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Review Article

Microneedle Based Insulin Transdermal Drug Delivery Systems (Tdds)

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ABSTRACT

Diabetes mellitus has a worldwide cost, and subcutaneous insulin injections are associated with pains, lack of compliance, infections, and needle phobia in patients with type 1 diabetes that require numerous insulin injections every day. Transdermal drug delivery systems (TDDS) are based on microneedle (MN) to traumatize stratum corneum to insulin delivery into viable epidermis/dermis with minimal invasiveness and painlessness. This review describes MN principles, skin structure, and TDDS and its superiority over oral routes (first pass) and hypodermics. Discussing solid (poke-and-patch), hollow (infusion), coated, dissolving (e.g., PVP/CMC) and hydrogel-forming MNs, it indicates such biocompatible and mechanically strong materials as stainless steel, titanium, PLGA, and ceramics. The preclinical diabetic models display rapid hypoglycemia, high bioavailability (>90%), and secondary release like injections. Challenges related to scalability, high-dose requirements, cost, and regulatory approval persist. Advancements in 3D printing, micro-molding, and smart glucose-responsive microneedles integrated with sensors enable automated glucose control, reducing fluctuations and healthcare costs.MN-TDDS represents a patient-centric shift in diabetes management, improving adherence and treatment outcomes.

INTRODUCTION

The chronic illness known as diabetes mellitus (DM) alters how the body uses sugar. This occurs because of either insufficient insulin production or improper insulin utilization. If a diabetic's blood sugar levels remain too high, they may develop severe health issues such as heart disease, blindness, strokes, or even death. Type 1 and type 2 DM are the two primary varieties. About 5–10% of people are affected by type 2, which is the most prevalent [1]. Microneedles (MNs) were first used as a new way to give medicine in 1998 [2]. In hospitals, drugs are often given through IV injections, muscle shots, under the skin, or on the skin. IV injections work best because they deliver medicine directly into the blood, but they can hurt, carry a risk of infection, and need a vein to work.

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Muscle shots are used for quick delivery of certain medicines, like painkillers, but they also have similar issues [2]. For people with type 1 diabetes, insulin is the best way to control blood sugar. But insulin doesn't work well when taken by mouth because it breaks down in the stomach and liver. So, it's usually given under the skin with a needle. This method can be uncomfortable and painful, making it hard for people to follow the treatment regularly [3]. Insulin injections should be administered to diabetic’s multiple times daily. Since they have to modify the dosage according to their blood sugar levels, this calls for training and cautious supervision. Frequent injections can lead to infections, skin problems, or nerve damage. To help with these problems, scientists have looked into other ways to give insulin without using needles. These include oral, inhaled, nasal, and through the skin [4]. Drug delivery systems (DDSs) are constructed to target and release the right amount of medication to specific target areas while maintaining the best drug concentrations. Current research in DDS focuses on liposomes, nanoparticles, implants, microencapsulation, microneedle transdermal drug delivery, and polymers. This approach allows for easy discontinuation of the medication in cases of toxicity. It ensures continuous drug release and may reduce side effects. Patients find microneedle transdermal patches a convenient way to take medication because they are painless and can be used on their own. Due to the physicochemical properties of the medicine, traditional drug delivery methods, like oral and injection routes, often have limitations [5]. For instance, oral administration is tied to significant hepatic breakdown, largely reducing its systemic absorption. Injections are intrusive and usually uncomfortable. They can also create needle anxiety in patients, especially children. Additionally, injections often require administration by qualified professionals. In contrast, microneedles (MNs) enable active ingredients to bypass the skin's outer defensive layer and penetrate into deeper skin layers for enhanced efficacy [6].

2 Fundamentals Of Transdermal Drug Delivery

2.1 Cutaneous structure & routes of percutaneous drug transport

We must first describe the intricate structure of the skin and the various drug uptake pathways to comprehend the fundamental pathways of active ingredient permeation cutaneously. "The integumentary system is the most extensive organ, encompassing a surface area of about 1.5–2.0 square meters and is vital for protecting the body from environmental influences. There exist predominantly three layers:

1. Epidermis

2. Dermis

3. The outermost layer

The entire body's exterior is covered in a stratified, self-renewing squamous epithelium called the epidermis. The two primary components of the epidermis are cornified keratinocytes, and spinous layer. The clear layer, granular layer, spiny layer, and basal layer of the epidermis are the four separate layers that make up the viable epidermis. A barrier called the cornified layer limits the flow of chemicals both inward and outward [7].

2.2. Transdermal drug delivery system:

When medications are administered through the skin, usually for generalized impact, this is referred to as TDD or skin patches. It is now widely accepted in medical practice. Over twenty transdermal drugs have been sanctioned by the

FDA. The advantages of these drugs include self-administration, easy elimination, controlled and prolonged drug delivery, and prevention of gastrointestinal and hepatic metabolism problems [8]. These dosage forms are made to deliver a therapeutically exact and effective amount of drug through a patient's skin and into their bloodstream. For transdermal drug delivery systems to work well, the drugs should be able to easily get through the skin and to the target area. The transdermal drug delivery system makes it easier for patients to follow their treatment plan. An effective and minimally invasive way to deliver insulin is through a transdermal delivery system that moves the insulin through the skin barrier. The Altea Therapeutics PassPort™ System was the first product that lets you give insulin through a patch on your skin without having to cut it open. It has a patch for the reservoir and an applicator [6].

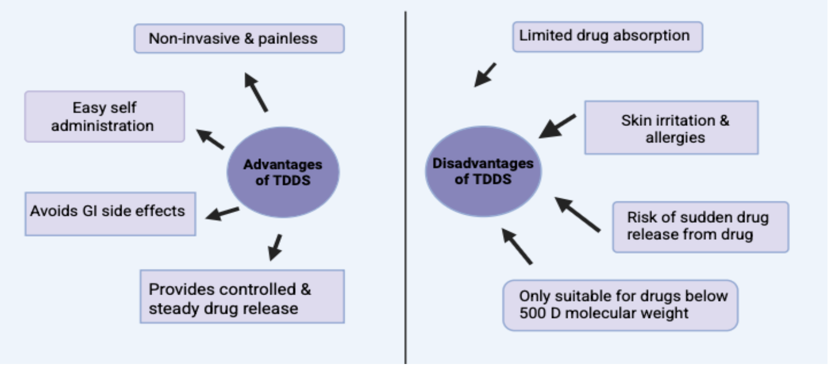

Fig 1. Advantages and Disadvantages of TDDS [9]

3.MICRONEEDLE (MN'S)

A new method of transdermal administration of macromolecular biologics, including as proteins, peptides, and genes, has been made possible by microneedle (MN) technology. Multiple micro-scaled needles with heights ranging from 25 to 2000 μm make up MN arrays. MNs can deliver drugs to the skin's epidermis and dermis by painlessly penetrating SC. Inhibiting long-term skin damage, MN-induced micro-channels are momentarily exposed for drug transport and recovered shortly after MN removal [10].

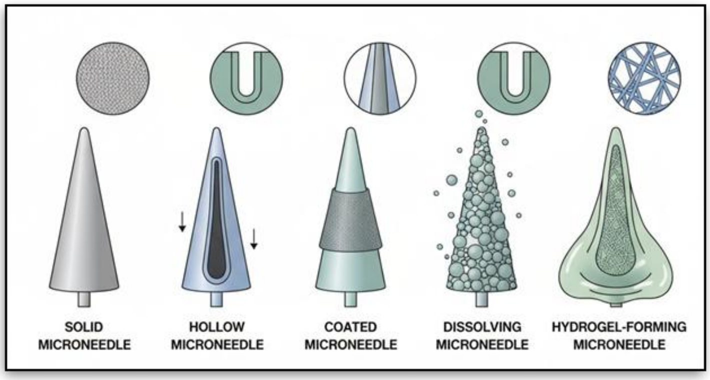

Fig 2. Types of Microneedles

3.1. Solid Microneedles: - Solid MNs for skin pretreatment are composed of silicon or metal and don't contain any drugs. Another name for the solid MN- assisted transdermal administration is the "poke with patch" approach. To create micro-channels on the skin for the medicine to diffuse through, solid microneedles with a pointed shape can be used to disrupt the protective barrier. The skin is punctured by the microneedles, and the capillaries absorb the medication for systemic effects. In diabetic rats, Prausnitz and colleagues demonstrated MN for the hypoglycemic impact of insulin. After the diabetic rats were given this insulin solution, a set of 105 microneedles was created by laser cutting stainless steel sheet and placed against their skin for four hours [11].

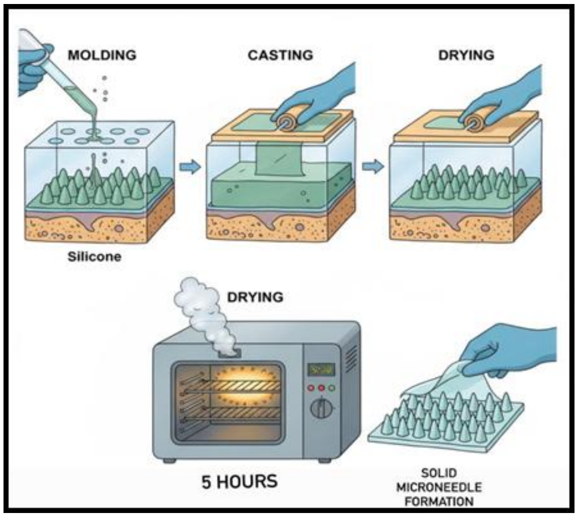

Fig 3. Solid Microneedles

3.2. Hollow Microneedles: - Before being injected intra-dermally, the medication is already poured within the hollow MN's body, which has a hole at the tip, and pressurized using a syringe or micro-pump. Of all MN forms, hollow MNs have the most accurate dosage and the biggest one-time infusion volume; also, the rate can be readily adjusted (similar to injection).

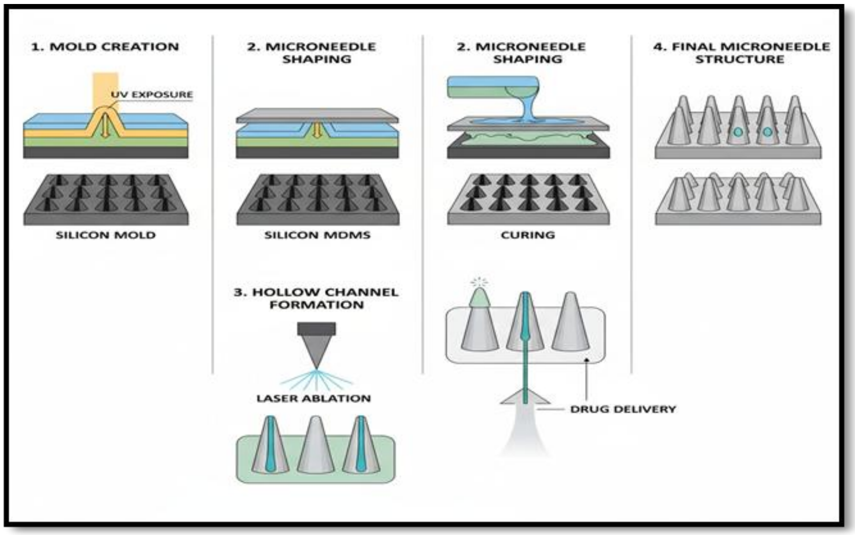

Fig 4. Hollow microneedles

In general, hollow microneedle designs come in two varieties [10]. One has one microneedle that looks like a traditional hypodermic needle. The other is a collection of several hollow microneedles. Compared to hypodermic administration, fluid mixtures allow for more rapid dispersion and cover a wider area [26]

Drawbacks: - It is costly and has a few limitations, including the pinhole of the needle being Skin tissue can easily hinder the improper angle of the needle wall, and the absence of muscle power, which makes the needle break and remain in the skin after the inject [12].

3.3. Coated Microneedles: - In this procedure, a medication formulation is applied to solid MNs, which are then implanted into the skin to dissolve there. Additionally, this medicine is applied to the MN's surface via coating, dipping, or spraying. Water-soluble medications are most suited for this procedure due to their quick absorption, frequent use, and simple dosage management [10].

Advantages: - 1. Unlike uncoated solid MNs, which need a two-step method, it allows for a straightforward one-step application approach.

2. MNs have been functionalized with a diverse range of medicinal compounds, including aqueous-soluble/lipophilic small molecules drugs and biopharmaceuticals.

Drawbacks: -One of the method's drawbacks is the small amount of medicine that can be applied to the tiny MN structure surface. This is because the thick coatings cause MNs to become less sharp, which lowers the effectiveness of skin delivery [13].

3.4. Dissolving Microneedles: - "In contrast to coated systems, degradable polymer microneedles are developed to undergo complete dissolution in the epidermis, which means they do not leave behind any dangerous sharp waste after use". Chen and colleagues created a dissolving microneedle patch comprising the starch and gelatin for transdermal insulin delivery. Degradable micro-needles are commonly fabricated using micro-molding techniques. These molds are filled with polymeric substances, which are cast to form specific, conical configurations. Upon curing within the mold, the acute-tipped needles are combined with pharmaceutical agents. Various biocompatible substances, including carboxymethylcellulose (CMC), chondroitin sulfate, polyvinylpyrrolidone (PVP), PLA copolymers, and fibroin, are utilized to fill the cavity structures to produce the needles [14]. Kim et al. created a different method by utilizing droplet born air blowing to shape the polymer droplets directly to solidify the microneedles. A reduction of glucose level in diabetic mice and enhanced bioavailability validated the effectiveness of insulin delivery.

3.5. Hydrogel-forming Microneedles: - Because the embedded bevel may instantly absorb the skin fluid between cell after applying the MN arrays to the skin, the hydrogel-forming MN process involves the production of the hydrogel from the reservoir-type patch to the capillary circulation beneath the skin tissue. The effectiveness of such MN technology as a tool for enhancing transdermal administration of macromolecular medications, such as insulin, was demonstrated by experiments carried out in Donnelly group. Additionally, they investigated how MN and iontophoresis (ITP) are coupled [15].

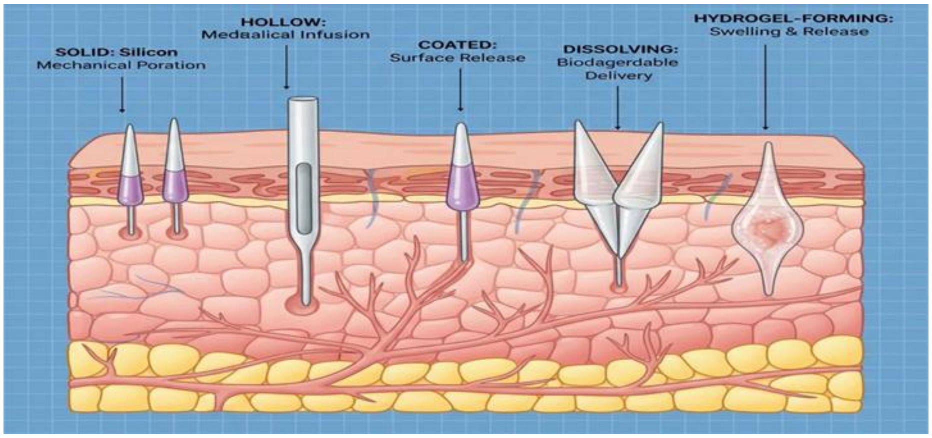

Fig 5. Skin Microneedle Interaction

Table no.1 Microneedle type comparison

Parameter	Solid	Hollow	Coated	Dissolving	Hydrogel Forming
Structure	Non-drug containing solid needles	Hollow core with drug reservoir	Solid needles with drug coating	Biodegradable Matrix with encapsulated drug	Cross linked hydrogel Matrix
Mechanism	Poke and patch approach	Direct injection/ infusion	Rapid coating dissolution	Matrix dissolution/ degradation	Swelling and controlled Diffusion
Drug Loading Capacity	Low (depends on patch)	High (reservoir capacity)	Low medium (coating thickness)	Medium (matrix loading)	Medium high (reservoir+ swelling)
Release Profile	Sustained	Controllable	Rapid	Fast to sustained	Sustained
Applications	Pretreatment, vaccines	Insulin, vaccines, high MW drugs	Delivery, no residue	Vaccines, insulin, protein	High dose drug, biosimilars
Advantages	Simple, reusable, cost, effective	High dose, Precise control	Rapid delivery, no residue	Complete dissolution, no waste	High capacity, controlled release
Disadvantages	Two-step process, slow on set	Complex fabrication, clogging risk	Limited dose, Contamination risk	Incomplete insertion, dissolution delay	Complex removal, higher cost

4.Materials Used In Microneedle Formulation

Generally, the materials to fabricate microneedles must be capable of penetrating the skin. Microneedles consist of a diverse range of materials, such as metal and polymers, and silicon, depending on the patch design or the components. They are made up of thousands of microneedles that are 100–1000 µm long and have a pointed tip.

Depending on the type of microneedle, the drug is either loaded onto the microneedle, coated on the microneedle, or applied to the needle tip. The following lists the characteristics of many of the materials used to make microneedles [16].

Table no.2 Different type of material used in Microneedles

Material type	Example materials	Fabrication methods	Advantages	Limitations	Types of Microneedles
Metals	Stainless steel, titanium, nickel, iron, palladium, nitinol	Laser cutting, etching, electroplating, MEMS	Excellent mechanical strength, reliable skin penetration, reusable	Potential bio-waste, some metals can be toxic, not dissolvable or biodegradable	Solid, hollow, coated
Polymers	PVA, PLGA, HA, PCL, PEGDA, PGA, PLA, PVP, PDMS, Cellulose acetate	Micro molding, casting, embossing, photolitho-graphy, FDM, 3D printing	Tunable solubility/ degradation, biocompatible, ease of drug loading, suitable for dissolving MNs	Lower mechanical strength than ceramics/metals, sometimes costly, potential irritability	Solid, hollow, coated, dissolving
Ceramics	Alumina (Al_2O_3), calcium phosphate ($CaHPO_4 \cdot 2H_2O$), calcium sulfate ($CaSO_4 \cdot 2H_2O$)	Micro molding, lithography, ceramic sintering	High biocompatibility, strong mechanical strength,	Brittleness, risk of fracture in vivo	Solid, hollow

4.1. Metal: - Metal materials possess a high tensile and mechanical strength, hence can penetrate the skin easily. Pharmaceutical applications have long utilized metals, primarily titanium and stainless steel for devices like needles and prostheses. These two materials dominate the landscape of metallic microneedles. Although Ti alloys are more expensive than stainless steel, they have greater mechanical strength [10]. However, stainless steel is the most widely used metal to fabricate microneedles, Silicon is often used to fabricate solid and coated microneedles due to it having the mechanical strength required for implantation in the skin.

Table 2. Advantages and Limitations of different type of material [10].

Stainless steel	Strong, durable, cost-effective, widely available	Possible corrosion, risk of allergic reactions (nickel content in some grades)
Gold	Excellent biocompatibility, corrosion-resistant, stable in biological environments	Very expensive, limited large-scale use
Platinum	High biocompatibility, chemically stable, corrosion-resistant	Extremely costly, difficult for mass production
Titanium	Excellent biocompatibility, strong, lightweight, corrosion-resistant	Expensive, requires specialized equipment for fabrication
Nickel	Strong, relatively cheap, easy to fabricate	Allergenic potential, possible toxicity issues

Iron	Abundant, inexpensive, moderate strength	Corrosion-prone, lower biocompatibility compared to noble metals

4.2. Polymers: - The most common technique used for the fabrication of polymer microneedles is solvent casting. A wide variety of polymers like poly (methyl methacrylate) (PMMA), poly lactic acid (PLA), poly (lactic-co-glycolic acid) (PLGA), poly glycolic acid (PGA), poly (carbonate), cyclic-olefin copolymer, poly (vinylpyrrolidone) (PVP), poly(vinyl alcohol)(PVA), polystyrene(PS), poly (methyl vinyl ether-co maleic anhydride), and SU-8 photoresist have been reported to be used in the preparation of microneedles [18].It is utilized in Microneedles Water-soluble, mechanically robust, and biocompatible polymers will be utilized to fabricate microneedles that are injectable into the skin. Polymers are utilized due to their economic effectiveness, biocompatibility, and biodegradability. Biodegradable polymers are water-insoluble but become soluble when exposed to fluids through chemical reactions.

4.3. Ceramics: - Ceramic is another material used to produce Microneedles. Research has explored the utilization ceramic materials in producing microneedles because they are biocompatible and have sufficient mechanical strength.

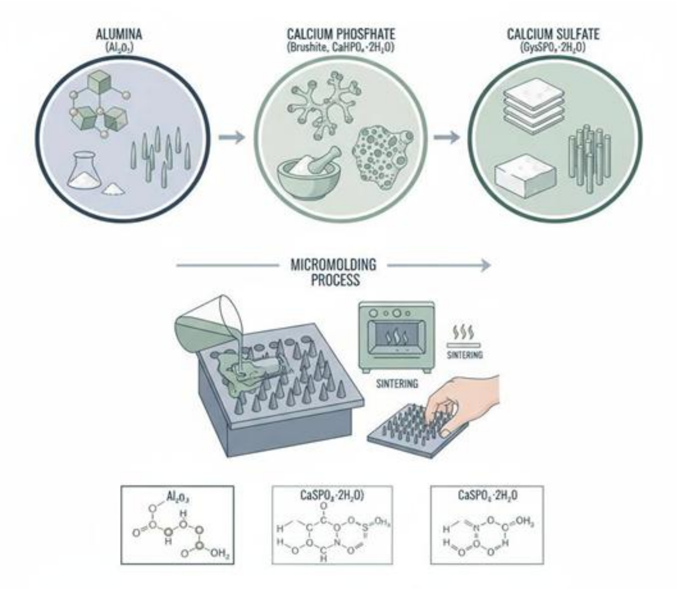

Fig 6. Ceramic Microneedles Production

They are primarily made through a micro-molding process, pouring a ceramic suspension into a mold to form small-scale parts. Micro-molding methods are beneficial to the development of device products as an inexpensive process, due to the possibility of technological saturation [19]

Table 3. Material used in Ceramics [19]

Ceramic Material	Fabrication Method	Advantages/Properties	Notes
Alumina (Al_2O_3)	Micro molding	Remarkable chemical resistance, stability from strong ionic & covalent bonds b/w O and Al atoms	Most extensively utilized ceramic for microneedles

Calcium Sulfate ($CaSO_4 \cdot 2H_2O$, gypsum)	Micro molding	Newer ceramic used in microneedle fabrication	Provides structural support
Calcium Phosphate ($CaHPO_4 \cdot 2H_2O$, brushite)	Micro molding	Biocompatible, resorbable	Newly explored for MN use

5. CHALLENGES: - MNs based insulin delivery system has been extensively examined during the last 20 years. Nevertheless, yet remain certain limitations persisted for clinical implementation and additional commercialization. Under some circumstances, the hormone insulin is thought to be proliferative. Research on microneedles made of biodegradable polymers is necessary [20]. According to some studies, a larger volume of insulin would be needed for the auxiliary pump system to provide continuous insulin delivery and quantitative regulation, while a smaller volume of insulin could sustain microneedles [21]. In diabetic patients, the less frequent infusion of slow-acting insulin would take longer to start working under a typical treatment plan [22]. It may be possible to administer short-acting insulin more frequently with long-term regulated injections, preserving insulin concentration. Despite TDDS's many advantages, it also has drawbacks, including the requirement that medications possess certain physicochemical properties, its restricted applicability for high-dose medications, and the high expense of complex formulations [23].

Fig 7. Applications of microneedle transdermal patch

CONCLUSION:

An increasingly viable alternative to conventional subcutaneous injections for the treatment of diabetes is microneedle-mediated transdermal insulin delivery systems. Comprehensive preclinical and clinical research conducted in the past few years (2019–2025) has shown that microneedles can overcome the limitations of existing insulin therapy by enabling painless application, lowering the risk of needle-related infections, and significantly improving patient compliance. The creation of dissolving, hydrogel, and empty microneedle platforms with improved skin penetration, tunable release patterns, and a greater capacity for insulin loading has been made possible by advancements in manufacturing technologies, including 3D printing, micro-molding, and biodegradable polymer synthesis.

Interestingly, studies show that these systems minimize patient discomfort and tension while offering a quick beginning of insulin action and consistent glycaemic control, often comparable to or better than injections. Recent developments also explore the integration of closed-loop insulin pumps, wearable glucose sensors, and microneedles, paving the way for genuinely automated and customized diabetes treatment. Furthermore, research shows that microneedle patches can lower health care costs by improving adherence and lessening the impact of diabetes-related diseases. The need for large-scale production techniques that offer batch-to-batch uniformity, regulatory certainty, long-term skin safety, and cost effectiveness for low-resource regions are among the remaining obstacles, though. In conclusion, microneedle-based insulin administration has advanced from proof-of-concept to a clinically viable strategy. With additional development, it could revolutionize diabetes treatment by providing patient-friendly, safe, and effective treatment.

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