



## Needle-free Diabetes Management

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### Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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## ABSTRACT

According to this article microneedles are used in automated diabetes therapy systems. By bridging diagnostics and therapeutics, advanced bioengineered systems could constitute a "smart" system for diabetes treatment. Oral, hypodermic, through the nose, and other modes of delivery all have limitations, such as pain and other side effects. Physical entities are transferred through the skin by most glucose monitoring devices and conservative insulin treatments. It is well known that automated diabetes treatment systems involve very multifaceted interdependencies between various entities, and as such require multidisciplinary research programs. To develop an iterative noninvasive bioengineered interface such as microneedles, we need a better understanding of the human skin's molecular architecture and its functioning as a functional unit of the body. Specifically for auto-diabetes therapy, The microneedle interfaces system in this article is examined from the perspective of application-specific requirements.

**Keywords:** Bio-microelectromechanical systems; diabetes therapy; microneedles.

## 1. INTRODUCTION

### 1.1 Diabetes Mellitus and its Treatment

Diabetes Mellitus is a chronic metabolic disorder associated with carbohydrate and protein

metabolism. After a certain period, it is often accompanied by specific microvascular, macrovascular, and neurologic complications. In the year 2014, it is estimated that around 422 million people globally had diabetes compared to 108 million in 1980. It has also been observed

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that the number of diabetic patients among adults has increased by 4.7%–8.5% since 1980, which is thought to have doubled 1980. There is an increase in overweight and obese risk factors as well [1,2].

## 1.2 Diabetes Comes in Two Forms

First diabetes is typically managed using insulin, whereas second diabetes is usually managed using oral hypoglycemic agents. It is a metabolic disorder that is associated with a host of Companion problems and contributes to death before its time. Comorbidities such as heart attacks, strokes, failure of the kidneys, amputations have been reported, There have been reports of vision loss and nerve damage [3].

Presently, there are several different types of insulin preparations available, each of which acts differently. In reality, manual insulin administration is an estimated therapy. The most common side effects include nausea and an upset stomach. As a result, the immune system becomes weak, leading to additional complications. Due to its breakdown by the gastrointestinal tract, insulin is incapable of passing through the gastrointestinal membrane [1,3].

Different delivery mechanisms for insulin exist depending on how it is administered: whether it is given by injection, injection under the skin, intraperitoneal injection, or nasal injection. Injection under the skin is the most common mechanism due to its precise dosage control [4].

It is very tedious and difficult to produce insulin in natural form; additionally, the obtainable technique could not either reproduce or qualify the highest insulin levels, Because of limitations on oral Injecting insulin, discomfort, trauma, and low compliance with injectable forms of insulin, researchers have begun experimenting with the transdermal application of insulin. Therefore, this review describes the delivery of insulin via microneedles into the stratum corneum via the transdermal route [5,6].

## 1.3 A Model for Drug Delivery

The main functions of the skin are to act as a physical barrier and as a receiver of peripheral stimuli. The skin is made up of three layers: the epidermis, dermis, and hypodermis.

Insulin is delivered intravenously through microneedles through the stratum corneum. The stacked dead cells are continuously replaced by new cells formed in the basal layer. Hair follicles, sweat glands, and blood vessels are found in the core dermis, which is connected to nerve endings by nerve ending connections. Adipose tissue is found in the hypodermis, which provides insulating characteristics for the body [7,8].

The main function of the skin is to protect the body from harmful substances and microorganisms. In addition, besides that, the stratum corneum in our skin is the best barrier against diffusion because it isn't very good at letting electricity move through it. Up to 90% of the time, transdermal drugs can get through the stratum corneum, which is the most important thing that stands in the way of diffusion [9,10].

## 1.4 The Transdermal Drug Delivery System

Transdermal drug delivery through the skin provides a convenient method of deep penetration into the systemic circulation and is employed for controlled drug delivery. Drugs are transported into the skin layer so they can be administered systemically. Drug formulations are applied to healthy skin and then deep into the dermis and epidermis without getting trapped in the dermis. Transdermal Drug delivery is a painless method to deliver drugs systemically. The drug penetrates the stratum corneum, and then passes through the deeper epidermis and dermis without getting trapped in the dermis [11]. Using patches to deliver hydrophobic drugs is a unique and brilliant solution. This is overcome with micrometer-scale needles which utilize a unique technological approach to enhance drug permeation across the skin, resulting in better insulin delivery compared to needles that require infection for delivery. Several issues with drug development have been solved using transdermal delivery in recent years. For instance, only a few transdermal drugs are currently available, despite their many benefits; in addition, many of them have limited permeability across the stratum corneum. Transdermal delivery of many drugs is said to be able to get around many of the things that make oral, injectable, or inhaled drugs less effective [12,13].

The use of skin patch systems for the effective delivery of drugs systemically has of advantages, including compliance among patients improved,

and eliminating Metabolism of first-pass hepatocytes oral drug delivery systems are more efficient than injectable drug delivery systems [14,15]. The use of this system prevents adverse reactions caused by overdosing and is convenient, especially in terms of transdermal patches, which need to be applied only once a week, resulting in patient adherence to drug therapy. It can enhance the bioavailability and can deliver high concentrations of drugs to the site of action, thereby reducing systemic drug levels. . Because transdermal delivery doesn't cause as much pain and inconvenience as intravenous injections, it's a good way to transport drugs or biological compounds [16,17].

This had some limitations, such as local irritation, erythema, itching at the site of application, or swelling caused by other excipients, especially with patch formulations. The limited permeability of the skin can limit the number of drugs that can be delivered. To overcome these limitations, numerous efforts have been made to develop conventional methods of delivering drugs [18].

Transdermal drug delivery may have enabled a greater increase in lipophilic drug delivery in the transdermal system than oral and injectable delivery. In addition, iontophoresis may have helped to increase the amount of lipophilic delivery of the transdermal system. There is no physiochemical property of the drug; therefore some physical or chemical enhancers are needed to improve the diffusion of the drug. Therefore, electroporation, sonophoresis, iontophoresis, and MN have all been developed [19,20].

### 1.5 Microneedles: A New Approach

Nanoneedles are recently developed systems for the delivery of drugs that are similar or similar to traditional needles, except they are created on a micron-scale and can range from 1-100 microns in diameter and length [21]. Microneedles are needles arranged on a transdermal patch in a microneedle pattern and are currently used to enhance the delivery of small and large molecules through transdermal delivery systems. Medical MN devices are used to treat the condition; tiny microchannels can be created by way of the stratum corneum. There are different brands and variants of these devices available. The University of Marburg, Germany, tried the MN method and found that both lipophilic and hydrophilic compounds get into the body more easily when they are given by MN [22].

Drug delivery by transdermal means can be improved with this technology since they are designed to penetrate only the skin surface without going deep and stimulating the dermal nerves. Due to the short needle length of MN patches, the nerves are not stimulated in the stratum corneum are not stimulated [23].

Micron-sized pores in MNs facilitate the delivery of micromolecular-size drugs into the body. It has been suggested that large molecules might be coated on MNs, which may then be injected through the skin. MN is a hollow state. Alternatively, the drug is directly injected into the skin, whereas microneedles dissolve when you apply and release the side-effect-free drug currently, clinical trials are being conducted into the development of microneedles that deliver macromolecules like insulin, parathyroid hormone, and influenza vaccine [24]. As with conventional needles, the microneedles can be arranged into arrays at the microscale. Additionally, microneedles can be made into patches that can be applied to the skin. Often, transdermal drug delivery fails to deliver drugs to the skin at a therapeutic rate; this results in a statistically limited success rate. Therefore, the use of microneedle patches was found to be effective in increasing transdermal drug delivery as well as enhancing the skin's permeability [25].

### 1.6 Solid Microneedle

In passive diffusion, solid microneedles increase skin permeability by creating microchannels, and then they are applied with a patch that contains drugs. To prevent the spread of pathogenic bacteria or toxic substances, it is necessary for microchannels to promptly close once the needles have been removed [26,27]. As mentioned in numerous published studies, solid MN arrays have been shown For instance, insulin, calcium, naltrexone, or proteins can get through the skin better [28].

Solid arrays of microneedles (MNs) coated with macromolecules are used to "coat and poke" ingredients onto the stratum corneum.. Drug coating of the MN array can be accomplished in many ways. It has proven effective to deliver macromolecules such as nucleic acids, proteins, and vaccines through MN arrays that are coated with gelatin. Drug coating of the MN array can be accomplished in many ways. It has been shown that coated MN arrays are effective at delivering macromolecules like proteins, nucleic acids, and

vaccines to the skin. It might be possible to coat a MN with a powerful drug or vaccine, but it's not a good way to get a lot of active molecules [29].

### 1.7 Hollow Microneedle

The hollow MNs deliver drugs using a "poke-and-flow" approach. Like with hypodermic injections, the fluid drug can flow constantly into the skin as it flows through the holes in the hollow MNs [30]. A micropump, for example, can be used to precisely control the flow rate of the drug. As compared to hard microneedles, hollow microneedles are additionally probable to facilitate fluid flow driven by force. As a result, drugs can be delivered faster. Further, hollow MNs can provide painless, continuous, and long-term drug delivery to meet the specific needs of each patient, with precise and tunable dosages [31,32].

### 1.8 Dissolving Microneedle

Microneedles that melt into the skin after insertion of the active substance are dissolved or biodegraded into the matrix. For the manufacture of microneedles, micromolding techniques are

used. The most commonly used substances are sugars, carbohydrates, and synthetic polymers to create these arrays which can deliver insulin, high combining dissolving microneedle with iontophoresis improves the delivery of the drug to the skin as it is combined with molecular-weight heparin, ovalbumin, vaccine antigens, and photosensitizers [33].

### 1.9 Hydrogel-Forming Microneedle

Microneedles with hollow bores have a hollow bore located in their center. Drugs are defused by hydrogel-forming microneedle arrays by absorbing interstitial fluid via distended microprojections. They are created from artificial polymers. Micro and macromolecules can be distributed through microneedle hydrogels [34].

A microelectromechanical system is an integrated mechanical, sensor, actuator, and electronic device built using microfabrication. A skill like this will make it possible to integrate the complete system on a chip, allowing for better glucose control and management. This technology makes it possible to deliver drugs to the body without being invasive or hurting the body [35].

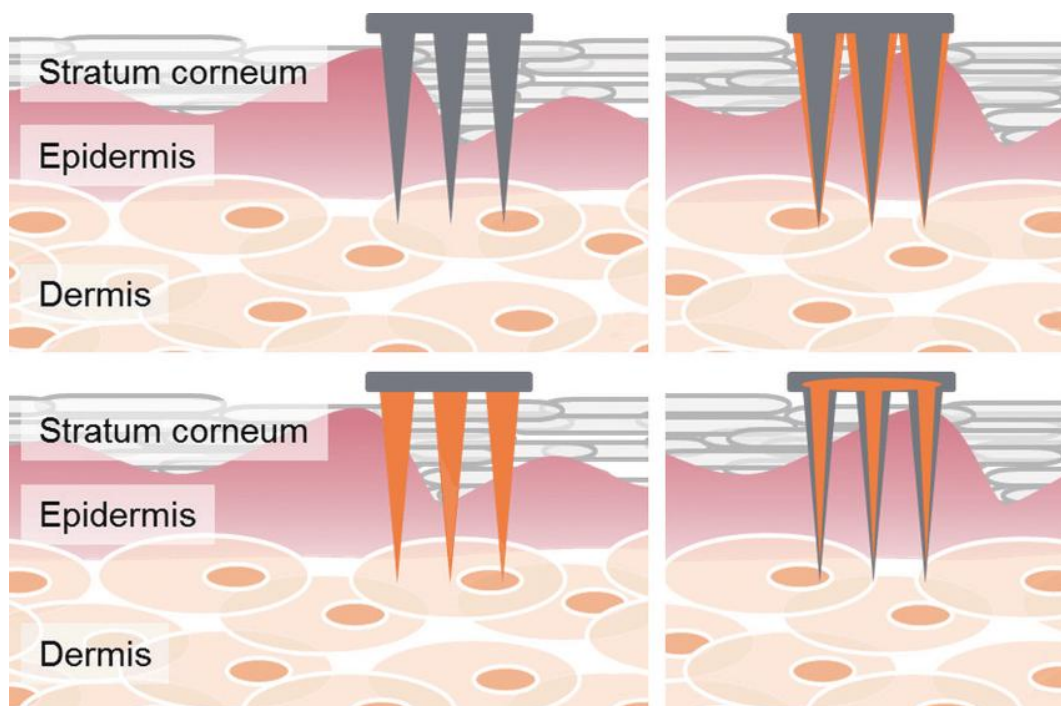


Fig. 1. Four types of microneedles. Solid microneedle (A), coated microneedle (B), dissolving microneedle (C), and hollow microneedle (D) [1]

### 1.10 Autonomous Diabetes Management

Many of the problems that come with manually injecting insulin can be solved with an insulin treatment system that uses automatic glucose monitoring and changes the way insulin is injected. [36]. The following generic devices are important: An insulin delivery system that binds the glycemic level and insulin delivery gap using (a) glucose devices and (b) a response device. An insulin therapy device's response mechanism is a key component. Glucose adsorption triggers insulin production, which is a very complex process. The program should be able to tailor glucose levels versus insulin delivery schemes that optimally match the patient's real metabolic activities should be matched [37,38].

Researchers in diabetes research are increasingly using closed-loop systems utilizing microneedles due to their high priority features. It is only possible to design MNs that are application-specific and algorithm-dependent. MN involves multiple parameters to consider and highly application-specific designs [39].

### 1.11 Microneedle for Glucose Sensing

Many studies have shown that blood glucose levels differ from those measured by ISF. Both methods can be used to determine blood glucose levels. A period break of 0 to 45 minutes is usually made based on observations rate at which glucose travels from blood to the ISF [40].

As soon as equilibrium is reached, blood and ISF levels correlate. The depth of penetration of the microneedle should be about 50-150  $\mu\text{m}$  for ISF to be extracted. Consequently, the application of shorter needles of the same diameter can withstand more pressure without failing without fracture caused by buckling, and without buckling caused by buckling. The reduction in height for a smaller needle diameter may prevent buckling. An array of MNs is used to detect changes in glycemic levels, and then inject insulin within 20 minutes [41,42].

### 1.12 Microneedle for Insulin Delivery

Despite the great changes in noninvasive glucose monitoring, the devices still rely on inexact mathematical algorithms, causing many complications. On the other hand, traditional methods use hypodermic needles that are painful and traumatic to the tissues [43].

It is considered difficult to deliver insulin transdermally because the particles are very big. These problems can be solved with microneedles as they are considered low-invasive tools for interacting with the skin. In the MN technology, miniature pores are created to allow insulin to penetrate the stratum corneum, preventing it from passing through. The stratum corneum is then able to receive insulin [44,45]. An enzyme, glucose oxidase, has recently been used in MN along with insulin. Blood tests to detect hypoxia and release insulin inappropriately. Pumps deliver the fluid, which is controlled by a feedback system. Active pumping eliminates capillary force dependence. Consequently, the role of material choice Based on the degree of hydrophilicity, hydrophilic properties play a key role. Polymers and metals have all been used for microneedles that deliver insulin painlessly into the stratum corneum. For a painless delivery of insulin to the stratum corneum, the microneedle tip's lumen diameter should be between 10 and 100 microns [47- 49].

By delivering insulin through MN technology, glucose levels in animals have been reduced substantially. A 47% to 80% reduction in glycemic levels was observed in studies when 0.05 to 0.5 units of insulin were delivered [50]. When MN is inserted into the stratum corneum to insert insulin, likely MN can occasionally become clogged or trapped. To deliver insulin through MNs painlessly and for a prolonged period, It is possible to arrange and place 100 microneedles 200 $\mu\text{m}$  apart in the array. By doing this, in a short-half-life, it is possible to deliver insulin more frequently from the stratum corneum into the stratum membranous [51,52].

### 1.13 Preparation and Evaluation of Microneedles Patches

This study, PDMS micro-mold was used to fabricate microneedles that were manufactured by micro-moulding technique using PMS micro-mould. PDMS can be used to prepare chemically inert, Thermostable, mechanically durable, and non-hygroscopic microneedles [53].

Microneedle patches are prepared by mixing a fresh polymer solution well to ensure uniform dispersion of the drug. However, long stirring usually causes bubbles to form and may adversely affect the casting process. Also, bubbles can weaken the mechanical strength of microneedles, which might be problematic in some situations. For this reason, a centrifugal

force of 2000 rpm for 20 minutes was selected.. After centrifugation, bubbles were successfully removed [53].

### 1.14 Test Using Light Microscopy

If microneedles are to be inserted successfully into the skin without failure, they must possess sufficient mechanical strength. Parafilm has a slightly lower penetration depth than porcine skin, but it is acceptable for insertion studies when replacing biological tissue, as reported by Larreneta et. al's 27 research.. Even though holes did not form in the third layer of parafilm, microneedles were able to reach insertion depths of 254 \* 3.560 m and 381 \* 3.560 m [54].

### 1.5 In-Vitro Release Test

Microneedles loaded with rHuKGF released their contents rapidly within 30 minutes when incubated in 150 mL of phosphate-buffered saline solution with pH 6.2. Figure 1 shows that 95.67% of rHuKGF was released successfully within 15 minutes, and 100% of rHuKGF was released after 30 minutes. Generally, either the drug diffuses through the polymer or the polymer is degraded during release from microneedles. Molecular weight and size are important factors in diffusion-controlled release. However, in dermal applications, the surface of the microneedles will be what determines how fast small molecules diffuse from the microneedle arrays into the skin. A number of other variables affect drug delivery, Microneedle penetration quality, microneedle application method, and the type of skin. Polymeric microneedles should be studied for their ability to deliver drugs to the skin in vivo in order to gain insights into their functionality [55,56].

Providing exogenous insulin by injection or pump during mealtimes is part of the treatment plan for adults with insulin-dependent diabetes mellitus. Hypoglycemia occurs when blood glucose levels fall below the normal range, i.e. 70-140 mg/dL, and causes increased mortality and morbidity. Diabetes is typically treated and controlled through a series of regular insulin injections, Additionally, their blood sugar levels must be monitored continuously and precisely in order to maintain a range of 70 to 140 mg/dL

## 2. CHALLENGES

Translating MNs from lab benches into feasible products in relevant markets will be a challenging

task in the future. In order to use this advanced technology, every step needs to be done well; the following questions and challenges need to be addressed as soon as possible. All these, and other challenges to this field, are discussed herein, as are active strategies to resolve these issues, which could play a crucial role in its future [58,59].

Failure of MNs could cause the wrong dose to be given because they must be strong and reliable for repeated penetration and long-term use [60]. It is also important to consider the level of biocompatibility because of its continuous use requirements. Even though silicon is more versatile than some other metals for microneedle construction, its biocompatibility varies based on the application. Silicon is a versatile material for microneedle fabrication, but it is the grade of application-dependent biocompatibility [61,62]. The use of recyclable polymer-based microneedles needs to be explored. Certain investigators believe that the continuous distribution of insulin via a supplementary pump system requires a constant source of insulin, whereas a microneedle maintains the same level of insulin using less insulin. Traditionally, an infrequently occurring slow-acting injection of a longer time is needed for insulin to take effect in patients with diabetes. Long-term controlled injections could maintain insulin concentration by delivering short half-insulin more frequently [63,64].

## 3. CONCLUSION

Microneedle-based drugs will likely be marketed soon. Researchers are conducting extensive research to deliver therapeutics efficiently via microneedles. It is urgent for methods for delivering drugs transdermally to be developed for hydrophilic Matrices, macromolecules, proteins, and conventional medicines for use in new therapeutic indications. Transdermal delivery of microneedle either as patches or arrays appears to be a rational method to better manage diabetes through effective insulin delivery. Compared to other injectable methods, the microneedle approach is painless, efficacious, safe, and effective. Because they don't hurt, they could also be a major tool for controlled drug release in the future. An MN interface would provide a noninvasive, bioengineered way to understand the skin; this approach can be implemented in several ways. A painless insertion may reduce discomfort and the likelihood of noncompliance among

patients reducing the risk of human error. Additionally, microneedling has attracted much attention because of its concept of minimal training that is particularly useful for children with diabetes. Microneedles are therefore a possible option for improving control of blood sugar, allowing for more efficient and contented diabetes organization, and reducing the risk of long term complications associated with diabetes. Thus, it shows that when it comes to better patient compliance and management, transdermal delivery of MN-based technology is a lot better than other injectables.

### CONSENT

It is not applicable.

### ETHICAL APPROVAL

It is not applicable.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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