release	[207, 208]
pH sensitive	Bioactive glasses, zinc oxide (ZnO) quantum dots incorporating enzymes (GO_x /CAT)	Diabetic mice	ZnO degraded under acidic conditions triggering insulin release	[209]
Dual glucose and H_2O_2 -sensitive	Triblock polymeric MN composed of phenylboronic acid and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzyl acrylate	Diabetic rats	Indicated triblock dissociation and insulin release	[210]
Dual hypoxia and H_2O_2 -sensitive	1. Polymersomes incorporated MN	Diabetic mice	Regulated BGLs for 10 h post-administration	[211, 212]
	2. Polymeric gel consisting of PVA, glucose responsive elements and nanogel H_2O_2 -scavenging enzymes	Diabetic mice	Insulin leases rapidly under hyperglycaemic conditions and effectively controlled BGLs for 40 h without causing sever hypoglycaemia	[211, 212]
Dual H_2O_2 and pH-sensitive	Sheath-structured MN coated with catalase-containing nanogels	Diabetic mice	BGLs was effectively regulated	[213]
MN-embedded, insulin-secreting pancreatic β -cells	MNs embedded with insulin secretion from exogenous β -cells containing glucose signal amplifiers (GSAs)	Diabetic mice	Rapid BGLs reduction and sustained blood glucose control for over 6 h	[214]

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conditions [102]; PBA demonstrates instability at physiological pH, thus requiring the development of structurally modified PBA derivatives to improve responsiveness under neutral pH environment [207, 208]; enzymatic agents, such as Gox, are prone to denaturation when exposed to specific pH and temperature conditions, potentially reducing shelf life in the absence of appropriate stabilisation strategies and GOx may lose catalytic activity in dry states or under oxidative stress; and the production of reactive by-products, notably H_2O_2 , as a result of GOx activity, may compromise insulin stability or degrade the surrounding matrix. Therefore, the incorporation of catalase or alternative scavenging agents into the formulation is essential to mitigate these effects [211, 212].

Achieving uniform MN arrays with reproducible drug loading, mechanical strength, and glucose sensitivity remains technically cumbersome. Fabrication techniques, such as micromolding, photolithography, and 3D printing, require precise optimisation to enable mass production. Additionally, the moisture and temperature sensitivity of polymers, enzymes, and insulin introduces packaging and storage challenges, necessitating compliance with stringent sterility standards. Furthermore, the incorporation of biosensors, enzymes, and functionalised polymers significantly increases production costs, raising concerns regarding the economic viability of such systems for chronic use in diabetic patients.

6.7 Comparison of MN technologies

Among the various types of MNs discussed in this review, dissolving and biodegradable MNs appear to be the most suitable for the transdermal delivery of protein-based drugs, like insulin. These MNs allow for a controlled, sustained release that minimises the need for frequent dosing, thereby maintaining consistent insulin levels for effective blood glucose management. It is also important to note that in insulin delivery, rapid onset is clinically essential to counteract post-meal blood glucose spikes, a feature that dissolvable MNs can accommodate. In contrast, solid MNs create transient micropores in the skin, limiting drug absorption due to the rapid closure of these channels, typically within 1 h [89]. Additionally, solid silicon MNs are costly, prone to breakage, and do not allow for dose adjustment or precise flow control [6]. Thus, the accuracy of dosing is limited [101]. Hollow MNs facilitate the microinjection of larger drug doses. However, the hollow MN production process is complex and costly. Hollow MNs also present several limitations, including the potential for dermal blockage, dependence on specialised equipment, and the requirement for an external injection-driving power source is needed [101]. In summary, MN-based approaches for insulin delivery have demonstrated relatively higher transport efficiency, which is comparable to subcutaneous injections. Owing to the convenient, easy-to-use, and painless transdermal delivery platform, MNs are well-suited for self-administration by individuals

with diabetes. Additionally, the incorporation of glucose-responsive elements emphasises the capability for continuous and effective blood glucose regulation.

7. LIMITATIONS IN TRANSDERMAL INSULIN DELIVERY

Significant efforts have been devoted to developing transdermal delivery systems for insulin, yielding promising results via different formulation approaches and strategies. MN technology seems to be gaining attention due to the painless, efficient, self-regulating systems with several MN formulations reaching phase 1 clinical trials [196, 221, 222]. Nevertheless, challenges remain in maintaining therapeutically effective insulin concentrations for the long-term management of chronic diabetes, particularly in addressing acute glycaemic fluctuations. Specifically, current transdermal delivery systems may not yet sufficiently meet the immediate physiological demands required for rapid and effective postprandial BGL reduction. Research has explored a wide range of physical and biological approaches utilising diverse materials and technologies in search of the most effective transdermal insulin delivery system. However, limitations, such as maintaining insulin bioactivity and stability throughout the treatment period and addressing long-term side effects associated with material composition over longer treatment period require further investigation.

8. FUTURE PERSPECTIVES

Given the extensive research on transdermal insulin delivery to date, there is now a solid foundation for refining this formulation approach for clinical application. Future efforts should prioritise optimising formulation parameters and tailoring drug properties with precise considerations given to the pathophysiological conditions of diabetes. The goal is to create a safe, user-friendly, and effective transdermal delivery system capable of continuous and predictable insulin release to reduce dosing frequency, while being responsive to physiological BGLs. This goal would help prevent hyperglycaemia and other adverse effects. Additionally, delivery platforms should enable rapid release to meet patients' immediate needs. Ultimately, the development of a simple, patient-friendly, scalable, and cost-effective transdermal insulin system remains essential for commercial viability and to improve health outcomes for diabetic patients.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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