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MICRO NEEDLE-MEDIATED DRUG DELIVERY FOR DIABETES MANAGEMENT: RECENT ADVANCES AND THERAPEUTIC PERSPECTIVES

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Abstract

Diabetes mellitus is a major health problem worldwide due to the high blood sugar levels caused by either the insulin resistance or the pancreatic malfunction. Microneedle technologies are being investigated as a painless alternative to conventional therapies due to problems such as patient non-adherence and adverse effects. This is a PRISMA-guided review of research on microneedle applications in the management of diabetes from 2015 to 2026. The literature search identified 1300 records of which 90 studies were relevant. Microneedles are painless needles that prick the skin to deliver insulin and are available in many forms. The process of making microneedles was adapted to use flexible biocompatible polymers. Among the innovations are "smart" devices for automatic release of medication that are as effective as injections. Future applications could include the combination of AI with continuous glucose monitoring, but issues related to dosage and long-term safety are barriers to a wider adoption.

Keywords: *Biocompatibility, Closed-loop insulin delivery, Diabetes mellitus, Glucose-responsive systems, Microneedles, Transdermal drug delivery*

INTRODUCTION

DIABETES MELLITUS: GLOBAL BURDEN AND PATHOPHYSIOLOGICAL BASIS

On the basis of these publications a review of diabetes microneedle technologies from 2016 to 2026 can classify MN types, materials and smart/closed-loop systems; compare preclinical and early clinical results with conventional patches and injections (1-5).

Summarize recent advancements and clinical data, emphasizing human and animal data on insulin and GLP-1 RA delivery, pharmacokinetics, glycemic outcomes, pain and tolerability, and device safety (1, 4). Further research opportunities include scalable production, dose loading for high-dose biologics, long-term skin safety, regulatory processes and integration with continuous glucose monitoring, and customized closed-loop MN systems (2, 3).

Types of Diabetes mellitus are of three types: Type 1 (T1DM), Type 2 (T2DM) and Gestational Diabetes Mellitus (GDM). T2DM, which accounts for over 90% of cases, is characterized by insulin resistance and β-cell dysfunction and is closely associated with obesity. T1DM is an autoimmune disease that needs lifelong insulin therapy (6). Pregnancy-associated GDM increases the chances of developing T2DM for both the mother and her unborn baby. There is chronic hyperglycemia due to oxidative stress and inflammation following the derangement of the physiological process of glucose metabolism (7). This persistent hyperglycemic state not only exacerbates pancreatic β-cell exhaustion but also induces epigenetic modifications in the fetus, predisposing it to metabolic syndrome later in life. Conventional oral hypoglycemics and insulin therapy are often limited by transplacental pharmacokinetic variability and the need for frequent dose adjustments during gestational progression. However, despite progress, patient adherence issues make optimal glucose control difficult, thus creating interest in novel drug delivery methods like microneedle systems (8, 9).

PATHOPHYSIOLOGY OF DIABETES MELLITUS

Diabetes mellitus is an umbrella term for a range of metabolic disorders wherein high levels of blood glucose exist as a result of defects in the production of insulin, action of insulin, or both. Diabetes mellitus, regardless of the type, is always marked by a malfunction in the pancreatic β cells (10, 11).

Diabetes is caused by a combination of environmental factors (diet, obesity, inactivity, social determinants), genetic predisposition, and coordinated malfunction of β-cells, liver, skeletal muscle, and adipose tissue (11). While T2DM is a heterogeneous state of insulin resistance and progressive β-cell failure, T1DM is characterized by immune-mediated β-cell death; GDM is induced during pregnancy and shares many processes with T2DM (10-13). The Table I provide the primary molecular abnormalities and typical clinical presentation windows for Type 1, Type 2, and Gestational Diabetes Mellitus (GDM) are compiled in table I. It emphasizes how the common factor among all diabetic etiologies is pancreatic beta-cell susceptibility, which can range from autoimmune destruction to compensatory secretory failure.

Table I. Pathophysiological characterization and clinical context of primary diabetes phenotypes

Type	Core Defect	Typical Context	References
Type 1	Autoimmune β-cell destruction → absolute insulin deficiency	Often childhood/young adult	(10, 11, 14-17)
Type 2	Insulin resistance + β-cell dysfunction	Adults, obesity/metabolic syndrome	(11, 12, 18-20)
GDM	Pregnancy-induced insulin resistance + inadequate β-cell response	2nd–3rd trimester	(13, 21-24)

DIABETES MELLITUS'S OVERALL PATHOPHYSIOLOGY

Chronic hyperglycemia of all kinds is caused by β-cell loss or dysfunction: essential in T1D, T2D, and GDM (11-13, 25). Obesity, ectopic lipids, inflammation, oxidative stress, and ER stress are common causes of insulin resistance (IR) in muscle, liver, and adipose tissue (11, 12, 18, 20, 23). Dyslipidemia, increased free fatty acids, and organ damage (kidney, retina, nerves, cardiovascular system) are systemic metabolic effects (11, 12, 18, 19).

DIABETES MELLITUS TYPE 1

Insulin-producing β-cells are destroyed by CD4+ and CD8+ T lymphocytes in type 1 diabetes (T1DM), an autoimmune illness that results in complete insulin insufficiency and lifelong insulin reliance (10, 11, 15, 17). Mechanistic characteristics All immunity complicates β-cell transplantation; autoreactive T cells target islet antigens. β-cells are not passive targets; inflammatory reactions, ER stress, and intrinsic biosynthetic stress make them more vulnerable and may contribute to the onset or exacerbation of autoimmunity (16, 17, 25, 26). Fig. 1 demonstrating how environmental and genetic variables compromise beta (β) cell homeostatic machinery (inducing ER stress and biosynthetic overload). Rather than acting as a passive bystander, the distressed β cell upregulates human leukocyte antigen (HLA) presentations and chemokine cues, shifting a state of baseline "benign" autoimmunity into an active CD4+/CD8+ T-lymphocyte-mediated clearance cascade (27). Environmental factors (such viral infections) and genetic variations (including those in antiviral and stress pathways) influence β-cell stress and local inflammation, facilitating the transition from "benign" autoimmunity to overt T1D (15, 26).

DIABETES MELLITUS TYPE 2

Progressive decrease of β-cell insulin production on a background of insulin resistance is the hallmark of type 2 diabetes. Fundamental mechanisms Obesity, ectopic lipid deposition, inflammation, oxidative and ER stress, mitochondrial dysfunction, and gut dysbiosis all contribute to insulin resistance in muscle, liver, and adipose tissue (12, 18, 19, 25). Genes and environmental factors contribute to type 2 diabetes and obesity, where obesity and insulin resistance result from their interplay. Type 2 diabetes develops when genes related to aberrant β-cell activity are present alongside those affecting body obesity as

shown in Fig. 1. Under prolonged nutritional and inflammatory stress, β-cell failure includes decreased secretion, dedifferentiation, mitochondrial dysfunction, and death (11, 12).

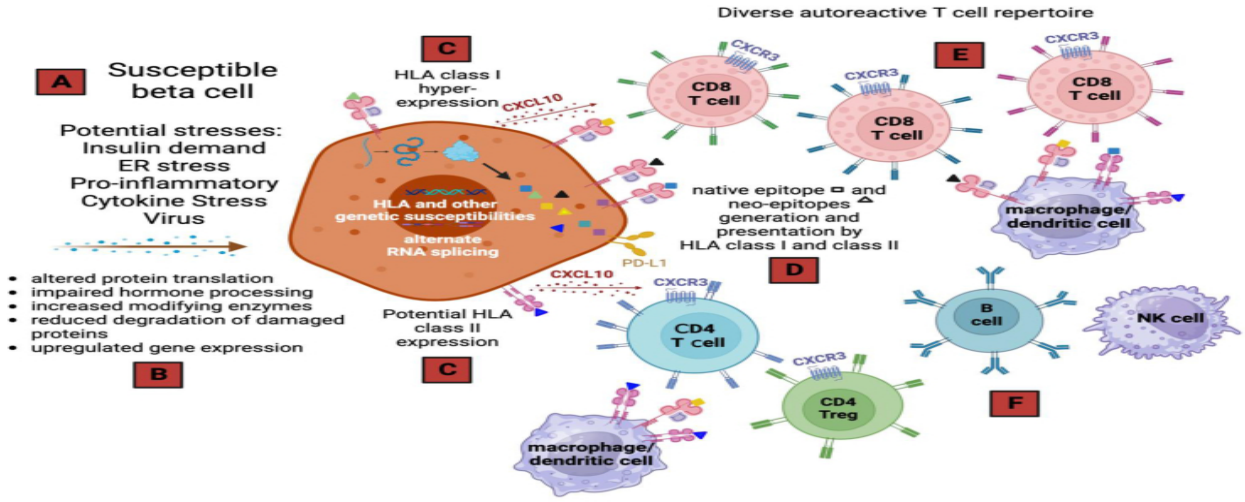

Fig. 1. Schematic demonstrating how environmental and genetic variables compromise beta (β) cell homeostatic machinery (inducing ER stress and biosynthetic overload). Rather than acting as a passive bystander, the distressed β cell upregulates human leukocyte antigen (HLA) presentations and chemokine cues, shifting a state of baseline "benign" autoimmunity into an active CD4+/CD8+ T-lymphocyte-mediated clearance cascade *[Adapted from Roep et al., 2020 (14)].*

DIABETES MELLITUS DURING PREGNANCY

GDM, or glucose intolerance first identified during pregnancy, is typically caused by β-cell malfunction on top of both normal pregnancy-induced insulin resistance and chronic insulin resistance (13, 21-24, 29). Pathophysiology in GDM, β-cells are unable to sufficiently boost insulin secretion, although pregnancy often causes physiological insulin resistance to favor fetal glucose supply. Through lipolysis, increased free fatty acids, and compromised insulin signaling (IRS/PI3K/Akt), placental hormones (human placental lactogen, growth hormone-variant, estrogens, progesterone) and obesity-related variables raise IR.Insulin action and β-cell function are further disrupted by inflammatory cytokines (TNF-α, IL-6), adipokine imbalance (hyperleptinemia, hypoadiponectinemia), ER stress, and oxidative stress(13, 21-24, 29). While genetic abnormalities influencing β-cell activity drive the path to hyperglycemia when insulin production fails to compensate for increasing metabolic demand, environmental factors contribute to obesity and insulin resistance as shown in Fig. 2. Obesity and GDM are linked by placental and maternal molecular changes (such as ANGPTL4-induced ER stress and GH2 secretion; modified exosomes and metabolomic signatures), which also offer new biomarkers and treatment options (21, 22, 24, 29).

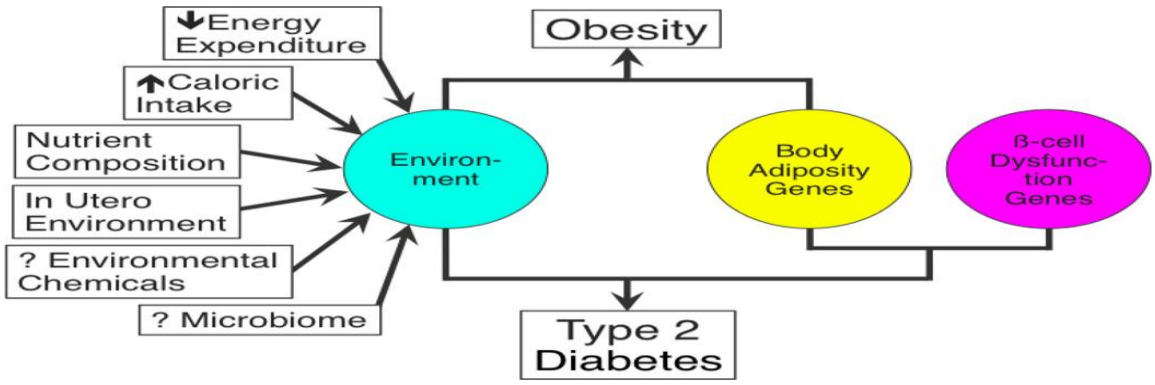

Fig. 2. Genes and environmental influences play a significant role in type 2 diabetes and obesity. While obesity and insulin resistance stem from these interactions, type 2 diabetes arises when specific genetic factors related to β-cell activity are involved *[Adapted from Kahn et al., 2014* (28)*].*

METHODOLOGY

METHOD FOR SEARCHING LITERATURE

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) standards were used in conducting this study. Between March 1, 2025, and April 30, 2025, a thorough search of the

literature was conducted using the electronic databases PubMed/MEDLINE, Scopus, Web of Science, Science Direct, and Google Scholar. The reference lists of eligible articles were manually screened to find other pertinent publications.

Finding peer-reviewed research on the creation, characterization, preclinical assessment, clinical use, safety, regulatory considerations, and future prospects of microneedle (MN)-based drug delivery systems for diabetes treatment was the goal of the study.

SEARCH STRATEGY

Boolean operators ("AND" and "OR") were used in the search method to integrate free-text keywords with Medical Subject Headings (MeSH).

Table II. Literature retrieval search approach

Database	Search string
PubMed/MEDLINE	("Microneedles" OR "Microneedle Patch") AND ("Diabetes Mellitus" OR "Insulin Delivery" OR "Transdermal Drug Delivery")
Scopus	TITLE-ABS-KEY (Microneedles AND Diabetes AND Insulin AND Transdermal Delivery)
Web of Science	TS=(Microneedles AND Diabetes AND Drug Delivery)
ScienceDirect	Microneedles AND Diabetes AND Insulin Delivery
Google Scholar	"Microneedles for diabetes", "Smart microneedles", "Glucose-responsive microneedles", "Transdermal insulin delivery"

Microneedles, microneedle patch, diabetes mellitus, insulin delivery, transdermal drug delivery, dissolving microneedles, hydrogel-forming microneedles, coated microneedles, solid microneedles, hollow microneedles, glucose-responsive microneedles, smart microneedle systems, and closed-loop insulin delivery were the main search terms.

ELIGIBILITY CRITERIA

Studies were eligible for inclusion if they were published in English between January 2015 and April 2025, focused on microneedle-based drug delivery systems for diabetes treatment, and examined aspects such as formulation development, manufacturing processes, wearable technologies, glucose-responsive systems, preclinical or clinical investigations, commercialization, regulatory considerations, or future advancements in microneedle technology. Eligible article types included original research, systematic reviews, meta-analyses, randomized clinical trials, and observational clinical studies published in peer-reviewed journals. Studies were excluded if they were published before January 2015, were not written in English, consisted of conference abstracts, editorials, commentaries, letters to the editor, patents, dissertations, or book chapters, were duplicate publications, addressed microneedle applications unrelated to diabetes, did not involve microneedle-based drug delivery, or lacked sufficient methodological or experimental detail.

EXAMINE SCREENING AND SELECTION

The PRISMA 2020 framework was used in the study selection procedure. Using both manual reference screening and electronic database scanning, 1,300 records were found. 1,055 distinct articles were left for title and abstract screening after 245 duplicate data were eliminated.860 studies were eliminated after the first screening because they did not meet the predetermined eligibility requirements. The eligibility of the remaining 195 full-text publications was evaluated.105 studies were eliminated after full-text review for the following reasons:

Following full-text assessment, 105 studies were excluded for predefined reasons. Specifically, 35 articles were excluded because they were not focused on diabetes or insulin delivery, while 25 studies did not investigate microneedle-based drug delivery systems. An additional 20 articles were excluded due to insufficient methodological or experimental information that limited critical evaluation. Furthermore, 15 publications, including conference abstracts, editorials, letters to the editor, book chapters, and patents, were

excluded because they did not meet the eligibility criteria for peer-reviewed scientific evidence. Finally, **10** duplicate or overlapping publications were removed to ensure that each study was represented only once in the qualitative synthesis. Consequently, 90 studies fulfilled all predefined inclusion criteria and were included in the final review. In the end, 90 research met all qualifying requirements and were added to the qualitative synthesis.

The PRISMA flow diagram (Fig. 3) shows the entire identification, screening, eligibility evaluation, exclusion procedure, and final study inclusion.

DATA EXTRACTION AND EVIDENCE SYNTHESIS

Relevant information from the eligible studies was extracted independently and organized into standardized categories, including:

- Microneedle type
- Materials and fabrication techniques
- Drug loading strategies
- Mechanism of drug delivery
- Glucose-responsive technologies
- Insulin and non-insulin antidiabetic delivery
- Preclinical and clinical outcomes
- Safety and biocompatibility
- Manufacturing approaches
- Commercialization and regulatory status
- Challenges, limitations, and future perspectives

Because considerable heterogeneity existed among the included studies with respect to microneedle design, fabrication methods, biomaterials, drug formulations, experimental models, and outcome measures, a qualitative narrative synthesis was performed rather than a quantitative meta-analysis.

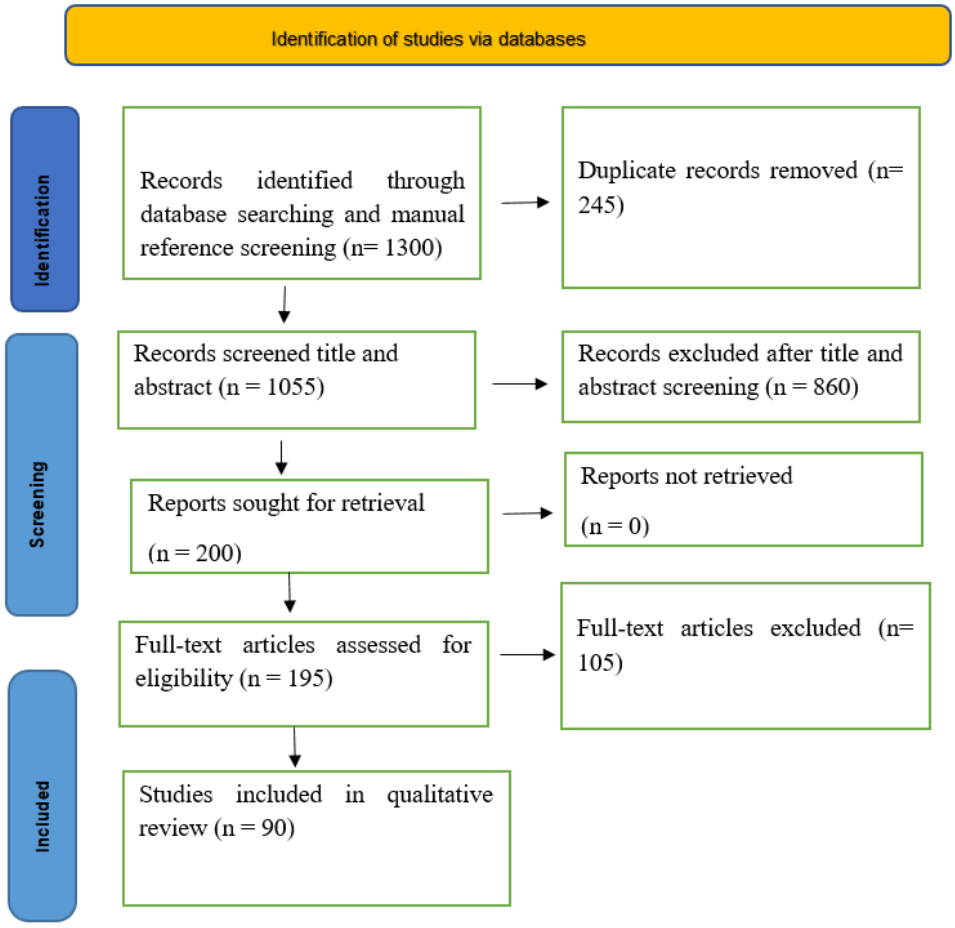

Fig. 3. Steps involved in choosing a study, such as database searches, eliminating duplicate and ineligible records determining eligibility, and adding the studies to the systematic review

CURRENT PHARMACOLOGICAL APPROACHES FOR DIABETES MANAGEMENT

From life-saving insulin to a wide range of oral medications, injectables, and experimental cell/immunotherapies, pharmacological diabetes therapy has changed over time. Current approaches focus on lowering cardiovascular, renal, and quality-of-life burdens in addition to glycemic management (30). Nearly sixty antidiabetic medications in various groups, such as insulin, metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, GLP-receptor agonists, and fixed-dose combos, are licensed for type 2 diabetes (T2DM) (31). Combination medication and customization depending on weight, hypoglycemic profile, and cardiovascular/renal risk are key components of modern treatment (31). Table III categorizes key pharmacological strategies in diabetes management into four areas: insulin therapy for Type 1 and advanced Type 2 diabetes; first-line oral therapies, including metformin and triple-combination regimens; GLP-1 receptor agonists, which are cardioprotective and promote weight loss; and emerging biological therapies for β-cell replacement and immune modulation, establishing a clinical baseline for innovative transdermal treatments like microneedle drug delivery systems (32-36).

Table III. Principal pharmacological classes, therapeutic roles, and associated clinical literature references in contemporary diabetes management

Class / Approach	Key roles in current practice	References
Insulin	First-line in type 1, frequent in advanced T2DM; increasingly optimized by analogs and devices	(30, 37-40)
Metformin & other oral agents	Foundation therapy; expanded to triple oral regimens (metformin + DPP-4i + SGLT2i)	(31, 41-43)
GLP-1 receptor agonists	Glucose control plus CV, renal, and weight benefits	(32-36)
Emerging biological/cell & immunotherapies	Aim at β-cell replacement or immune modulation, especially in type 1	(34, 44-47)

CHRONOLOGICAL HIGHLIGHTS OF INSULIN THERAPY

Since its discovery in 1921, type 1 diabetes has changed from being lethal to chronic (30). A century later, improved formulations and delivery methods have resulted in significant improvements in outcomes (30, 39). Mealtime analogs and pumps facilitate intense regimens in type 1 diabetes, while long-acting and ultra-long analogs (e.g., glargine, degludec) allow straightforward basal-only beginnings in T2DM (40). To lessen injection stress and increase adherence, new approaches include once-weekly basal insulins, hepato-preferential insulin, and oral insulin (37, 39).

ORAL MEDICINES FOR DIABETES

Metformin's effectiveness, safety, and affordability make it a mainstay first-line medication (31). Since 2006, DPP-4 inhibitors have been utilized as a second-line treatment after metformin and in triple combinations with insulin or SGLT2i (41).They increase endogenous GLP-1, reducing HbA1c ~0.5–1.0%, weight-neutral, low hypoglycemia risk, and CV-safe. SGLT2 inhibitors are essential to contemporary algorithms and offer glucose control as well as robust cardiovascular and renal protection in type 2 diabetes(48). Triple oral medication (metformin + DPP-4i + SGLT2i) is recommended by current guidelines for long-term management with good tolerance in a variety of T2DM groups (31, 41, 43, 48).

GLP-1 RECEPTOR AGONISTS

GLP-1 Receptor Agonists GLP-1RAs are cardiometabolic agents that have emerged from glucose-lowering medications (41). With weight loss and no significant safety signals, large CV outcome trials and umbrella/meta-analyses demonstrate ~10–12% relative risk reductions in MACE, CV and all-cause mortality, stroke, and renal composite outcomes in T2DM (31). Benefits are frequently chosen in patients with known or high CV risk, and they are at least as good as or better than DPP-4 inhibitors and sulfonylureas. This incretin

paradigm is expanded by dual GIP/GLP-1 agonists like tripeptide, which significantly reduce MACE, CV, and death in high-risk T2DM when compared to placebo (31, 42).

TRANSDERMAL DRUG DELIVERY: OPPORTUNITIES AND BIOLOGICAL CHALLENGES

Transdermal drug delivery systems (TDDS) deliver drugs locally or systemically through the skin. They are appealing because they can increase patient convenience, decrease side effects, and improve absorption, but they are essentially constrained by the robust outer skin layer barrier. TDDS uses patches, vesicles, microneedles, and related platforms to deliver medications to skin tissues or into the systemic circulation (49). From basic patches to "first-fourth generation" systems that use nanocarriers and physical enhancement techniques, they provide a non-invasive, frequently self-administered substitute for oral and injectable approaches (49-52).

SKIN STRUCTURE AND BARRIER FUNCTION

The skin consists of three layers: the epidermis, dermis, and hypodermis, with the stratum corneum (SC) as the main barrier to drug permeation. The SC's “brick-and-mortar” structure limits the permeability of most drugs, especially hydrophilic and larger molecules (>500 Da) (49, 50, 53-57). Drug penetration occurs via transcellular, intercellular (paracellular), and appendageal routes, but the SC often limits transdermal absorption. This barrier calls for the application of permeation enhancers, vesicles, microneedles, heat, and other physical methods to enhance drug delivery (49, 54, 55, 57-60).

PROBLEMS IN TRANSDERMAL DELIVERY OF MACROMOLECULES

Due to their large molecular structure and hydrophilic properties, macromolecules such as proteins, peptides, vaccines, and polymers have difficulties diffusing across the stratum corneum (SC). There is the resistance of SC to the diffusion of hydrophilic drugs and the stability issues associated with some biopharmaceuticals requiring precaution, among others, which form some of the major challenges facing the development process (5, 49, 50, 53, 57, 58, 60). Novel polymers and microneedles are examples of emerging technologies that try to overcome these hurdles but face formulation, regulatory and clinical challenges. TDDS offer a non-invasive, patient-friendly method for drug delivery that circumvents first-pass metabolism and maintains steady drug levels. However, their efficacy is limited by the protective stratum corneum. While small, lipophilic drugs are successfully used, delivering macromolecules through transdermal systems is still difficult and requires advanced enhancers and devices to safely breach the skin barrier (5, 49, 53-55, 57-62).

MICRONEEDLE TECHNOLOGY: EVOLUTION, CLASSIFICATION, AND SIGNIFICANCE IN DIABETES MANAGEMENT

Transdermal medication delivery has evolved from straightforward patches to intelligent, integrated therapeutic and diagnostic systems thanks to microneedles (MNs). Diabetes has emerged as a major application as research has gradually progressed from early silicon solid needles to polymeric, dissolving, hydrogel-forming, and theranostic platforms. Diabetes medication delivery systems have evolved from traditional insulin injections to sophisticated microneedle systems that respond to glucose (63, 64). Fig. 4. shows syringes, insulin pens, and pumps are examples of traditional methods that have gradually changed to minimally invasive transdermal platforms. Painless insulin delivery, real-time glucose-responsive medication release, and integration with biosensors and artificial intelligence for closed-loop diabetes control are all made possible by recent advancements in microneedle technology. adapted from new developments in transdermal medication delivery systems mediated by microneedles (65).

HISTORICAL DEVELOPMENT AND EMERGENCE

Early transdermal systems focused on the stratum corneum's barrier function, leading to physical enhancement methods like microneedles (MNs) (66). Patented in 1976, MNs became feasible with microfabrication advancements, enabling experimental silicon microneedles in 1998 (5, 67). This spurred

extensive MN research, positioning them as a "third-generation" transdermal delivery system over the last two decades, which has expanded drug delivery options and improved patient comfort (66, 68-70).

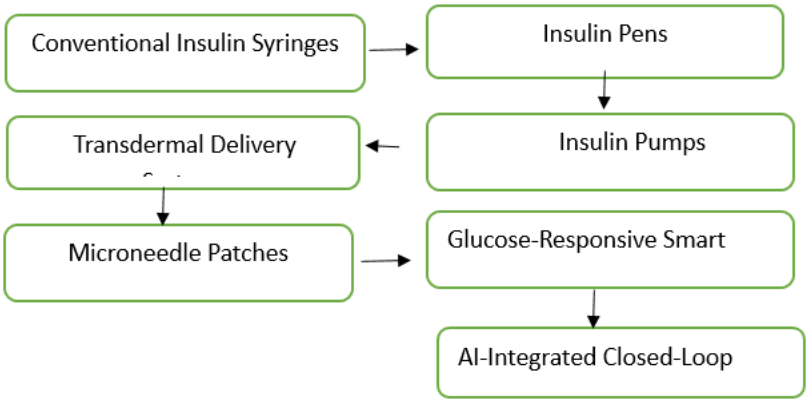

Fig. 4. Evolution of diabetes drug delivery technologies and the emergence of microneedle-based systems *[Adapted from T Liu et al., 2021 (65)]*

DEVELOPMENT OF SYSTEMS BASED ON MICRONEEDLES

Microneedles (MNs) have diversified into types such as solid, coated, dissolving, hollow, hydrogel-forming, and hybrid, utilizing materials like silicon, metals, polymers, and hydrogels (2). Each type serves specific functions: solid MNs "poke and patch," hollow MNs "poke and flow," coated MNs "coat and poke," dissolving MNs "poke and dissolve," and hydrogel-forming MNs "poke and release" for controlled drug delivery (67).Recent innovations include 3D/4D bioinspired MNs, nanoparticle-loaded MNs, and integrated sensing–delivery systems, enhancing personalized healthcare through minimally invasive fluid sampling for biomarker monitoring (5, 71).

RELEVANCE IN THE MANAGEMENT OF DIABETES (CHRONOLOGICAL TREND)

Microneedles (MNs) have evolved from vaccine delivery to role in transdermal insulin delivery and glucose monitoring, showing effectiveness in sustained release (69, 72). Innovations feature glucose biosensing patches for syringe-free, responsive insulin delivery in diabetic models and a closed-loop system utilizing mesoporous microneedles with iontophoresis for real-time monitoring and delivery (73). These advancements emphasize MNs' potential for painless, self-managed glycemic control in diabetes management (2, 5, 74, 75).

MICRONEEDLE DRUG DELIVERY SYSTEMS

Microneedles (MNs) are tiny needles (about 0.1–1 mm) that puncture the stratum corneum to transport medications into the epidermis or dermis with little discomfort (67). This allows for the administration of molecules that are unable to passively pass through the skin barrier (76).They are currently being researched for vaccines, biologics, small compounds, and cosmetics; the first items on the market have undergone many clinical trials (77). Overview of Drug Delivery Systems Using Microneedles the epidermal barrier limits transdermal distribution, which circumvents first-pass metabolism (68). MNs are a physical augmentation technique that produces microchannels without causing any discomfort's can be self-applied as patches and facilitate theragnostic (drug delivery + sample) (78).

MAIN MICRONEEDLE TYPES AND KEY FEATURES

MNs are arrays of tiny needles (10–1000 μm) that are shaped like cones or pyramids and are usually applied on a patch (67). They are intended to puncture only the stratum corneum and higher layers of skin (72). All varieties function by creating microchannels through which medications are subsequently transported via diffusion, matrix dissolution, or pressure-driven flow through a hollow lumen (79).The table IV provides a comprehensive overview of the five primary microneedle categories—solid, coated, hollow, dissolving, and hydrogel-forming—by contrasting their structural delivery principles and typical fabrication materialsIt highlights the crucial medical compromises involved, as it moves from strict protocols using

multi-step devices such as solid needles to patient-compliant polymer-based matrix systems with the ability to swell or dissolve without creating any dangerous sharps waste (67).

Table IV. Structural classification, delivery mechanisms, material compositions, and comparative advantages/limitations of the major microneedle types utilized in biomedical applications

Type	Delivery principle	Typical materials	Key pros / cons	References
Solid	Poke-and-patch: create pores, drug applied separately	Silicon, metals, some polymers	Simple, strong; needs 2-step application	(67, 68, 72, 76, 78, 80, 81)
Coated	Drug coated on solid MN, dissolves in skin	Metals, silicon, ceramics	Single step, rapid release; low drug load	(2, 67, 72, 76, 78, 82)
Hollow	Lumen for liquid infusion	Silicon, metals, polymers	Larger volumes, controlled infusion; complex, costly	(67, 72, 78-80, 82)
Dissolving	Matrix dissolves, releasing drug	Water-soluble polymers, carbohydrates	High loading, no sharps waste; limited dose/tip strength	(2, 67, 68, 72, 77, 78, 82-84)
Hydrogel-forming	Swellable network creates channels	Crosslinked polymers	Sustained release, multifunctional; slower onset, removal needed	(2, 67, 68, 72, 77, 78)

MATERIALS USED IN THE PRODUCTION OF MICRONEEDLES

Metals: Solid, coated, and hollow MNs are made of metals such nickel, titanium, and stainless steel. They have exact geometries and high mechanical strength, making them ideal for deep or repetitive insertion (72). However, they can be fragile or corrosive, and if they break, they could cause discomfort or inflammation (68).

Silicon: Due to its suitability with microelectronics processes (photolithography, etching, DRIE), silicon was one of the first MN materials (67). Although it is fragile and prone to fracture, it enables intricate 3D structures and hollow forms; porous silicon can increase biocompatibility (72).

Polymers: Because they are tunable, biocompatible, frequently biodegradable, and appropriate for dissolving and hydrogel-forming MNs, polymers (such as PLA/PLGA, PVP, PVA, polycarbonate, acrylates, and hydrogels) have dominated current MN research (77). Polymeric MNs are appealing for scalable casting and micro molding and can be tuned for mechanical strength, drug loading, and dissolving rate (77, 85).

MATERIALS BASED ON CARBOHYDRATES

For biodegradable MNs, natural polysaccharides and sugars such as hyaluronic acid, chitin, chitosan, cellulose, starch, dextran, maltose, trehalose, chondroitin sulfate, alginate, xanthan gum, and pullulan are frequently utilized (86).They exhibit good biocompatibility for dissolving MNs and natural-polymer MN arrays, and they offer an abundance of functional groups for adjusting mechanics and drug release(86).Formulations high in carbohydrates, such as carboxymethylcellulose + trehalose + HA, can produce pseudoplastic solutions that are appropriate for micro molding and dissolving MN patches (77, 83, 84, 86, 87).

FABRICATION TECHNIQUES

Micro molding is an efficient technique for producing microstructure molds for dissolving polymer microneedles (MNs) (84). It utilizes high-aspect-ratio molds created from master structures via photolithography, laser machining, or 3D printing, enabling mass production (67). Key methods include lithography for silicon MNs and laser cutting for material patterning, which support 3D complexities (76). Additionally, 3D printing facilitates the creation of custom MNs with high precision and integration with microfluidics (79, 81, 88, 89).

MECHANISM OF DRUG DELIVERY THROUGH MICRONEEDLES

Transdermal microneedles (MNs) were created to get beyond the stratum corneum's robust barrier while maintaining a less invasive and frequently painless mode of delivery (90). Compared to oral methods,

they improve bioavailability and prevent first-pass metabolism by enabling the local or systemic distribution of small and macromolecules (5, 91). Microneedles (MNs) are effective in delivering drugs through the stratum corneum into the viable epidermis, reducing pain and bleeding (92, 93). Factors such as tip radius and application force affect penetration efficiency, which can be enhanced through active forces (94, 95). MNs create microchannels that improve drug transport, significantly increasing permeation rates, especially when used with iontophoresis. The pharmacokinetic profiles vary with MN characteristics, influencing drug distribution and systemic exposure. Dissolving MNs enable prolonged drug delivery and better therapeutic outcomes in chronic conditions, while minimizing variability and toxicity (93, 95, 96). Fig.5 Schematic overview of microneedle (MN) methods for enhanced transdermal drug delivery includes: (A) Solid MNs creating transient micropores; (B) Drug-coated solid MNs for immediate delivery; (C) Drug combined with dissolvable polymeric/carbohydrate MNs that dissolve in skin fluids; (D) Hollow MNs for active liquid drug infusion; (E) Hydrogel-forming MNs that absorb interstitial fluid, improving drug diffusion from lyophilized wares (97).

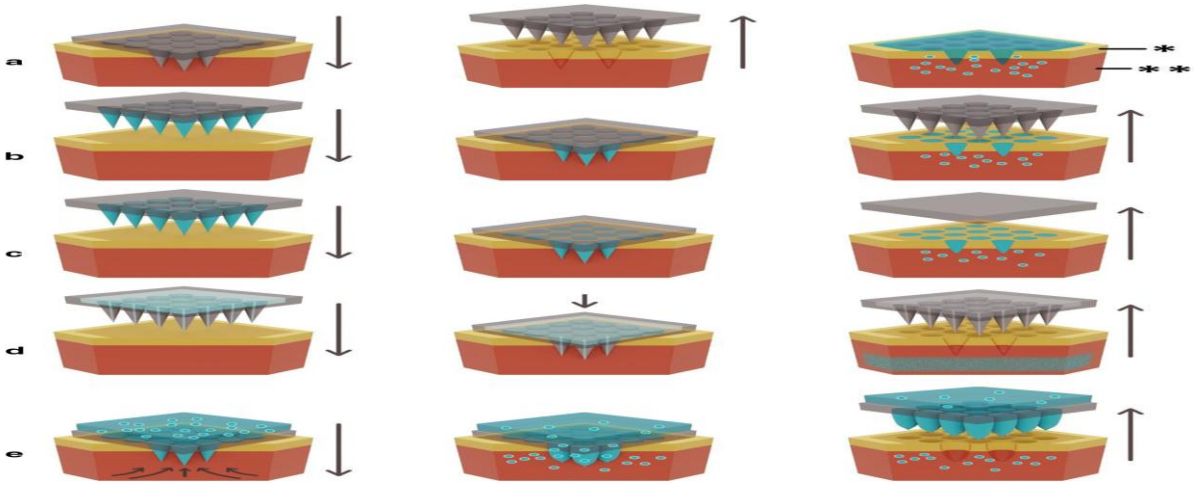

Fig.5. Microneedle Mediated Transdermal Delivery of Protein, Peptide and Antibody Based Therapeutics: Current Status and Future Considerations *[Adapted from M Kirkby et al., 2020 (97)]*

GLUCOSE-RESPONSIVE AND SMART MICRONEEDLE SYSTEMS FOR CLOSED-LOOP DIABETES MANAGEMENT

Glucose-responsive smart MN systems are state-of-the-art devices that mimic the pancreas by sensing blood glucose levels and secreting insulin accordingly (7, 98). These less invasive approaches reduce the risk of hypoglycemia and improve patient compliance and provide a painless alternative to traditional insulin injection (99, 100). Several methods have been formulated for controlled release of insulin by glucose depending on its nature that may include polymeric materials using phenylboronic acid (PBA) and enzymatic system using glucose oxidase (GOx) (101). GOx microneedles trigger the release of insulin because of pH changes due to glucose concentrations, but glucose-responsive hydrogels/copolymers can manage the process by using reversible glucose responsive bonds (102). The recent progress has yielded closed-loop devices comprising wearable bioelectronics, iontophoretic devices, and insulin delivery using microneedles and biosensor systems (6, 103). Even though there are some unresolved concerns regarding the longevity, biocompatibility, and clinical application of such devices, they have demonstrated significant potential in offering personalized treatment for diabetes. In the near future, fully automated artificial pancreases may be constructed based on biosensing technology and artificial intelligence (6, 100, 103, 104).

The application of insulin and other anti-diabetic agents using microneedles (MNs) would allow for transdermal administration that is not associated with any pain. Besides being used to sense blood glucose levels, MNs will be able to create closed-loop systems. They hope that they will enhance patient compliance, eliminate pain and infections associated with injections, and minimize complications such as diabetes-induced fibrosis (105, 106).

MICRONEEDLE-BASED INSULIN ADMINISTRATION

One of the most widely used applications for microneedles for diabetes is insulin delivery through various patch mechanisms like hydrogel, solid, coated, hollow, dissolving, and glucose-sensitive patches (107). Another application for non-insulin antidiabetics is MN hydrogels, which are typically administered using iontophoresis, along with metformin and pioglitazone as well (108).

Insulin-loaded microneedles (MNs) are being developed as potential alternatives to subcutaneous delivery, providing superior pharmacokinetic profiles and patient tolerance (105). There are some clinical studies confirming the efficiency of various types of MNs, including solid, coated, hollow, dissolving, and hydrogel-forming MNs (106). Particularly, dissolving MNs with PVA/sucrose tips have shown insulin release and hypoglycemic effects similar to hypodermic injections in diabetic mice (107). Hollow and MEMS-based MNs improve glycemic control in animal studies. Innovative systems such as glucose-responsive and thermosensitive (109). MNs allow for self-regulated insulin delivery, demonstrating efficacy in rodents and mini-pigs. Furthermore, smartphone-enabled iontophoresis-MN patches enhance insulin delivery and hypoglycemia management (110). Future advancements may involve next-generation insulins, like insulin aspart or degludec, for better postprandial glucose control and flexible dosing (111).

PRECLINICAL AND CLINICAL EVALUATION OF MICRONEEDLE-BASED DIABETES THERAPIES

In order to replace or enhance traditional subcutaneous (SC) insulin injections, research has progressed from bench (in vitro) to animal to human. With comparatively few human trials, the majority of research is still preclinical, particularly for oral, buccal, and transdermal nanoparticle systems (112).

Preclinical and clinical studies have demonstrated significant progress in the development of non-invasive insulin delivery systems, including oral, transdermal, buccal, inhaled, and microneedle-based formulations (113). In vitro investigations have shown enhanced insulin permeation and controlled drug release through the use of nanoparticles, iontophoresis, ionic liquids, and polymeric carriers (114, 115). Animal studies further confirmed the ability of these systems to achieve prolonged glucose reduction, sustained insulin release, and improved glycemic control with minimal toxicity (116, 117). Clinical trials have reported promising outcomes for inhaled insulin, buccal formulations, microneedle-assisted delivery, and long-acting insulin analogs, with some approaches providing faster absorption and improved postprandial glucose control compared with conventional subcutaneous administration (118, 119). Although non-invasive routes of administration offer the advantage of improved patient compliance, reduced pain, and sustained regulation of blood glucose, problems associated with bioavailability, dosage, device efficiency, and safety persist based on studies on pharmacodynamics and pharmacokinetics (116, 120, 121). Taking everything into account, the findings have proven that such insulin delivery techniques are promising candidates to become effective alternatives to traditional insulin injections; however, more clinical proof is needed for their practical use (122-124).

MEDICAL AND WEARABLE DEVICE SAFETY AND TOXICOLOGICAL CONSIDERATIONS

Simple tests for irritant effects are now obsolete as more advanced methodologies are used, focusing on sustained biocompatibility, understanding mechanism, and highly sophisticated in vitro tests, in biomaterial and medical device safety assessment (125, 126).

TRANSITION TO NON-ANIMAL AND IN VITRO TESTING

- Irritation Testing: Reconstructed human epidermis (RhE) models, such as Epidermis and Skin Ethic, have virtually supplanted the traditional rabbit Draize testing. With an astounding ~98% inter-laboratory agreement for identifying low-level irritants in device extracts, they are currently the recommended techniques under ISO 10993-23:2021(127).
- Sensitization: Without the need for animal testing, kinetic tests (like DPRA and Keratino Sens) enable the evaluation of sensitization risks in wearables and adhesives (128).

- Knowledge Gaps: Despite these developments, there is still a dearth of information on the toxicology of carbon-based nanomaterial's (CBNs) and more recent forms of graphene, with only 3.8% of articles addressing this topic. As a result, dangers such as phototoxicity and irritation remain poorly understood (129, 130).

INFECTION CONTROL AND BIOFILM MITIGATION

- The Problem: Rapid bacterial adherence and biofilm formation—typically brought on by Staphylococcus aureus in orthopedic implants—protect germs from the host's immune system and antibiotics, increasing the risk of infection (131).
- Risk variables: The risk of chronic infections is greatly increased by patient-specific variables such as diabetes, smoking, immunosuppression, and renal illness (132).
- Solutions: From basic bactericidal surfaces to sophisticated antibacterial coatings, surface chemical alterations, and immunomodulatory biomaterials intended to strengthen host defenses, prevention has improved. Simultaneously, bioelectronics that are soft and conformable are being created to reduce the irritation and mechanical damage that rigid devices inflict (133, 134).

INDUSTRIAL, COMMERCIAL AND REGULATORY LANDSCAPE OF MICRONEEDLE TECHNOLOGIES

Microneedles used in the delivery of drugs through the skin have to undergo several considerations before commercialization. These include industrial development, market acceptability, and the regulation process. Regulatory bodies such as the FDA and EMA consider microneedle products to be combination drug devices and need to undertake comprehensive safety, effectiveness, biocompatibility, and long-term performance testing. Several products incorporating the use of microneedles have been commercialized recently in areas such as transdermal drugs, cosmetic use, and vaccine administration, thus proving the clinical viability of microneedle technology. The growing trend of wearables, smart drug delivery systems, microneedles, and technological innovations in manufacturing processes can be attributed to a greater number of patents and investments in the sector. As a result of industrial research and development activities, combined with new regulation, microneedles are advancing from laboratory tests to widespread clinical and therapeutic applications.

MODERN BIOCOMPATIBILITY STANDARDS & TESTING VARIANCES

- Critical Measurements: Bioinertness, bioactivity, and biostability of materials are highly affected by the mechanical property and surface chemistry of a material (125).
- Challenges: In spite of ISO 10993's demand of testing hemocompatibility and cytotoxicity, the present cytotoxicity tests have limitations since the level of serum and exposure period are inconsistent (135).
- Novel Materials: Cytotoxicity data for advanced materials like graphene or MXenes differ depending upon their flake size, dosages, and even material contamination (136, 137).

LONG-TERM SAFETY AND RISK FRAMEWORKS

- Long-term surveillance: For studying the long-term safety profile, analysis of degradation, chronic toxicity, and immune reactions through life (e.g., fibrosis and oxidative stress) is needed (126, 138).
- Case Studies: Studies on the use of zinc implants and recombinant collagen-based devices have demonstrated safety in terms of degradation and biosafety (139).
- Even though the silicon dioxide nanoparticles caused permanent tissue changes, patients regained their health eventually.
- Future Outlook: The development of novel anti-fibrosis bonding materials, along with advances in the interaction of implants with tissues, is improving the safety and longevity of implantable medical devices (140, 141).

CHALLENGES AND LIMITATIONS IN CLINICAL TRANSLATION OF MICRONEEDLE TECHNOLOGIES

Though microneedle-based drugs delivery has witnessed significant developments in the treatment of diabetes, yet there are several factors that pose a challenge in the implementation of these techniques for clinical purposes. Large scale human clinical trials have not been conducted till date; therefore, there is no practical implementation of the promising preclinical outcomes in clinical practices. Most of the available data has been based on in vitro and animal testing. Technical challenges include a lower drug loading capacity of current MN devices, maintaining the stability of the insulin and obtaining uniform drug delivery regardless of the skin characteristics and the depth of the insertion of MNs.

The prohibitive cost and complicated nature of large-scale production processes, along with the stringent Good Manufacturing Practices (GMPs) that must be followed, hinder commercialization. In addition, as MNs fall into the category of combination drug-device products, there is a need for extensive evaluation of safety, efficacy, biocompatibility, sterility, and longevity, which makes regulatory approval difficult. Moreover, market acceptance is complicated by economic challenges, including the rise in cost of production and lack of payment systems. In addition, there are emerging problems with the reliability of the device, security of data, and its interoperability when combining microneedles with wearable devices, artificial intelligence, and CGM. The successful implementation of microneedle technology in the practice of diabetes treatment depends on addressing these scientific, regulatory, manufacturing, and economic barriers through interdisciplinary collaboration.

CLOSING THE GAP BETWEEN BENCH AND BEDSIDE

MN-based drug delivery devices have demonstrated immense promise in various preclinical animal experiments and laboratory tests, yet there remain several challenges in order for the technologies to become a part of diabetes therapy. A combination of progress in pharmaceutical production, regulatory science, clinical trial, economic analysis, and gadgets development is vital in closing the gap between bench and bedside.

METHODS FOR QUICKENING MICRONEEDLE TECHNOLOGY'S CLINICAL TRANSLATION

The successful transfer of microneedle technology from lab research to standard clinical practice may be aided by a number of useful tactics.

PUBLIC-PRIVATE PARTNERSHIPS

There will be a boost in product development and commercialization through effective collaboration between academics, government agencies, pharmaceutical firms, medical devices manufacturers, hospitals, and regulators. Besides reducing the cost risks associated with developing new combination products, public-private partnerships help in sharing resources, manufacturing at large scales, conducting multicenter trials, and faster regulatory communication.

STANDARD TESTING PROTOCOLS FOR MICRONEEDLES

The absence of any standardized experimental procedures is one of the main barriers hindering microneedle studies at present. The development of global standardized test procedures will be very helpful in evaluating such parameters of microneedles as mechanical strength, insertability, loading capacity, dissolution properties, sterility, stability, skin irritation potential, biocompatibility, and safety.

CLINICAL TRIALS METHODOLOGICAL DEVELOPMENT

The development of clinical trials in a systematic and planned fashion is important for clinical translation. Safety, skin tolerability, pharmacokinetics, and device application in healthy subjects or small cohorts of patients should be the primary objectives of the first phase of trials. The optimization of preliminary glycemic data, insulin secretion properties, and the dosing regimen should all take place during

phase II studies. Microneedle devices must then be assessed against standard insulin pen devices or insulin pumps in large multi-center Phase III randomized controlled trials using clinically meaningful endpoints like reduction of HbA1c levels, hypoglycemia incidences, patient-reported outcomes, adherence to therapy, quality of life, and safety.

QUALITY BY DESIGN AND MANUFACTURE STANDARDIZATION

In order to ensure consistent quality from batch to batch, large-scale manufacturing must employ an automated manufacturing system along with Quality by Design and Process Analytical Technology. In order to facilitate regulatory acceptance and mass manufacturing, there is a need for international standards with regard to the following factors.

PHARMACOECONOMIC EVALUATION

It is recommended that drug development be coupled with comprehensive pharmacoeconomic evaluation in order to determine if improvements in patient adherence, decreased incidence of complications due to diabetes, reduced hospital admissions, and improved QALYs justify increased expenses associated with manufacturing the drug. To receive payment from health insurance organizations, it will be crucial to prove cost-effectiveness.

COOPERATION AMONG VARIOUS DISCIPLINES IN THE PROCESS OF REGULATING

The cooperation of researchers, manufacturers, doctors, regulators, and digital health experts at an early stage when it comes to the safety and quality of a product helps to facilitate the process of regulatory approval. This is especially important for products that use artificial intelligence technology and have a glucose response system in their structure. The clinical translation of microneedle drugs for diabetes treatment should be conducted systematically.

OVERCOMING PRODUCTION CHALLENGES, MAINTAINING QUALITY, AND TRANSLATION OF REGULATORY REQUISITES

It is important to overcome considerable difficulties in terms of production, quality, and regulation to ensure the translation of the MN technique into clinics. At the moment, laboratory-based techniques such as micromolding, photolithography, laser micromachining, and three-dimensional (3D) printing are used to produce most MN patches. Even though the methods are precise, they remain expensive and hard to scale up for production purposes. It is important to focus in the future on developing scalable and automated technologies to follow GMP standards with consistent quality. One more important requirement that needs to be fulfilled for regulatory approval is consistency from batch to batch. The release of insulin and the effectiveness of the treatment might be influenced by any modifications in microneedle geometry, drug loading, polymer formulation, and physical properties. Utilizing QbD and PAT technologies along with standardized manufacturing processes might contribute to improving reproducibility.

This is supported by the availability of clinical devices such as the MicronJet® hollow microneedle for drug delivery within the dermis layer and the MicroHyala® dissolving microneedle patch, although no product based on this technique has been approved for treating diabetes. Nevertheless, favorable results from flu vaccine microneedle studies indicate the safety and tolerability of the vaccine. Despite this, MN devices that are intended to treat diabetes pose unique regulatory challenges since they incorporate drug delivery with wearable technology, CGM, and AI technologies. Before their clinical application, an assessment of safety, quality, performance, and efficacy of the device is warranted.

USABILITY STUDIES, HUMAN FACTORS, AND PATIENT ACCEPTABILITY

Clinical success cannot be guaranteed merely through technical success. Acceptability by the patients plays a significant role in adoption in the long run, particularly in diabetes where continuous therapy is required. Usability studies have been performed relatively rarely in spite of the nature of

microneedle patches which minimize pain and needle phobia. These factors, including simple application procedure, accurate application, patient satisfaction, treatment compliance, skin compatibility, and comfort on repeat use, among others, should all be evaluated in further research. In order to ensure safety and efficiency during home use, human-factor engineering research must take into account packaging issues, patch application process, method of disposal, and patient education requirements.

ECONOMIC EFFICIENCY IN THE CONTEXT OF TRADITIONAL INSULIN THERAPY

The application of the microneedle technology in medical practice will largely depend on its economic efficiency. The possible benefits that can result from such technology in terms of improved compliance and less complications may prove more valuable than the increased costs for manufacturing as opposed to traditional insulin therapies. Future pharmacoeconomic studies must rely on cost-utility, cost-benefit, and cost-effectiveness studies to compare microneedle technologies with traditional methods based on factors such as hospital admissions, costs, and QALYs. Reimbursement from insurance agencies will be contingent on favorable economic results.

MULTIDISCIPLINARY COLLABORATION AND CLINICAL TRANSLATION

Scientists from pharmaceutical industries, biomedical engineers, physicians, regulatory agencies, manufacturers and health practitioners need to collaborate in order for the microneedle technologies to be translated to the clinical practice. Multicenter randomized trials involving various types of patients need to be carried out in order to ensure safety, effectiveness, device reliability and patient reported outcomes in the long run. Standardized guidelines for combined drug delivery device products incorporating biosensors, artificial intelligence and continuous glucose monitoring technologies need to be set up by regulatory authorities.

FUTURE PERSPECTIVES OF MICRONEEDLE-BASED DIABETES MANAGEMENT

The future of microneedles in the treatment of diabetes relies not only on technological advances but also on overcoming the barriers that currently hinder the widespread implementation of the technique in clinical practice. Multicenter large-scale randomized trials involving patients of different demographics need to be conducted in the future in order to assess the safety, effectiveness, acceptability, and cost-effectiveness of the microneedles versus the conventional form of insulin delivery.

Improvements in methods that increase drug loadability without compromising the stability and bioactivity of insulin must also not be overlooked. Increased dose levels, prolonged duration of release, as well as increased mechanical strength can all be realized without compromising patient comfort due to advancements in biodegradable polymers, nanocomposites, and hydrogel structures.

Standardization of manufacturing technology is equally important. In order to ensure consistent quality of products while reducing manufacturing costs, automation of micro-fabrication technologies, scalable 3D printing, and continuous manufacturing methods need improvement. This will be aided by international standardization of mechanical testing procedures, sterilization techniques, and quality control standards.

In the future, guidelines for smart microneedle combination products which make use of wearable technology, artificial intelligence, and biosensors need to be established. Early collaboration would allow for faster development and faster approval procedures among academia, pharmaceutical firms, regulatory agencies, and health care facilities.

The most promising future trends may be associated with the use of microneedles in conjunction with cloud computing, AI technologies, Internet of Medical Things (IoMT) systems, and continuous glucose monitoring devices. Such totally integrated closed-loop systems will help to avoid hypoglycemia and optimize long-term glucose regulation by monitoring blood glucose, forecasting glycemic fluctuations, and adjusting insulin dose accordingly.

Future research would need to evaluate patient satisfaction, quality of life, compliance, usability among children and elderly individuals, as well as the advantages of the technology from an economic perspective. Universal coverage and application would require demonstrating increased patient satisfaction together with reduced hospital admissions and costs for medical care.

In all, the interlinked development of the above-mentioned disciplines including materials science, pharmaceutical sciences, biomedical engineering, regulatory sciences, clinical medicine, and digital health would be essential for incorporating microneedles into routine diabetes treatment. With the above-mentioned challenges addressed, microneedle technologies would advance faster from being an intriguing experimental tool to becoming a widely available therapy for personalized diabetes care.

RESULTS

According to the PRISMA guideline, out of the 1,300 citations identified through literature searching, only 90 quality articles published from 2015 to 2026 were selected. The findings revealed that the use of MNs as transdermal drug delivery devices effectively perforate the skin's stratum corneum layer, delivering drugs to the epidermis and dermis layers without causing pain and bleeding associated with conventional injection therapy. The five categories of MNs include solid poke and patch arrays, coated needles, hollow MNs, polymer dissolving MNs, and hydrogel forming MNs. Organic polymers and flexible biocompatible substrates have taken the place of hard surfaces during the evolution of materials due to improved customization possibilities and enhanced safety. Importantly, platforms utilizing glucose oxidase or phenylboronic acid as mechanisms for controlling the release of insulin based on the concentration of glucose in the bloodstream have become prevalent. Research shows that such systems are capable of producing similar results to subcutaneous injections in lowering glucose concentrations.

Treatment using the above-discussed conventional therapies, including lifelong insulin therapy for type 1 diabetes mellitus (DM), metformin, DPP-4 inhibitor, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors for type 2 DM, or GLP-1 receptor agonist therapy, which protects against cardiopathies, is the focus of standard medical algorithms used in treating diabetes mellitus. Nonetheless, these treatment approaches have been constrained by the associated pain caused by injections, poor compliance, and continuous risks of hypoglycemic complications. The development of microneedles provides a solution to these traditional constraints because it provides a painless alternative. Going beyond the limitations of traditional transdermal patches and developing an intelligent system that uses glucose-responsive PBA or GOx matrix to emulate natural functioning of the pancreas in order to provide controlled permeation of the drug through the delivery system according to metabolic demand, is the real paradigm shift clinically. There are several challenges in terms of technology involved in developing these devices for mass scale use by humans in the form of commercial products. These challenges include different standard procedures followed during biocompatibility analysis (for example ISO 10993 cytotoxicity test) due to different levels of serum concentrations and exposure times. Moreover, due to different sizes of flakes in material used along with manufacturing defects, addition of latest materials such as carbon-based nanomaterials, graphene, and MXenes poses a risk of toxicity, including irritation and phototoxicity. This is because the constant needling of the skin can lead to oxidative stress, tissue fibrosis, sustained local immune reactions, or even biofilm production in the case of significant bacterial populations, particularly those of staphylococcal origin. In addition, the technological aspect that poses a challenge to mass manufacture via industry-standard techniques of micro-molding and 3D printing is the limitation posed by size packaging.

CONCLUSION

Microneedle technology is an innovative development in the field of transdermal drug delivery systems that have brought diabetes management closer to automated, customized, and pain-free treatment. By making use of biocompatible substances and the glucose-responsive nature of microneedles, these intelligent needles can bypass the skin barrier, causing neither pain nor generating any hazardous waste productsThe future innovations will incorporate these patches with AI and CGM technologies in order to

create automated artificial pancreases. However, standardization of international regulations on safety and efficiency, capacity increase for delivering biologics, and conducting adequate clinical trials are essential for commercial success.

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Authors' contribution:

AN & SS Conceptualized and structured the review; SSK Analyzed recent literature; SA Collected references and critically editing; MJ & ZB Literature review and language editing.

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