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Original Article

Microneedles: A Promising Future for Efficient Drug Delivery in Diabetes Management

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Abstract:

This review's objective is to draw attention to the use of microneedles (MNs) as a state-of-the-art, novel drug delivery method for the effective management of diabetic patients. Oral, subcutaneous, nasal, and other administration methods have numerous drawbacks, including discomfort and numerous other adverse effects. As a result, this drug delivery study has shown great promise in integrating therapeutic and diagnostic components to improve diabetes treatment. The majority of glucose-sensing methods and traditional insulin treatments work by transferring physical substances through the skin. A non-invasive or minimally invasive approach can be used to administer medication using an MN-based system, which can be advantageous for painless administration, easy handling, discrete, continuous, and regulated release. In order to create a "smart" system that is specifically designed for autonomous diabetic treatment, the study discusses the latest developments in bioengineered systems such as MNs. Microneedle (MN) technology represents a transformative approach in diabetes management, offering a minimally invasive, pain-free alternative to traditional insulin delivery methods. These micro-scale needles facilitate transdermal insulin administration, bypassing gastrointestinal degradation and enhancing bioavailability. Advancements in MN design, including glucose-responsive systems and integration with nanomaterials, enable real-time glucose monitoring and controlled insulin release, mimicking pancreatic function. Such innovations not only improve glycemic control but also enhance patient compliance by reducing discomfort and simplifying administration. Moreover, MNs' potential in combining therapeutic and diagnostic functions positions them as a promising tool in personalized diabetes care. Continued research and development are essential to overcome existing challenges and fully realize MNs' capabilities in clinical settings.

Keywords: *Skin, Transdermal Drug Delivery, Microneedle (MNs), Diabetes Mellitus, and Diabetic management.*

Introduction

At the time of diagnosis, diabetes can be divided into different types based on etiology and clinical symptoms. Diabetes is a general term used to describe a group of metabolic diseases characterized by chronic hyperglycemia. The pathophysiology of diabetes is caused by insulin secretion errors, impaired insulin, or both.

- **Type I diabetes (T1DM):** Insulin-producing beta cells of the islets of Langerhans are disrupted in type 1 diabetes (T1DM), leading to a complete lack of insulin. Type 1 diabetes, also known as insulin-dependent diabetes, is immune-mediated diabetes, where the immune system destroys beta cells in different groups of patients with different rates. Type 1 diabetes mellitus, also known as idiopathic diabetes, occurs when no known cause of insulin deficiency is found, and no autoimmune mechanism of beta-cell destruction is found.
- **Type II Diabetes mellitus(T2DM):** Type 2 diabetes (T2DM), formerly known as non-insulin-dependent diabetes, affects 90–95% of diabetic patients. T2DM is frequently linked to obesity, and many individuals have been undiagnosed for years. Type 2 diabetes mellitus is the most common type of diabetes mellitus, with relative insulin deficiency and insulin resistance resulting from genetic or environmental factors [1].
- **Gestational diabetes mellitus:** Any level of glucose intolerance that initially appears or is diagnosed during pregnancy, whether or not it persists beyond pregnancy, is a hallmark of gestational diabetes mellitus.

Patients with type 1 diabetes mellitus (insulin dependency) require insulin. In order to preserve blood glucose homeostasis, patients with advanced type 2 diabetes mellitus (insulin resistance) also require insulin. An A chain with 21 amino acids and a B chain with 30 amino acids make up the human insulin molecule (molecular weight 5.8 kD) that is secreted by pancreatic islet cells [2]. Due to its lower cost, higher delivery efficiency, and higher bioavailability, subcutaneous (SC) injection using a syringe, insulin pen, and insulin pump remains the most widely used method of insulin therapy today [3, 4]. Despite the development of long-acting injections (up to 24 hours), patients still need to receive injections two to four times per day.

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Regular injections will result in poor patient compliance since they induce pain and certain skin problems at the infusion sites, such as redness, swelling, infection, and local tissue necrosis [5, 6]. Chronic hyperglycaemia is the main clinical finding in diabetes and has a significant risk of causing long-term organ failure or malfunction. The heart, kidneys, eyes, nerves, and blood vessels are the organs most severely impacted. T2DM typically carries a higher risk of microvascular and macrovascular complications [1].

Approximately 463 million persons worldwide between the ages of 20 and 79 have diabetes, and by 2045, that figure is expected to rise to 700 million, according to the International Diabetes Federation's (IDF) Diabetes Atlas 9th Edition 2019 [7]. In order to address this 21st century challenge, it is necessary to investigate the landscape of medication delivery systems to enhance blood glucose monitoring and diabetes treatment due to the complications that lead to early death and financial strain on healthcare systems. Daily insulin injections can provide the constant insulin supply needed for type 1 diabetes, whereas hypoglycaemic drugs (metformin) being the most often prescribed drug are used to treat type 2 diabetes. Some T2DM patients additionally use injectable insulin. Furthermore, real-time injection dose adjustments are required to produce a quick hypoglycemic response following a meal and a gradual but sustained reduction in blood glucose levels prior to sleep. Because it might be challenging to get the right dosage, both hyperglycemia and hypoglycemia frequently happen. Furthermore, insulin is a biological peptide with poor stability that requires storage and distribution at temperatures between 2 and 8 °C [8], making storage and transportation more challenging in certain developing nations. Therefore, developing more stable, practical, painless, long-acting, and glucose-monitoring insulin preparation has become the main goal of insulin drug product development.

In order to increase patient compliance, researchers are dedicated to investigating non-invasive injection methods, such as oral, percutaneous, pulmonary, and nasal [9]. Transdermal delivery system (TDDS) is one of them that is appealing and provides a number of advantages. The transdermal route of insulin delivery offers a number of therapeutic consequences through the skin [10]. Thus, using microneedle (MN)-based technology, the current review clarifies the transdermal route of insulin delivery into the stratum corneum.

The Skin as a Mechanism for Drug Delivery

The epidermis, dermis, and hypodermis, or subcutaneous tissue, are the three main layers that make up the skin. As seen in Figure 1, the skin acts as both a physical barrier and a receptor for external stimuli. About 100 μm thick, the epidermis is the outermost layer of the skin. Its main components are the stratum corneum, which is made up of stacked dead cells that are constantly being replaced by new cells created in the basal layer, and the barrier layer.Hair follicles, sweat glands, and blood vessels that are connected by nerve endings are all found in the core dermis. An adipose tissue layer, about 1 mm thick, that aids in heat insulation is found in the hypodermis. The hypodermis is around 100 times thicker than the stratum corneum and also acts as an energy source. This Known as the skin's microcirculation, the dermis is made up of tiny vessels that are crucial in delivering medications into the systemic circulation and regulating body temperature. The primary role of the skin is to shield the body from dangerous substances and microbes that are found outside. The largest organ in the human body, the skin is considered to give the body flexibility and toughness for mobility. Our skin's lipids shield us from electricity since it is a poor electrical conductor. Indeed, the most important barrier to diffusion is the stratum corneum [10], which contributes to diffusion in around 90% of transdermal medication administrations.

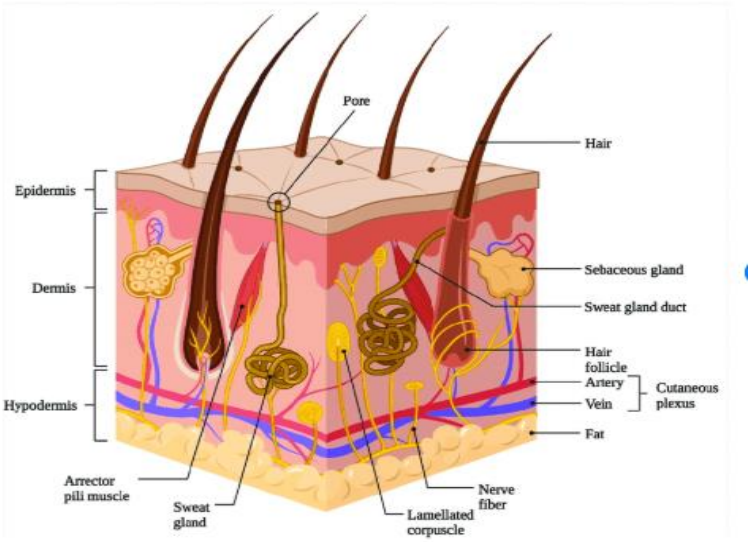


Fig 1: According to (Anatomy of skin), the skin, which is primarily composed of three layers—the epidermis, dermis, and hypodermis or subcutaneous tissue—has two primary functions: it acts as a physical barrier and a receiver of peripheral impulses.

Transdermal drug delivery systems

The method of delivering a medication into the skin layer for systemic distribution is known as transdermal drug delivery. Hydrophobic medications can be administered into the skin in a novel and effective way via patch-based drug delivery. The outer stratum corneum of the skin acts as an impenetrable barrier to transfer insulin [11]. To get around this, a special technological method in micrometre-scale needles improves medication penetration through the epidermis, allowing for improved insulin delivery that would otherwise need infection. A precise, fixed, and regulated quantity of drug molecule is encased in a device for transdermal drug delivery, which allows it to enter the systemic circulation at a predefined rate through the intact skin surface. Transdermal delivery has made incredible strides in recent years in resolving a number of drug development challenges. Many medications have been reported to be delivered transdermally, circumventing many of the drawbacks of oral, injectable, or inhaler administration methods. Additionally, it was noted that around 74% of oral medications lacked the therapeutic efficacy required [11].

Advantages of TDDS:

1. The skin's surface area is approximately 1-2 m^2, which offers a large surface area for drug administration [12].
2. TDDS is less invasive than painful injections, which helps to reduce the side effects associated with frequent injections, thereby increasing patient compliance and improving the quality of life for diabetic patients.
3. insulin delivered through the skin can also bypass the gastrointestinal tract degradation and hepatic first-pass metabolism, which are major limitations of insulin oral administration [13, 14].
4. TDDS can also continuously release insulin to maintain normal glucose levels for a longer period of time with fewer glucose fluctuations [13, 15], which greatly lowers the risk of concentration-related side effects.

Transdermal drug delivery has significantly helped achieve the goal in comparison to injectable and oral drug delivery. Additionally, lipophilic drug delivery has increased with the use of iontophoresis in the transdermal system. Microneedles and electroporation are the main methods used in the current drug delivery system to target the stratum corneum [16]. Physical and chemical enhancers such as electroporation, sonophoresis, iontophoresis, and MN are among the many methods that have been created. It is believed that the stratum corneum is lipophilic because it creates a barrier that renders individuals resistant to a wide range of medications. Since the drug lacks any physiochemical properties, some kind of vehicle is needed to enhance the diffusion.

Microneedles (MN): An Innovative Method

The usage of the medical MN device, which comes in a variety of brands and variations, creates tiny microchannels via the stratum corneum layer. A study conducted by the University of Marburg in Germany discovered that the MN method improves the skin penetration of both hydrophilic and lipophilic substances. Another name for this Minnesota strategy is "the vaccine of the future." These MNs can be of several varieties, some of which have regulatory approval, including hollow, solid, coated, dissolving, and hydrogel forming. Additionally, MN devices and patches have demonstrated effectiveness in the realm of nanomedicine by effectively delivering medications in the form of nanoparticles [16].

Microneedle: Mechanism of Action

To administer medications and vaccinations into the skin, a microneedle array made up of hundreds of microneedles that are less than 1 mm long is used. A microneedle patch is created when an array of microneedles is affixed to an adhesive backing to improve its adhesion to the skin [17]. According to the drug delivery approach, the medication and vaccination are deposited in the dermis, where they are readily accessible to the targeted area, after a brief mechanical rupture of the skin. Additionally, without affecting blood, microneedles provide tiny drug delivery routes. Both the dermis and the epidermis have functional arteries and nerve terminals. Large doses and larger molecular sizes can therefore be administered more easily, increasing the effectiveness of drug administration [18,19,20]. Consequently, microneedle arrays are regarded as minimally invasive tools that can take blood from the skin without causing pain [21].

The microneedles, which are inserted into the skin, are coated with or contained by the medication or vaccination in the form of biomolecules. As soon as the microneedles are inserted into the skin, the medication is released into the dermis. In order to obtain a therapeutic response, microneedle devices with a large number of tiny needles can deliver the required amount of medicine in the dermis while avoiding the SC barrier [22].

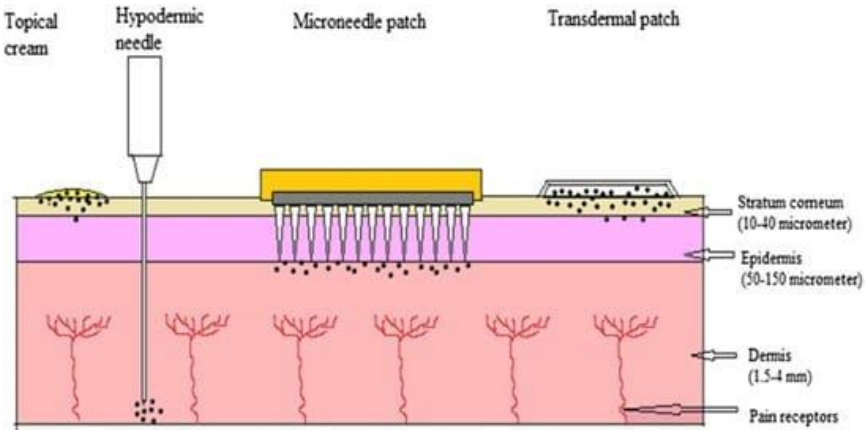


Fig. 2. Comparison of Hypodermic syringe, Topical cream and Microneedle Patch [26]

Types of Microneedles

The five different types of microneedles: solid, coated, hollow, dissolving, and hydrogel/swellable can all be used in microneedle drug delivery technology.

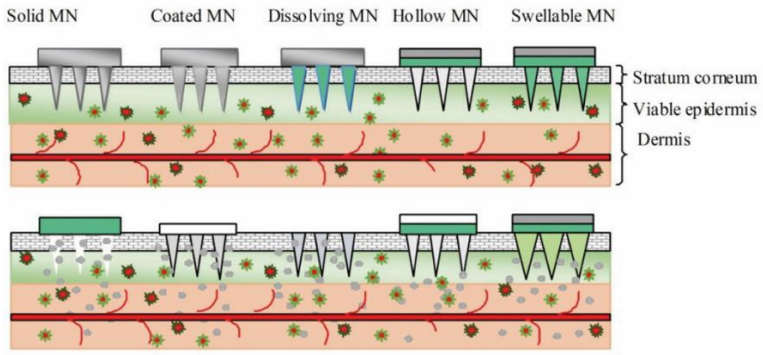


Fig. 3. Different types of microneedles with intra/transdermal drug delivery pattern [23]

Solid microneedles

MN development for solids is a two-step process called "poke with patch." Applying solid MN arrays to the skin in the first stage creates a tiny microchannel in the stratum corneum into which the body may easily absorb the pharmaceuticals. The permeability of the stratum corneum is increased by the tiny microchannel by the use of the passive diffusion approach. Solid MNs are composed of polymers, metals, or silicon. According to several published research, the usage of solid MN arrays has enhanced the transdermal penetration of various substances, including proteins, calcein, insulin, and naltrexone. In To improve the effectiveness of transdermal distribution, MN arrays are frequently advised in conjunction with other combination techniques, such as iontophoresis.

The use of solid MNs array coated with a macromolecule (drug or vaccination) is another strategy known as "coat and poke." The formulation that is coated onto the MN is deposited following the application of MN onto the stratum corneum. There are numerous tactics that can be used to successfully coat the medication into the MN array. Protein, nucleic acid, and vaccines are examples of macromolecules that have been successfully delivered into the skin by the coated MN. Coated MNs are not suitable for delivering large quantities of active compounds, but they might be a useful option for delivering vaccines or potent drugs.

Dissolving microneedle

The active ingredient in dissolving MNs is part of a soluble/biodegradable matrix; following insertion, the needle matrix dissolves into the skin to deliver the medication. To create these MNs, micro-molding techniques are used. Adenovirus vectors, insulin, low-molecular-weight heparin, ovalbumin, vaccine antigens, photosensitizers, and precursors can all be delivered using these kinds of arrays, which are often composed of sugars, carbohydrates, or synthetic polymers. When dissolved MN is used in conjunction with iontophoresis, the medicine is more effectively delivered into the skin [24]. Water-dissolvable polysaccharides, including sodium alginate, amylopectin, sodium chondroitin sulfate, hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), hyaluronic acid (HA), and dextran, consist up the bulk of dissolving MNs. Biodegradable polymers including gelatin, poly-γ-glutamic acid (γ-PGA), polyvinyl pyrrolidone (PVP), poly (vinylpyrrolidone-co-methacrylic acid) (PVP-MAA), PVP-cyclodextrin (PVP-CD), and polyvinylpyrrolidone-polyvinyl alcohol (PVP-PVA) are also used to make dissolving MNs. Different micro-molding techniques, including casting, hot embossing, and injection molding, can be used to create dissolving MNs [25].

Hollow microneedle

The hollow microneedle has the capacity to handle a greater dose or volume of medication solution than the solid microneedle. A hollow microneedle can also be used to deliver the medication into the living dermis or epidermis, which is suitable for higher molecular weight drugs. It is also suitable for use with liquid vaccine formulations since it controls medication release over time. Solid microneedles primarily elute medicines based on the osmotic gradient, whereas hollow microneedles, an active drug delivery method, create a conduit for drug diffusion into the dermis based on a non-pressurized drug reservoir. It is possible to achieve adjustable release kinetics by utilizing the hollow microneedle's fabrication parameters and material formulation.

Depending on the application, matrix-loaded pharmaceuticals can allow for a steady-state drug release that lasts for days to weeks, while higher concentration medications may produce burst release drug profiles. Like hypodermic needles, hollow microneedles can be made to allow for pressure and flow rate adjustment. Microneedle aspect ratio (height to base diameter ratio) is one process parameter that can be adjusted for time-varying delivery rate, gradual infusion, or quick release. Many vaccines and inoculations have been effectively administered using hollow microneedles over the years. Although the hollow microneedle has been successfully used for a number of vaccines and inoculations over the years, it has received less attention than the solid microneedle because it is comparatively weaker and requires intensive care in terms of needle design and insertion technique [26].

Hollow MNs are made up of an empty cavity needle (5–70 μm wide) and an external auxiliary device, like a syringe, pump, gas, or electrical support, that allows the liquid formulation to be continuously injected into the skin through the needle cavity (typically 10–100 μL/min) [25]. Hollow MNs share the same fundamental construction as a typical subcutaneous injection needle. The dosage of coated or dissolving MNs is restricted to the needle area and number, whereas the delivery capacity of hollow MNs is greater than that of other MN types because the dose quantity and flow rate of hollow MNs can be regulated by an external auxiliary device [25]. Hollow MNs can be made from many different materials, such as silicon, metal, glass, ceramic, and polymers. Recently, there has been an increase in interest in polymers with high biocompatibility, such as metal electroplated polymer, clay reinforced polyimide, and SU8 polymer [25]. Microelectromechanical systems (MEMS), including lithographic molding, X-ray photolithography, etching, and laser ablation/cutting, can be used to create hollow MNs. Using laser micromachining technology makes it simple to manage and produce various MN shapes in a single exposure device, avoid exposure and chemical etching, and prevent multilayer masking and patterning [25].

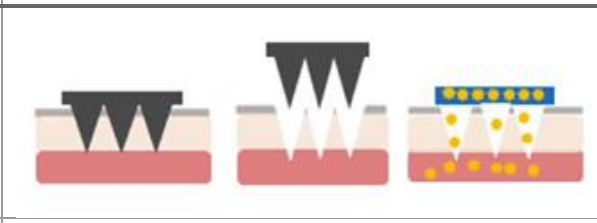
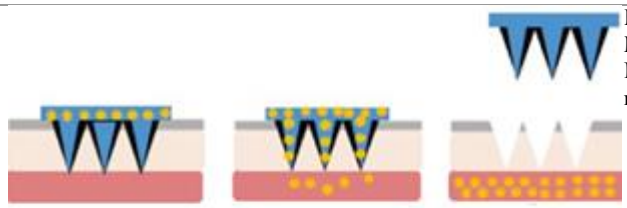
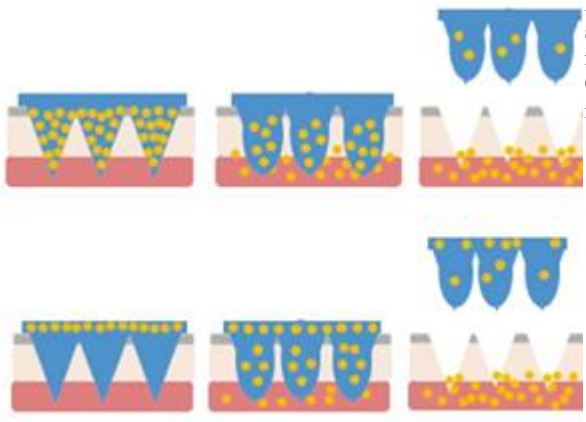
Hydrogel-forming microneedle

MN arrays that contain a drug reservoir and a swelling substance are known as hydrogel-forming MN arrays. By absorbing the interstitial fluid (ISF) through the swelled micro projections, the drug reservoir and swelling material in the hydrogel-forming MN array both diffuse the medication. MN arrays that generate hydrogel are composed of synthetic polymers. Hydrogel-forming MN can be used to spread macro and micro molecules. A microelectromechanical system is a microfabrication technique that combines electronics, sensors, actuators, and mechanical components on a silicon substrate. With the help of this technology, it will be possible to integrate the entire system on a chip, improving glucose management and control. Parenteral administration has the advantage of entering the bloodstream directly, avoiding the body's physical barrier and deterioration. Because to its length and dimensions, MN can carry the medicine into the bloodstream by reaching the stratum corneum's capillary-rich layer. The technology's painless and non-invasive medication administration method will open up a world of possibilities in the subcutaneous drug delivery field [24].

Coated microneedles

Coated microneedles are solid microneedles with a drug layer applied to their surface, enabling precise, minimally invasive transdermal drug delivery in a single step. Upon insertion into the skin, the coating dissolves, releasing the drug into the underlying tissues. Common coating techniques include dip coating, spray coating, and electrohydrodynamic atomization (EHDA). While this method offers efficient delivery, the limited surface area for coating may restrict the dosage, making it more suitable for potent drugs [27].

Table 1: Advantages and disadvantages of different MN types [25]

MNs Types	Figures	Advantages	Disadvantages
Solid MNs		High mechanical strength Reasonable drug load	Poor dose accuracy Two application process Poor biocompatibility
Coated MNs		Elevated mechanical strength used with low-dose medications	Minimal drug load Inadequate biocompatibility Migration of formulations during manufacturing and storage
Hollow MNs		Precise dosage High drug load Faster delivery rate	Requirement of auxiliary devices Poor mechanical strength Poor biocompatibility
Dissolving MNs		Easy manufacturing Control of drug release	Poor mechanical strength Dose limitation Poor biocompatibility
Hydrogel MNs		No residual in skin Easy manufacturing Control of drug release	Poor mechanical strength

Potential of Microneedle

Fabricating microneedles in a variety of shapes, sizes and materials allows delivering large molecules with significant therapeutic interest such as insulin, proteins produced by the biotechnology industry, and nano particles that could encapsulate a drug or demonstrate the ability to deliver a virus for vaccinations.

Microneedles may prove useful for

- Because they may be used by people with no medical experience, microneedles may be helpful for mass vaccination campaigns in underdeveloped nations or for administering antidotes in bioterrorism occurrences.
- Individual cells could receive highly targeted medication delivery from extremely tiny microneedles.
- Due to their tiny size, these needles can be produced in large quantities on a single wafer by using a silicon substrate. As a result, the fabrication cost is moderate and the accuracy and reproducibility are high.
- Because they may be stored in a precisely controlled microvolume, microneedles can be used for biological drug stability augmentation, local delivery, complicated release patterns, and very accurate dosage.

- It is possible to utilize hollow microneedles to extract bodily fluids for examination, like blood glucose readings, and to provide microliter amounts of insulin or another medication when needed [28].

Applications of Microneedle

Three main areas of research have been identified for the use of microneedles for medication and gene delivery: systemic, local, and cellular delivery. Molecules can be delivered by microneedles to cultured cells, specific bodily tissue areas, and the circulatory system through the skin. A more developed body of research on microfabricated electrode arrays, which are primarily employed as neural probes, serves as the foundation for several of these microneedle technologies.

Cellular Delivery:

For a wide range of molecular and cell biology applications, membrane-impermeable compounds must be delivered into cells. Proteins, peptides, DNA, oligonucleotides, and a variety of other probes that alter or assess cell activity are among the substances of interest.

There are four types of currently accessible techniques for delivering chemicals into cells:

- Chemical (such as DEAE-dextran, ATP, and EDTA, among others)
- Vehicles (such as vesicle or erythrocyte fusion)
- Electroporation is an example of an electrical
- Mechanical (such as microprojectiles, sonication, hyposmotic shock, and microinjection)

The gold standard technique for loading cells is, in many respects, microinjection. With good cell viability and function, it can consistently transport a large number of macromolecules to the majority of cell types. However, this method is very labour-intensive and only works with tiny numbers of cells (less than 100 cells) because it involves injecting cells one at a time using separate glass micropipettes. It is recommended to use arrays of closely spaced microneedles to carry out microinjection on thousands of cells or more at once in order to simplify and speed up the process. The main drawback of microinjection is that numerous cells can be treated simultaneously when several needles are positioned in a high-density array.

DNA Vaccine delivery:

The body's first line of defence against infections that invade from the environment is provided by the Langerhans cells found in the skin. These cells find the infections' antigens and deliver them to T lymphocytes, which then promote the development of antibodies. Using microneedle technology developed using the dip and scrape technique, a DNA vaccine was delivered. The arrays were dipped into a DNA solution and then repeatedly scraped across the mice's skin in vivo. The luciferase reporter gene's expression was increased by a factor of 2800 by the use of micro enhancer arrays. Furthermore, the immunological responses brought on by microneedle delivery were more robust and less erratic than those brought on by hypodermic injections.

Delivery of Local Tissue:

Traditional drug administration involves administering the medication systemically, which treats the targeted area of the body while exposing other parts of the body to the drug, which may have adverse consequences. medicine distribution to a particular part of the body can reduce side effects, reduce the dosage of a costly medicine, or provide a means of delivering a treatment to a difficult-to-treat location. There have been discussions about two new gadgets that deliver medications to particular bodily tissue areas. Drugs have been administered into guinea pigs' neural tissue in-vivo using microfabricated neural probes, which also track and stimulate neuronal activity.

Systemic Transfer:

Biotechnology has created a number of powerful and advanced medications in recent years. Nevertheless, there are drawbacks to the ways in which these medications can be efficiently absorbed by the body. Due to drug degradation in the gastrointestinal tract or liver clearance, oral distribution of novel protein-based, DNA-based, and other therapeutic substances is typically not feasible. The most popular substitute for oral administration is an injection, either into the circulation or into tissues (such as an intramuscular or subcutaneous injection). Despite their effectiveness in administering high doses of medication, injections have a number of disadvantages, such as the necessity for skilled personnel to execute the procedure, the discomfort and trauma caused by the needle, and their inability to deliver easy controlled or continuous release. In order to overcome these limitations, microneedles have been designed to reduce the size of hypodermic needles, which would help patients experience less insertion pain and tissue trauma. Additionally, combining these needles with micropumps and other devices could result in more advanced needles that could potentially deliver drugs in a more controlled manner [28].

Autonomous Diabetes Management

Numerous issues with manual procedures might be resolved by an insulin therapy system that includes automatic glucose level monitoring and also modifies injectable therapy [29-31]. In general, generic devices that have two essential components are (a) a glucose sensor system and (b) a feedback system that connects the two for the purpose of detecting glycemic levels and administering insulin. The feedback mechanism of the insulin treatment device is one of the most important of these.The process by which glucose adsorption initiates insulin synthesis is a highly intricate one. Generally speaking, the application ought to enable patient-specific customization of the insulin administration plan in relation to glucose levels, which may precisely correspond to the actual metabolic processes.

There are three different kinds of self-management systems for diabetes:

a. A therapeutic system that has been pre-programmed and only relies on physician input to manage the insulin delivery mechanism is known **as an open-loop control system**.

b. **A closed-loop control system** that makes advantage of feedback from the glucose sensor.

c. **A partially closed-loop system** that incorporates feedback from a glucose sensor and a doctor's evaluation based on the needs of the patient [32,33].

Due to its higher priority features, the closed-loop system using an MN has attracted a lot of attention in diabetes research. There are only algorithm and application-dependent MNs.The design of MN is very application-specific and incorporates a number of factors. A number of attributes, including cost, ease of production, force, fluid flow rate, penetration, fragility, and biocompatibility, are always crucial.

Microneedle for Glucose Sensing

Blood samples or ISF can be used to measure blood glucose levels. The distinction between blood and ISF glycaemic levels is shown in numerous research [34-36]. The difference in time is typically seen to estimate the time it takes for blood glucose to be distributed to ISF, which is between 0 and 45 minutes. After equilibrium is reached, there is a correlation between blood and ISF levels. In order to extract ISF, the MN penetration depth must be between 50 and 150 μm. As a result, this MN depth insertion has the advantage of being painless [37]. The two primary MN failures are buckling and fracture induced. Therefore, using shorter needles with the same diameter allows for greater pressure to be applied without failing [38]. Lower heights for a smaller needle diameter could prevent bucking from being induced.

Insulin Administration Using a Microneedle

Despite significant advancements, non-invasive glucose monitoring approaches still fall behind many issues arising from gadgets that primarily rely on imprecise mathematical methods [39]. In contrast, hypodermic needles used in traditional procedures have been shown to cause extreme discomfort and tissue harm. Since it can result in a minimally invasive skin interface tool, MNs can address these issues. Because insulin is too large (approximately 50 A in diameter) to pass through the stratum corneum, transdermal administration of the molecule is believed to be difficult. It is possible to administer insulin into the stratum corneum by making microscopic holes with MN technology.Another enzyme that has been used recently in Minnesota is glucose oxidase, in addition to insulin.It functions as a glucose sensor, detecting hypoxia in the blood and releasing insulin at the wrong time and amount [40]. A feedback system regulates the pumping of the delivery component. The active pumping operation eliminates the capillary force reliance. Therefore, depending on the degree of hydrophilicity, material selection is crucial. Numerous MNs have been employed, including silicon dioxide, metals, polymers, and silicon [41-47]. In order to deliver insulin into the stratum corneum painlessly, the lumen diameter of the MN tip should be between 10 and 100 μm.It has been established that a single MN can infuse fluid at a flow rate of greater than 1 ml/h. A needle array may easily deliver a specific amount of dose via MN, even at low or slow rates. In animal models, it has been demonstrated that insulin delivery via an MN lowers blood glucose levels [48]. When 0.05–0.5 units of insulin were administered using MN technology, studies showed a reduction in glycemic level of about 47%–80%. It is possible that MN may occasionally become stuck or jammed in the stratum corneum while inserting insulin [49].By using multiple needles, it usually reduces the impact of passage obstructions or needle failure. It has been discovered that using array creation increases fluid flow rates. Insulin flows into the stratum corneum at a linear rate when there are more MNs positioned in the array [50].

Challenges

MNs should be dependable and robust enough to endure prolonged use and frequent penetration; otherwise, the doses may be administered incorrectly [51]. Because it must be used continuously, the level of biocompatibility is particularly crucial. Compared to some other metals, silicon is more adaptable for MN construction, however its biocompatibility changes with use. The degree of biocompatibility of silicon varies, despite its versatility for MN creation.

MN based on biodegradable polymers ought to be investigated. According to certain researchers, keeping a higher amount of insulin is necessary for the continuous administration and quantitative management of insulin via the auxiliary pump system, while in the case of MNs, it can be maintained with a lower volume of insulin. It takes longer for slow-acting, infrequent insulin delivery to start working in diabetes patients under a typical treatment plan [52]. Insulin concentration can be maintained by administering short half-insulin more frequently by controlled injections over a longer period of time.

Conclusion

Transdermal insulin delivery using microneedle (MN) technology has shown promise as a minimally invasive technique that provides a painless substitute for conventional subcutaneous injections in the treatment of diabetes. MN patches improve patient compliance and may help with glycemic control by facilitating the regulated release of insulin through the skin. Smart insulin patches with integrated glucose-responsive devices are the result of recent developments. These patches can imitate the body's natural insulin response by detecting high blood glucose levels and automatically delivering insulin as necessary. These closed-loop technologies seek to enhance overall diabetes care and lower the risk of long-term problems. Due to its ease of use and lack of pain, patients choose MN-based insulin delivery over traditional injections, which has been shown to be both safe and effective in clinical tests.

In conclusion, Microneedle -based transdermal insulin delivery systems represent a significant advancement in the management of diabetes by providing a painless, effective, and practical alternative to injectable methods. Further research and development in this field is expected to enhance the usability and efficacy of these systems, hence enhancing patient outcomes and quality of life.

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