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A Review on Insulin Microneedle Patches used in the treatment of Diabetes Mellitus

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Abstract

It has been determined that MN, either in the form of patches or arrays, is a sensible strategy for the efficient transdermal delivery of insulin in order to improve diabetes management. Compared to other injectable techniques, the MN approach offers a painless, efficient, and secure drug administration strategy. These painless methods are becoming more and more popular, and they may eventually be among the key tools for controlled medication release.

Keywords: Insulin, Microneedle, Patches, DM

Introduction

Diabetes Mellitus and Its Treatment:

An endocrine condition called diabetes mellitus impacts glucose metabolism, which occurs when the body is unable to use the insulin that is generated or when the pancreas does not make enough of it. Diabetes, one of the four noncommunicable illnesses, has been identified as a significant public health issue that academics from all over the world are concentrating on. Diabetes has risen in frequency and prevalence over the last few decades, leading to numerous negative effects. According to estimates, 422 million people worldwide suffer from diabetes in 2014, up from 108 million in 1980. Since 1980, the number of adults with diabetes has increased from 4.7% to 8.5%, which is thought to have doubled internationally (age-wise standardization). This indicates a rise in associated risk factors, such being obese or overweight.

Diabetes prevalence has tended to affect low- and middle-income countries more than high-income countries during the previous few decades. More than 572 million people are predicted to have diabetes mellitus by 2025. Type 1 diabetes and Type 2 diabetes are the two basic categories of diabetes. Insulin is the primary treatment for Type 1 diabetes, while oral hypoglycemic medications are the primary treatment for Type 2 diabetes. Diabetes is a metabolic syndrome that contributes to early mortality and a number of concomitant problems. It has been noted that there are comorbidities such heart attack, stroke, kidney failure, leg amputation, visual loss, and nerve damage. Severe problems and fetal death could result from uncontrolled diabetes during pregnancy.

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There are numerous insulin formulations on the market now, and they might differ greatly in terms of when they start working and how long they last.[1] Regretfully, administering insulin by hand is essentially an approximated therapy. Unfortunately, the majority of typical side effects associated with this insulin treatment include nausea and upset stomach. This makes it harder to regulate and results in a weakened immune system and other issues. As insulin is broken down by the gastrointestinal tract, it cannot cross the gastrointestinal barrier.[1]

Insulin injections are administered subcutaneously, and concurrent use of two anti-diabetic medications generally raises the risk of adverse effects. An easier and less painful insulin administration method might improve patient compliance. Since insulin is inactivated in the gastrointestinal tract, it was unsuccessful to administer it by nasal or gastrointestinal means. Insulin inhalers, however, were created and authorized.[2] Nasal delivery of insulin raises concerns since it may accumulate in intra-alveolar spaces and impair pulmonary functioning. As a result, alternative administration methods that would improve patient compliance and overall health are being investigated. Natural insulin production is incredibly time-consuming and challenging, and the current process is neither reproducible nor scalable. thehighest levels of insulin.[2] Researchers have started looking into the transdermal route of insulin administration due to limitations with the oral route, discomfort, trauma, and noncompliance with injection form. The transdermal route of insulin delivery offers a number of therapeutic consequences through the skin.[2] Thus, using microneedle (MN)-based technology, the current review clarifies the transdermal route of insulin delivery into the stratum corneum.

The Skin: A Mode for Drug Delivery:

The skin, which is primarily composed of three layers—the epidermis, dermis, and hypodermis, or subcutaneous tissue—serves as a physical barrier and a receptor of external stimuli, as shown in Figure 1. The epidermis, the skin's outermost layer, is around 100 µm thick and mostly made up of a barrier layer called the stratum corneum, which has dead cells stacked on top of each other and are constantly being replaced by new cells created in the basal layer.Hair follicles, sweat glands, and blood vessels that are connected by nerve endings are all found in the core dermis.

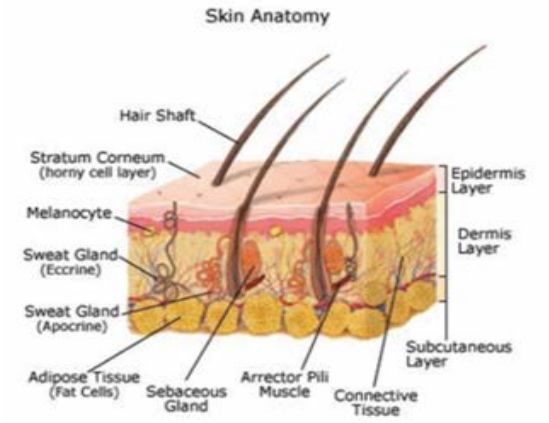

Figure 1: The skin, which is primarily composed of three layers—the epidermis, dermis, and hypodermis, or subcutaneous tissue—has two primary functions: it acts as a physical barrier and a receiver of peripheral impulses Skin anatomy.

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 acts as an energy source as well. The skin's microcirculation, which is made up of tiny vessels, is responsible for maintaining body temperature and distributing medications into the systemic circulation. 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 offer suppleness and durability for mobility. Our skin is a poor conductor of electricity, thus the lipids in it shield us from it. Actually, the stratum corneum offers the most important barrier to diffusion,[2] which approximately causes diffusion up to 90% of transdermal drug applications. On the other hand, to some minimal degree, it has been found that almost all molecules go through the skin.

The Transdermal Drug Delivery System:

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.[3] This is addressed with a novel technological method in micrometer-scale needles that improve medication penetration through the epidermis, allowing for improved insulin delivery that would otherwise necessitate infection. Transdermal drug delivery is a technique in which a precise, fixed, and regulated quantity of medication molecule is encased in a system to be administered at a predefined pace into the intact skin surface into the circulation throughout the body. Transdermal delivery has made incredible strides in recent years in resolving a number of drug development challenges. Many medications' transdermal distribution has been shown to overcome the drawbacks of oral, injectable, or inhaler administration methods.

Additionally, it was noted that around 74% of oral medications lacked the therapeutic efficacy required.[3] Transdermal drug delivery has emerged as a cutting-edge technique for medication delivery that addresses the problems associated with traditional drug administration techniques. Out of 129 substances, over 51% of medications on the US market are undergoing clinical studies after being tested for the transdermal or dermal system.

The FDA approved the first transdermal device, called "Transdermal SCOP," for the prevention of nausea and vomiting in 1979. Today, the transdermal patch technology has reached a height of $2 billion in the global market. Despite their many advantages, there are very few transdermal medications on the market, and many of them have poor permeability across the stratum corneum.[3]

Advantages of transdermal drug delivery system were as follows:

Providing a greater surface area and easier accessibility for medication administration helps prevent "first-pass" metabolism of medicines.

Drugs' peak plasma levels are lowered, which may result in fewer adverse effects.If a drug becomes harmful, the delivery can be stopped.

Patient compliance will increase and the frequency of doses will be decreased.[4]

Transdermal drug delivery has significantly aided in reaching the goal when compared to injection and oral drug administration. Lipophilic medication delivery has also increased with the use of iontophoresis in the transdermal system. Targeting the stratum corneum with MNs and electroporation is the main goal of the current medication delivery strategy.[5] Table 1 lists a few of the commercial formulations based on MN. Because it is located beneath the epidermis, the stratum corneum is thought to be lipophilic. It establishes a barrier that results in medication resistance. Since there are no physiochemical features in the medicine, some kind of vehicle is needed to improve the diffusion. As a result, numerous techniques have been created, including chemical and physical enhancers as MN, sonophoresis, iontophoresis, and electroporation.

Table 1: Marketed formulations based on microneedles as a transdermal delivery system[3]

Market product	Description	Manufacturer
AdminPen™	Microneedle array-based pen-injector device	AdminMed
Macroflux®	Microneedle array	Macroflux® Corporation, Inc.
AdminPatch™	Microneedle array	AdminMed
Microcore®	Dissolvable peptide microneedle patch	Corium
Microjet®	Intradermal microneedle injection system	NanoPass

Glucose-Responsive MN-Array Patch Systems for Diabetes Treatment:

There have been prior reports on the use of conventional MN-array patches for insulin administration.[6,7]Similar to standard subcutaneous administration, these open-loop MN-array patch systems are painless and simple to use, but they are unable to sense glucose concentrations, necessitating regular BGL monitoring and prompt MN-array patch application to maintain euglycemic conditions. Therefore, closed-loop MN-array patches that respond to glucose are preferred. Since it may catalyze the oxidation of glucose to create hypoxic, acidic, and H2O2-rich local

environments, glucose oxidase (GOx) has been widely used as a glucose sensor. These environments can act as biostimuli to initiate the release of therapeutic payloads.[8,9]

glucose+O+HOGOxgulconicacid+HO 2 2 2 2

This led Gu and colleagues to develop the idea of a "smart insulin patch" and show off a prototype patch that uses hypoxia as a biostimulus to control insulin release for the first time (Figure 1A).[10] In particular, GOx and insulin were coencapsulated into synthetic glucose-responsive nanovesicles (GRVs), which were subsequently incorporated into MNs based on hyaluronic acid (HA). These GRVs were produced by the self-assembly of HA modified with hydrophobic groups (2-nitroimidazole) that are sensitive to hypoxia and can be reduced to hydrophilic groups (2-aminoimidazole) in hypoxic environments. Due to GOx's enzymatic conversion of glucose to gluconic acid, which produced a local hypoxic environment and allowed for a hydrophobic-to-hydrophilic transition, oxygen was consumed as BGLs increased.

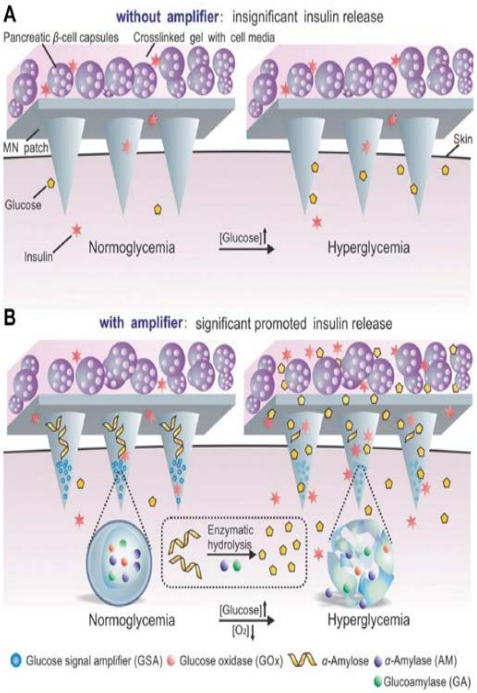

Figure 2: Diagram of the glucose responsive system (GRS), which consists of a microneedle-array patch combined with glucose signal amplifiers (GSA) and pancreatic β-cells. (A)

In the absence of GSA, the MN patch releases negligible amounts of insulin, neither in a normoglycemia nor hyperglycemia state. Cross-linked hyaluronic acid (gray) makes up the MN patch. (B) A hyperglycemia state causes a markedly increased insulin release with GSA. Cross-linked hyaluronic acid embedding assembles layers of GSA and α-amylose (from top to bottom) to form the MN patch. Reproduced from Ye et al.5 with permission.[11]

This successfully caused the vesicles to disassemble, releasing the insulin. According to in vitro findings, the GRVs demonstrated a quick and reversible insulin release in both normoglycemic and hyperglycemic conditions (Figure 1B). Furthermore, a single MN-array patch could be successfully inserted into the mouse's dorsum skin (Figure 1C), control BGLs to return to normal within 30 minutes, and keep diabetic mice in a normoglycemic state for up to 4 hours (Figure 1D). Crucially, the patch effectively reduced the possible risk of consequences from hypoglycemia by inhibiting insulin release once normal blood glucose levels were achieved.

Additionally, Ye et al. used a similar approach to create a novel MN-array patch that contains synthetic glucose-signal amplifiers (GSAs) and pancreatic β-cells for glucose-responsive insulin secretion (Figure)[11] Three enzymes—GOx, α-amylase, and glucoamylase—were encapsulated in the previously reported self-assembled glucose sensitive nanovesicles that were present in the GSAs. The vesicles disassembled when the glucose content increased due to the fast oxygen consumption, releasing the α-amylase and glucoamylase into MNs filled with α-amylose. AM degraded α-amylose into trisaccharides and disaccharides, which glucoamylase then transformed into glucose. Insulin "secretion" was triggered when externally positioned pancreatic β-cells detected this magnified glucose signal.

While the system without a glucose amplifying mechanism did not function as anticipated, in vivo studies demonstrated the effectiveness of the cell-based MN patches in tight glucose management for an extended length of time (up to 10 hours). As previously indicated, GOx produces H2O2 in a hyperglycemic environment, which can also be used to trigger the release of drugs. Consuming the generated H2O2 can help improve

biocompatibility by removing any possible toxicity issues related to H2O2. A glucose-responsive MN-array patch that included H2O2-responsive polymeric vesicles to provide a quick response was described by Hu et al.easy administration and strong biocompatibility.[12] Polyethylene glycol and phenylboronic ester-conjugated polyserine, two amphiphilic block copolymers, self-assembled to create the hollow spherical polymeric vesicles. The interior of the polymeric vesicles included encapsulations of both insulin and GOx. The dissociation of polymeric vesicles and the quick release of insulin can result from the hydrophobic PBE pendent's H2O2-mediated degradation to the hydrophilic one. According to the in vitro results, the amount of GOx converted into MNs swiftly altered the kinetics of insulin release, which reacted rapidly to the increased glucose concentration. In a diabetic mouse model, in vivo experiments showed that a single patch can effectively control BGLs with a lower risk of hypoglycemia.

Gu Lab created an additional novel insulin-loaded MN-array patch that integrates both H2O2 and hypoxia responsiveness in order to further improve the MN-array patches' sensitivity.[13] For the encapsulation of GOx and insulin, a stable polymersome was created using the dual responsive diblock copolymer, which is composed of poly(ethylene glycol) and polyserine modified with 2-nitroimidazole via a thioethermoiety.While the thioether acts as an H2O2-sensitive moiety that can make the polymer more hydrophilic after it is transformed into a sulfone by H2O2, the local hypoxic environment that results from GOx-mediated glucose oxidation can encourage the bioreduction of 2-nitroimidazole groups into hydrophilic 2-aminoimidazole. Under high BGLs, these modifications in the polymers' chemical structure encourage the dissociation of some polymer segments and the consequent release of the encapsulated insulin.. Crucially, GOx activity can be maintained and the damage to skin tissue can be avoided by eliminating H2O2. The translation of this technology is further supported by the in vivo investigations, which indicated that this MN-array patch was very successful in tightly regulating BGLs in diabetic mice and had little adverse effects related to H2O2-mediated inflammation.

Using catalase (CAT), a common enzyme present in almost all living things exposed to oxygen, is another method of scavenging excess H2O2 in GOx-based glucose-responsive systems. CAT can catalyze the breakdown of H2O2 into water and oxygen, shielding the cells from oxidative damage.[14-15] A crosslinked yet biodegradable core-shell MN-array patch for insulin delivery with enhanced biocompatibility was created by Wang et al. in a more recent study (Figure 3A).[16] An H2O2-sensitive bond was used to modify insulin with a phenylboronic acid (PBA) group, which was then anchored to the polyvinyl alcohol (PVA) matrix, which is the primary constituent of MNs. Under hyperglycemic conditions, GOx created H2O2, which caused insulin to be released from the polymeric matrix.Under hyperglycemic conditions, GOx created H2O2, which caused insulin to be released from the polymeric matrix. The PVA matrix was also crosslinked using an H2O2-labile short linker (N1-(4-boronobenzyl)-N3-(4-boronobenzyl) N1,N1,N3,N3-tetramethylpropane-1,3-diaminium); TSPBA) to further promote insulin delivery and boost responsiveness. Notably, GOx was encapsulated into the acrylatednanogel, which was subsequently fixed completely in the PVA matrix, in order to lessen its possible toxicity and preserve its enzymatic activity. The integrated CAT nanogels in the MNs shell were intended to remove the excess H2O2 produced by the system. The smart core-shell MN-array patches were successfully placed into the skin (Figure 3B) and successfully controlled BGLs without causing hypoglycemia (Figure 3C), simulating the function of pancreatic β-cells, according to in vivo experiments. More significantly, the protective shell with CAT efficiently removed H2O2, increasing GOx's reactivity and providing better biocompatibility (Figure 3D).

Zhang et al.64 described an H2O2 and pH cascade-responsive MN-array patch that used a similar approach to lessen the negative effects of H2O2 generated in the GOx-based systems. The matrix core of this patch was loaded with GOx-encapsulated nondegradable micelles (GOx-NCs) and insulin-encapsulated degradable micelles (Ins-NCs). To scavenge H2O2 produced in the core, the MNs were also covered with a thin sheath

encapsulating CAT. The GOx may have sustained enzymatic activity when it is in a nondegradable micelle state. H2O2-labile and positively charged amphiphilic block copolymers self-assembled to create the micelles. The H2O2 and gluconic acid produced by GOx under high glucose concentrations successfully caused the rupture of the micelles and decreased the electrostatic contacts between insulin and cationic polymers (isoelectric point-5.3), thus releasing insulin rapidly. They demonstrated neither oxidative nor acidic condition alone could cause the insulin release, while their combination was able to trigger release insulin. In addition, insulin was released in a pulsatile man ner when the system was alternatively exposed to the normoglycemic and hyperglycemic conditions. The in vivo results also confirmed the self-regulated insulin release capability in the diabetic mice. More importantly, utilization of the CAT embedding sheath successfully migrated the skin inflammation caused by H2O2

Chen and colleagues[17] have developed a GOx-based glucose-responsive MN for type 2 diabetes treatment that uses the pH drops brought on by the enzymatic oxidation of GOx in addition to insulin delivery. The MN included Exendin-4 (Ex4), a GLP-1 receptor agonist with FDA approval for the clinical treatment of type 2 diabetes. Ex4 was encapsulated in calcium phosphate particles (mineralized Ex4, m-Ex4), which were pH-sensitive and could dissolve spontaneously in acidic environments, to enable an on-demand Ex4 injection. In the meantime, to enhance and extend the enzymatic activity of GOx, it was immobilized in a stable hybrid nanoflower made of copper phosphate miner-alized particles (mineralized GOx, m-GOx) to prevent rapid leaking from MNs. Both m-GOx and m-Ex4 were included into an MN-array patch based on alginate. In the MNs, m-GOx transformed glucose signals into H+ signals when hyperglycemic. initiating the m-Ex4 particles' dissociation, which releases Ex4. Because of the quick dissociation of m-Ex4 and the prolonged glucose reactivity of m-GOx, the dual mineralized particle-containing MN-array patches displayed prolonged BGL control.

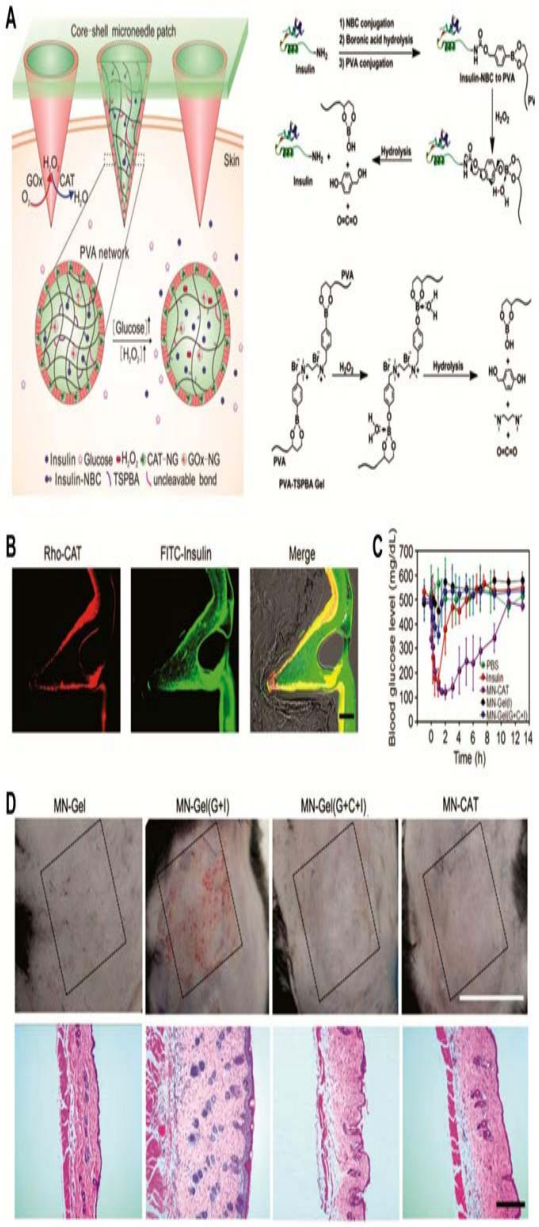

Figure 3: (A) Diagrammatic illustration of the H2O2-responsive PVA-TSPBA matrix-based glucose-responsive core-shell MN-array patch for insulin administration.

(B) Typical pictures of core-shell MNs placed into skins: the core labeled with insulin-FITC (green), the shell incorporating rhodamine B tagged CAT (red), and their overlap. 100 μm is the scale bar. (C) Type 1 diabetic mice's BGLs after receiving several MN-array patch types: (1) MN-Array patch of GOx-NG and insulin-NBC-loaded gels with a CAT-NG shell (MN-CAT); (2) human

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recombinant insulin administered subcutaneously; (3) MN-Array patch of GOx-NG and insulin-NBC-loaded gels (MN-Gel(G+I)) without a shell; (4) MN-Array patch of blank gel only (MN-Gel); (5) MN-Array patch of insulin-NBC-loaded gels (MN-Gel(I)); and (6) MN-Array patch of GOx-NG, insulin-NBC, and CAT-NG-loaded gels (MN-Gel(G+C+I)). (D) Typical picturesof the mice's treated skins and the accompanying H&E staining outcomes. Reproduced from Wang et al.[16] with permission.

Glucose oxidase-based MN systems:

One of the most popular glucose-sensing ingredients in the creation of intelligent transdermal insulin administration devices headquartered in Minnesota is glucose oxidase. An enzyme called glucose oxidase catalyzes the conversion of glucose to hydrogen peroxide (H2O2) and gluconic acid.[18]

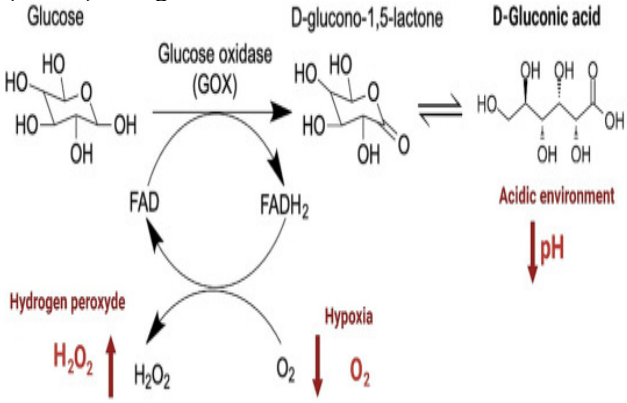

Figure 3: Schematic illustration of the glucose oxidase-catalysed oxidation of glucose and the distinct stimuli-triggered mechanism for glucose-responsive insulin release. Image created with biorrender.com

The localized hypoxic environment produced by oxygen consumption during this process can be used to initiate insulin delivery in response to hyperglycemia. It is also possible to use the hydrogen peroxide produced during glucose oxidation to cause MNs to release insulin. Finally, by adding pH-sensitive materials to the transdermal delivery system, the local pH decrease caused by the creation of gluconic acid can be used as an alternative to trigger insulin release. Therefore, stimuli-responsive materials (to hypoxia, H2O2, or pH) must be incorporated into smart transdermal insulin delivery systems based on glucose oxidase in order to achieve glucose-responsive insulin release (Fig) [19].

In addition to decreasing glucose oxidase function, hydrogen peroxide generated during the enzymatic oxidation of glucose can cause free radical oxidative stress on skin tissue. In order to maximize insulin delivery, H2O2-scavenging enzymes, like as catalase, are frequently incorporated into the formulation of these devices. All glucose oxidase-based MN systems that use stimuli-responsive materials for transdermal insulin delivery are together with published findings regarding their antidiabetic effects in animal models of diabetes that have been pharmacologically produced.

Hypoxia-triggered glucose oxidase-based MN systems:

The hypoxic microenvironment created by glucose oxidase was used by the first glucose-responsive transdermal insulin delivery system ever reported to cause a fast release of insulin in response to hyperglycemia. 2-nitroimidazole groups are typically present in the few hypoxia-responsive materials that are currently on the market [20]. In a hypoxic environment, these groups are diminished, which alters the materials' water solubility and ultimately causes the release of insulin. Using hypoxia-responsive nanovesicles composed of hyaluronic acid linked with 2-nitroimidazole and loaded with insulin and glucose oxidase, Yu et al. created a hyaluronic acid-based MN system [21]. The hydrophobic 2-nitroimidazole group is converted to a hydrophilic 2-aminoimidazole group in a hypoxic environment, which causes the nanovesicles to dissociate and release insulin.

The mechanism by which the nanovesicle-loaded MNs release insulin in response to hypoxia was initially shown in vitro using dissolving media with varying glucose contents. The antidiabetic impact of these MN systems was then evaluated in mice with type 1 diabetes caused by streptozotocin. The animals were split up into five groups and given an insulin dosage of 10 mg/kg: Hypoxic-responsive nanovesicles loaded with insulin and glucose oxidase (1 mg/kg), hypoxic-responsive nanovesicles loaded with insulin and half the dose of glucose oxidase (i.e., 0.5 mg/kg), MN arrays containing hypoxic-responsive nanovesicles loaded with both insulin and glucose oxidase, MN arrays containing free insulin, and v) Hypoxic-responsive nanovesicles loaded solely

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with insulin in MN arrays. According to the results, blood glucose levels were reduced below 200 mg/dL in 30 minutes and remained in this normoglycemic state for 3.5 hours only in MN arrays that contained hypoxic-responsive nanovesicles loaded with both insulin and glucose oxidase at the full dose. This showed that the hypoxic-responsive nanovesicles retained their integrity in the absence of glucose oxidase (group v), preventing insulin release and producing a blood glucose profile that was comparable to that of the control group. Likewise, blood glucose levels below 200 mg/dL were not attained when the glucose oxidase dose was cut in half (group iv) because the glucose oxidase dose was not high enough for the Hyperglycemic levels will cause the nanovesicles to separate. Finally, while normoglycemic values were quickly reached for MN arrays containing free insulin (group iii), hyperglycaemic levels were restored considerably more quickly (Fig. 2b). Overall, this study demonstrated that in order to induce effective hypoxia-mediated insulin release from the devices presented, a minimum glucose oxidase dose was required. The quick response of the MNs with hypoxic-responsive nanovesicles loaded with both insulin and glucose oxidase was further shown in diabetic mice in an intraperitoneal glucose tolerance test performed one hour after MN delivery. In fact, when it came to blood glucose levels, the diabetic mice that were given this treatment behaved similarly to the healthy mice. Finally, compared to MNs containing glucose, these glucose-responsive MNs dramatically reduced the risk of hypoglycemia in healthy mice.just insulin that is free. These outcomes demonstrated the glucose oxidase-based MN system's in vivo safety and effectiveness for hypoxia-triggered smart transdermal insulin delivery in response to hyperglycemia.

Phenylboronic acid-based MN systems:

More recently, phenylboronic acid-based glucose-responsive MN patches have been created as a substitute for glucose oxidase-based ones. Because of its Lewis acid characteristics, which allow it to reversibly form esters with cis-1,2 or cis-1,3 diols, including glucose, phenylboronic acid is a synthetic molecule that can function as a glucose sensor [22]. Both an anionic tetrahedral boronate structure and an uncharged trigonal configuration of phenylboronic acid are in equilibrium in aqueous environments. Although both configurations may form cyclic phenylborate complexes and bond with glucose reversibly, the anionic boronate structure has a significantly higher binding affinity. Considering that phenylboronic acid has a high pKa of 8.6 at physiological pH (7.4) Low glucose responsiveness is the outcome of the equilibrium being mostly moved towards the uncharged state. Therefore, the phenylboronic acid present in glucose-responsive MNs is chemically altered to become more acidic and ultimately lower its pKa in order to increase glucose responsiveness at physiological pH. In order to do this, the aromatic ring of the phenylboronic acid has been modified to include both ortho-substituents that can create intramolecular coordination bonds (for example, between B and N or B and O) and electron-withdrawing moieties (such as halogens, nitro, or carboxyl groups) [23], [24], [25]].Up till now, charge switch-triggered swelling, glucose competitive displacement, and crosslinking dissociation have been the clever insulin delivery strategies utilized using phenylboronic acid-based MNs (Fig. 3). All phenylboronic acid-based MN systems for transdermal insulin delivery are listed in Table 2, along with published findings regarding their antidiabetic effects assessed in animal models of diabetes that were created by pharmacological means.

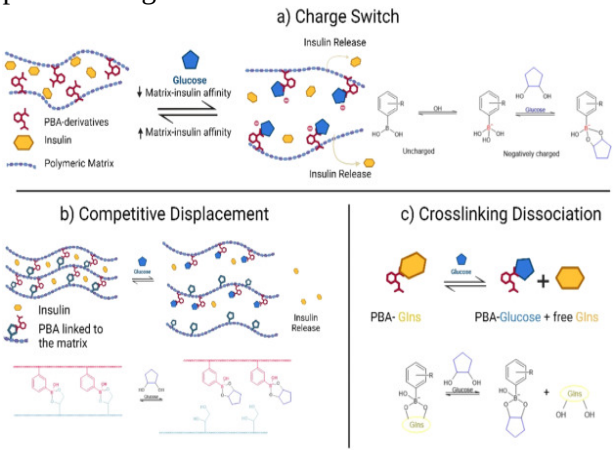

Figure 4: Diagrammatic representation of the phenylboronic acid-based glucose-responsive insulin delivery mechanisms: a) charge switch-induced swelling, b) competitive displacement, and c) crosslinking dissociation.

Biorrender.com was used to make all of the photos

MN systems based on the combination of glucose oxidase and phenylboronic acid:

Tong et al. created a dual-smart transdermal insulin delivery system based on phenylboronic acid and glucose oxidase in an effort to try to achieve a synergistic impact between the two processes [26]. To do this, dissolving MN patches composed of PVP and PVA were embedded with polymersomes containing insulin and glucose oxidase. An amphiphilic triblock copolymer comprising PEG, poly (phenylboronic acid pinacol ester), and poly (3-acrylamidophenylboronic acid) was used to self-assemble the polymersomes. Since ester bonds are hydrolyzed by the H2O2 produced during the glucose oxidase-catalyzed oxidation of glucose, the phenylboronicpinacol esters give the polymersomes H2O2-responsiveness. This ultimately contributes to the breakdown of polymersomes and the release of insulin by making the copolymer water soluble once it loses its phenylboronicpinacol ester side chains.However, the 3-acrylamidophenylboronic acid groups give the polymersomes the ability to swell in response to a charge switch. In fact, when glucose is bound under hyperglycemic conditions, the initially uncharged phenylboronic acid moieties increase their negative charge density. This results in the swelling of the polymer and a decrease of the binding strength between the polymer and negatively charged insulin, which causes insulin to be released.Four groups of rats with streptozotocin-induced diabetes were used to test the antidiabetic effects of these MN patches: i) MN patches with empty polymersomes(control group); ii) subcutaneous insulin injection (20 IU/kg); iii) MN patches with dual glucose-responsive polymersomes loaded solely with insulin (40 IU/kg); and iv) MN patches with dual glucose-responsive polymersomes loaded with both insulin (40 IU/kg) and glucose oxidase. While subcutaneous insulin (group ii) quickly reduced blood glucose levels to 80 mg/dL but was unable to sustain them for the next hour, treatment with MN patches in this final group kept glucose levels below 200 mg/dL for longer than their counterparts loaded only with insulin (i.e., 4 h versus 2 h). Collectively, these findings demonstrated that when glucose oxidase (group iv) was present,Because of their H2O2-responsiveness, the dual glucose-responsive polymersomes may hasten the release of insulin. Compared to the group that received glucose-responsive polymersomes loaded just with insulin, this led to a better blood glucose profile.

MN systems based on other mechanisms:

Other MN-based glucose-responsive technologies have just surfaced and are currently being developed Among these clever glucose-responsive techniques, electrochemical closed-loop systems combine electrical devices that facilitate insulin delivery with electrochemical glucose sensors to provide real-time tailored theranostic tools for diabetes treatment. Furthermore, comparable competitive displacement-triggered delivery systems based on physiological glucose-binding molecules have been developed to address some of the issues of phenylboronic acid-based systems, such as long-term toxicity.Although these new techniques offer a fresh viewpoint on glucose-responsive transdermal insulin delivery tactics, the outcomes still fall well short of the effectiveness rates of the previously mentioned approaches. To make these systems better, further study should be done.

- **Electrochemical closed-loop MN systems:**

Li et al. electrically improved the transdermal penetration of insulin and glucose by combining MN patches with iontophoretic technologies [27]. In fact, the first transdermal closed-loop system based in Minnesota was created by the authors to give insulin and check blood sugar simultaneously. Insulin administration and glucose extraction were greatly improved by coupling with iontophoretic technology. Three coupled modules made up the electrochemically adjustable closed-loop system: A flexible printed circuit board that can electrically regulate the iontophoretic release of insulin from the third module when a hyperglycemic state is detected; i) a glucose monitoring sensor based on mesoporous MNs enhanced with reverse iontophoretic extraction and electrochemical sensing based on the glucose oxidase-catalyzed oxidation of glucose; and iii) an iontophoresis-supplemented insulin delivery component based on mesoporous MNs. Crucially, there was no dose restriction on the insulin that could be placed into the insulin

delivery module. A skin tissue surrogate constructed with water-impermeable parafilm (to simulate the SC) on top of an agar gel was used to assess the release of insulin from the therapeutic module in vitro. Measurements of insulin release were made with and without an iontophoretic current (i.e., 0 vs. 0.5 mA, respectively).Because of the constant free diffusion of insulin through the mesoporous MNs, which accounts for the basal delivery of insulin, only 5.8 ± 0.15 percent of insulin was released after three hours in the absence of iontophoretic current. On the other hand, insulin release was 2.3 times greater when an iontophoretic current of 0.5 mA was present. This indicates an electrically-driven insulin bolus that might reduce blood glucose variations after meals. Furthermore, in a diabetic rat model, this closed-loop device showed that it could precisely monitor changes in blood sugar levels and react by releasing insulin to control hyperglycemia. Overall, diabetic rats treated with mesoporous MNs supplemented with iontophoretic current had blood glucose levels that remained normoglycemic for 3.3 hours longer than rats treated with mesoporous MNs or subcutaneous insulin injection (1.7 hours). MNs without iontophoretic current (0.3 h).

Competitive displacement-triggered MN systems based on glucose transporter GLUT:

The physiological glucose-binding transporter GLUT is currently the sole molecule that has been utilized for the formulation of glucose-responsive MN systems investigated in vivo, despite the fact that other glucose-binding molecules have been identified to induce glucose-responsive insulin release [20].

The sole transdermal glucose-responsive insulin delivery device based on the glucose transporter GLUT that has been reported to date was created by Chen et al. [28]. The glucose transporter GLUT, which is expressed on red blood cell vesicles and loaded into the tips of crosslinkedmethacrylated hyaluronic acid MNs, is coupled to glucosamine-modified insulin in this system. Insulin is competitively displaced by glucose binding to the transporter, which eventually results in glucose-triggered insulin release. Additional glucosamine-modified insulin was applied to the top layer of the MN patch to act as an insulin reservoir in order to get around the limited quantity of glucosamine-modified insulin that was attached to red blood cell vesicles because of the one-to-one unique interaction between glucosamine and GLUT. It is anticipated that this reservoir will attach to GLUT after its glucose supply is exhausted (after recovery of normoglycemic values) for the release of insulin in response to glucose. Furthermore, by attaching recombinant GLUT receptors to their membrane, this GLUT-based glucose-responsive insulin release mechanism has been expanded to liposomes. Remarkably, as compared to red blood cell vesicles, this formulation approach showed a greater concentration of GLUT receptor. Mice with type 1 diabetes caused by streptozotocin were used to examine the antidiabetic effects of these MN patches. Before progressively rising back to hyperglycaemic levels, GLUT-based MN patches were able to sustain normoglycemia for the first one to one and a half hours, and for roughly two and a half hours in the case of liposomes and red blood cell vesicles, respectively. Compared to the group receiving subcutaneous insulin injections, normoglycemic levels were maintained for a longer period of time in both situations. Furthermore, a test for intraperitoneal glucose tolerance was performed.one hour after the procedure. It's interesting to note that diabetic animals treated with either glucose-responsive MN patch responded to the glucose challenge with blood glucose levels comparable to control healthy mice, but mice treated with subcutaneous insulin injection had their blood glucose levels climb until they reached a hyperglycaemic condition. In healthy mice, the possibility of producing hypoglycemia as a result of insulin release under normoglycemic circumstances was also examined. The risk of hypoglycemia was lower with both glucose-responsive MN patches than with subcutaneous insulin infusion.

Microneedles: A New Approach:

Medical MN devices, which come in a variety of brands and variations, are used to form tiny microchannels through the stratum corneum layer. According to research from the University of Marburg in Germany, the MN method improves the skin penetration of both hydrophilic and lipophilic substances. This Minnesota strategy has also been dubbed "the vaccine of the future."

Some of these MNs have regulatory approval and come in a variety of forms, including hollow, solid, coated, dissolving, and hydrogel forming. In the field of nanomedicine, MN devices and patches have also been effective in delivering medications in the form of nanoparticles.

Because of their design, MNs merely pierce the skin's dermal layer, not deeply penetrating and activating the dermal nerve. Because they are stacked in an array, the MNs can be employed in a variety of ways to improve transdermal drug delivery. In order to essentially overcome both injections and patches, MNs—microscale needles assembled on the transdermal patch—are thought of as a cross between hypodermic needles and transdermal patches. Due to the short needle length, MN patches avoid the stratum corneum without activating the cutaneous nerves. MNs make tiny holes that let the medication to enter the body without irritating or hurting the skin. MN is a minimally invasive, painless procedure that combines the benefits of typical transdermal medication administration method in addition to using standard hypodermic needles.[5] MNs produce a pore that is large enough to allow the body to absorb the medication in the form of a micromolecular. According to some sources, the medication might be applied topically to the MNs and then injected into the skin. According to some research, an MN delivers the medication securely and without any negative effects after dissolving when applied. Conversely, the dissolved medication is directly injected into the skin using hollow MNs. At the moment, MNs are among the newest strategies which are created and developed through clinical studies, and they are utilized in the administration of macromolecules like influenza vaccine, insulin, and parathyroid hormone.[5] MNs are a carefully considered medication with efficient transdermal administration. This entails devices such as microelectronics that can painlessly pierce 100 mm into the epidermis. The use of MN technology can penetrate the stratum corneum, a physical barrier that restricts the entry of numerous medications.[29] MNs are identical to traditional needles, which are array-shaped and manufactured at the microscale. Numerous papers have demonstrated the utilization of glass, dextrin, maltose, and silicon or metal MNs. Additionally, MNs can be created as patch systems, which will be utilized for transdermal administration. Transdermal drug administration has a low success rate since most medications at the intended therapeutic rate frequently do not reach the epidermal layer. As a result, it has been essentially discovered that using MN patches improves skin permeability and increases transdermal drug delivery.

In this area, a great deal of study has been done on designing MNs. The five primary forms of MNs that are highlighted in this review are solid, coated, dissolving, hollow, and hydrogel-forming MNs.[29]

Solid microneedles:

A method known as "poke with patch" that entails two steps is solid MN development. The initial stage involves applying solid MN arrays to the skin, which forms a tiny microchannel on the stratum corneum into which the medications can be readily absorbed by the body. By using the passive diffusion approach, the tiny microchannel raises the stratum corneum's permeability. Solid MNs can be composed of polymers, metals, or silicon. According to numerous published research, the usage of solid MN arrays has enhanced the transdermal penetration of various substances, including proteins, calcein, insulin, and naltrexone.[29] MN arrays are frequently suggested in conjunction with other combination techniques, such as iontophoresis, to improve transdermal delivery effectiveness.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.[29] 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 may be a good choice for administering vaccines or powerful medications, however they are not appropriate for delivering significant amounts of active molecules.[29]

Dissolving microneedle:

After insertion, the needle matrix dissolves into the skin, delivering the medication. Dissolving MNs are composed of a soluble/biodegradable

matrix containing the active ingredient. These MNs are created using micromolding processes. These arrays, which can be used to distribute insulin, low-molecular-weight heparin, ovalbumin, adenovirus vector, vaccine antigens, photosensitizers, and precursors, are often composed of sugars, carbohydrates, or synthetic polymers. Iontophoresis and dissolving MN work better together to transfer the medication to the skin.[29]

Hollow microneedle:

The medication is administered with hollow needles found in hollow MNs. Made of a variety of materials, including silicon, metal, hollow glass, polymers, and ceramic, hollow MN is widely employed in the delivery of insulin.

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 microprojections, 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 micromolecules.[29]A microfabrication technique called a microelectromechanical system combines a mechanical component with sensors, actuators, and electronics on a silicon substrate. This technology will make it possible to integrate the entire system on a chip, which will improve glucose management and control. The benefit of the parenteral route is that it enters the bloodstream immediately, avoiding the body's physical barrier and deterioration. MN's dimensions and length allow it to enter the stratum corneum's capillary-rich layer and deliver the medication into the bloodstream. Due to its painless and noninvasive drug administration method, this technique will open up a world of possibilities in the field of subcutaneous medication delivery.

Conclusion

Due to their extremely intricate interdependencies, autonomous diabetes treatment systems guarantee interdisciplinary research projects. It is undoubtedly possible to apply the advancements of a noninvasive, bioengineered interface, like MNs, which offer a deeper comprehension of the skin. In general, the risk of patient noncompliance and human error may be decreased by using painless insertion. Additionally, it is hypothesized that MN's minimal training idea, which might be quite helpful for diabetic youngsters, is the reason for its increased demand. As a result, MNs are a practical way to lower the risk of long-term diabetes problems, enhance glucose control, and pave the way for better and more comfortable diabetes care. Therefore, it is determined that transdermal delivery of MN-based technology is significantly more effective and superior than other injectable in better patient compliance and management.

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