

## GLUCOSE-RESPONSIVE MICRONEEDLE PATCHES FOR DIABETES TREATMENT

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### ABSTRACT

People with diabetes require antidiabetic therapeutics including insulin as well as glucagon-like peptide 1 (GLP-1) and its analogs to regulate their blood glucose levels. For diabetic patients, insulin delivery systems with rapid response and controlled drug release as a treatment platform are essential. However, drug delivery systems often need to be designed in very complex ways to achieve this goal. In this study, we greatly simplified the preparation of this insulin delivery system. Microneedles (MNs) were fabricated with phenylboronic acid modified methacrylate hyaluronic acid (MA-HA-PBA) as a drug delivery carrier, using a dynamic bond between phenylboronic acid and gluconic acid modified insulin (GINS) as a controlled-release component. Nevertheless, conventional treatment based on hypodermic administration is generally associated with poor blood glucose control, patient noncompliance, and a high risk of hypoglycemia. An insulin microneedle patch was developed with simple preparation method, fast response, controlled release, high drug load and low residue. We validated this concept using the streptozotocin (STZ) method in type 1 diabetic rats. It provides direction for simplifying the concept and manufacturing of controlled-release insulin microneedle patches. Closed-loop drug delivery strategies, also known as self-regulated administration, which can intelligently control drug release kinetics in response to fluctuations in blood glucose levels, show tremendous promise in diabetes therapy. Meanwhile, advances in the development and use of microneedle (MN)-array patches for transdermal drug delivery provide an alternative method to conventional hypodermic administration. Therefore, glucose-responsive MN-array patches have attracted attention in recent years for the treatment of diabetes. This review summarizes recent advances in glucose-responsive MN-array patch systems. Their opportunities and challenges for clinical translation are also discussed.

**Keywords:** Microneedles , Diabetes Patches, Smart insulin delivery, Controlled drug delivery, diabetes treatment technology.

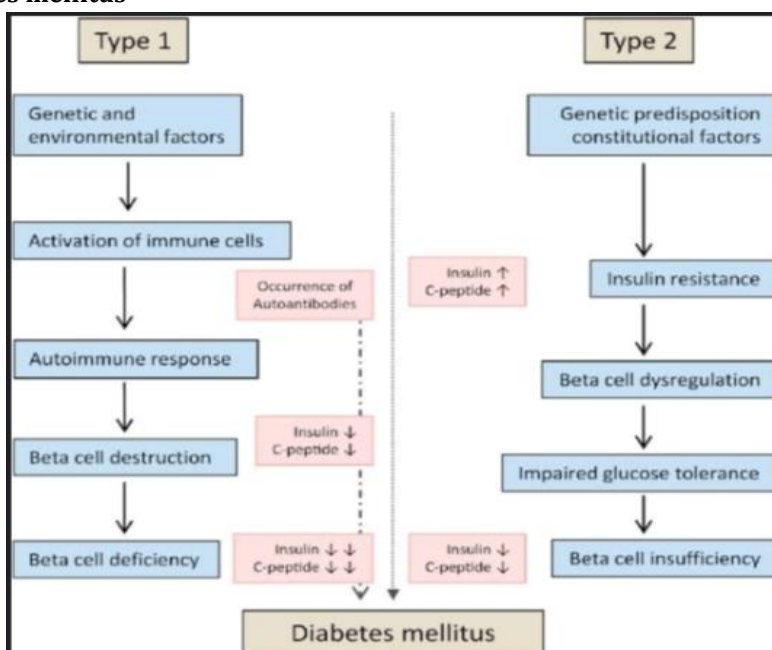
### I. INTRODUCTION

Glucose-responsive microneedles are a promising technology to improve the lives of people with diabetes by helping to regulate blood glucose levels. It is a disorder of glucose metabolism that results mainly from the destruction of insulin-producing  $\beta$  cells in the pancreas (type 1 diabetes) or the loss of  $\beta$  cell function over time with peripheral insulin resistance (type 2 diabetes). Diabetes increases the risk of death and disability, affecting more than 537 million people worldwide. In healthy individuals, pancreatic cells tightly control fluctuations in blood glucose levels. Elevated blood glucose levels stimulate increased insulin secretion from pancreatic  $\beta$  cells, while hypoglycemia inhibits further insulin secretion and maintains glycemic homeostasis with glucagon secreted from  $\alpha$  cells. Dynamic regulation of the balance between insulin and glucagon under different conditions is important for blood glucose.

- **What is diabetes mellitus ?**

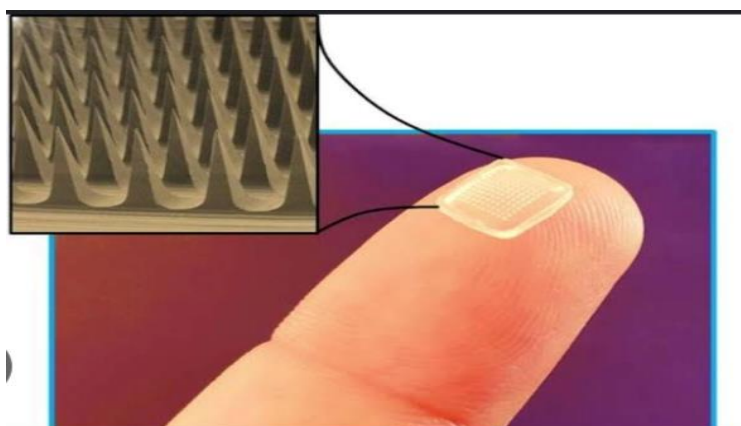
The term diabetes describes a group of metabolic disorders characterized and identified by hyperglycaemia in the absence of treatment. The heterogeneous aetio pathology includes defects in insulin action, or both, and disturbances of secretion. Carbohydrate, fat and protein metabolism.

**Dig: Type of Diabetes mellitus**



### • What is microneedle patches ?

Microneedle patches are a type of transdermal patch that has been embedded with an array of tiny needles to deliver the drug solution. Every microneedle patch has an adhesive layer that sticks to the skin and needles that puncture the skin to facilitate drug delivery.



**Dig. microneedle transdermal patch**

### ❖ Background of microneedle patches drug delivery

Microneedles were first mentioned in a 1998 paper by the research group headed by Mark Prausnitz at the Georgia Institute of Technology that demonstrated that microneedles could penetrate the uppermost layer (stratum corneum) of the human skin and were therefore suitable for the transdermal delivery of therapeutic agents. Subsequent research into microneedle drug delivery has explored the medical and cosmetic applications of this technology through its design. This early paper sought to explore the possibility of using microneedles in the future for vaccination. Since then researchers have studied microneedle delivery of insulin, vaccines, anti-inflammatories, and other pharmaceuticals. In dermatology, microneedles are used for scarring treatment with skin rollers. The major goal of any microneedle design is to penetrate the skin's outermost layer, the stratum corneum (10-15µm). Microneedles are long enough to cross the stratum corneum but not so long that they stimulate nerves which are located deeper in the tissues and therefore cause little to no pain. Research has shown that there is a limit on the type of drugs that can be delivered through intact skin. Only compounds with a relatively low molecular weight, like the common allergen nickel (130 Da), can penetrate the skin. Compounds that weigh more than 500 Dalton cannot penetrate the skin.

#### ❖ **Concept of Microneedle patches:**

Microneedles or Microneedle Patches or Microarray Patches are micron-scaled medical devices used to administer vaccines, drugs and other therapeutic agents. Microneedles were initially explored for transdermal drug delivery applications, their use has been extended to intraocular, vaginal, cardiac, transconj., vascular, gastrointestinal and intracochlear drug delivery.

Microneedles are produced by various methods, usually involving photolithographic processes or micromolding. These methods involve etching microstructures into resin or silicon to insert microneedles. Microneedles are made from a variety of materials, from silicon, titanium, stainless steel, and polymers. Some microneedles are made from drugs that are delivered into the body but are needle-shaped so they can penetrate the skin.

Microneedles range in size, shape and function but are used as an alternative to other delivery methods such as traditional hypodermic needles or other injection devices.

#### ❖ **Type of microneedle patches**

##### 1) Solid

This type of array is designed as a two part system; the microneedle array is first applied to the skin to create microscopic wells just deep enough to penetrate the outermost layer of skin, and then the drug is applied via transdermal patch. Solid microneedles are already used by dermatologists in collagen induction therapy, a method which uses repeated puncturing of the skin with microneedles to induce the expression and deposition of the proteins collagen and elastin in the skin.

##### 2) Hollow

Hollow microneedles are similar to solid microneedles in material. They contain reservoirs that deliver the drug directly into the site. Since the delivery of the drug is dependent on the flow rate of the microneedle, there is a possibility that this type of array could become clogged by excessive swelling or flawed design. This design also increases the likelihood of buckling under the pressure and therefore failing to deliver any drugs.

##### 3) Coated

Just like solid microneedles, coated microneedles are usually designed from polymers or metals. In this method the drug is applied directly to the microneedle array instead of being applied through other patches or applicators. Coated microneedles are often covered in other surfactants or thickening agents to assure that the drug is delivered properly. Some of the chemicals used on coated microneedles are known irritants. While there is risk of local inflammation to the area where the array was, the array can be removed immediately with no harm to the patient.

##### 4) Dissolvable

In a more recent adaptation of the microneedle design, dissolvable microneedles encapsulate the drug in a nontoxic polymer which dissolves once inside the skin. This polymer would allow the drug to be delivered into the skin and could be broken down once inside the body. Pharmaceutical companies and researchers have begun to study and implement polymers such as Fibroin, a silk-based protein that can be molded into structures like microneedles and dissolved once in the body.

##### 5) Hydrogel-forming

In hydrogel-forming microneedles, medications are enclosed in a polymer. The microneedles can penetrate the stratum corneum and draw up interstitial fluid leading to polymer swelling. Drugs enter the skin from the swollen matrix.

##### 6) Enzyme-Based Patches

**Glucose Oxidase (GOx) :** Microneedle patches can incorporate GOx, which catalyzes the oxidation of glucose, producing hydrogen peroxide. This reaction generates a signal that can be detected by integrated sensors, triggering insulin release.

**Glucose Dehydrogenase (GDH) :** Similar to GOx, GDH can also catalyze glucose oxidation reactions, providing a basis for glucose sensing in these patches.

**7) Smart Polymer-Based Patches :**

**Responsive Hydrogels :** These hydrogels change their swelling or permeability properties in response to glucose levels. This change can be used to control the release of insulin or other drugs from the patch.

**Conducting Polymers :** Some patches use conducting polymers that change their electrical properties in response to glucose levels, enabling electronic detection and feedback mechanisms.

**8) Combined Glucose Monitoring and Insulin Delivery Systems :**

**Integrated Sensors :** Microneedle patches may include integrated sensors (optical, electrochemical, or other types) that detect glucose levels in interstitial fluid.

**Closed-loop Systems :** Also known as artificial pancreas systems, these patches use real-time glucose data to regulate insulin delivery automatically, providing a closed-loop approach to diabetes management.

**9) Biocompatible Materials :**

**Polymer Microneedles :** Made from biocompatible materials like polymers (e.g., PLA, PLGA) or metals (e.g., stainless steel, titanium) that ensure compatibility with the skin and effective drug delivery.

**10) Wireless Communication and Monitoring :**

**Smart Patch Systems :** Some advanced patches may incorporate wireless communication technologies to transmit glucose data to external devices (e.g., smartphones, continuous glucose monitors), enabling remote monitoring and feedback.

**11) Customizable Patch Designs :**

**Customized Formulations :** Patches can be tailored to individual patient needs based on factors such as insulin sensitivity and glucose fluctuations, optimizing treatment efficacy.

Each type of glucose-responsive microneedle patch has its advantages and may be suited to different patient profiles or treatment preferences. Ongoing research and development continue to explore new materials, sensor technologies, and integration methods to improve the performance and usability of these innovative diabetes treatment solutions.

**❖ Working of Diabetes Patches:**

People age two or older can secure a diabetes monitoring patch (with adhesive, glucose sensor, and transmitter) to the upper arm, abdomen, or upper buttocks using an adhesive backing.

The diabetes patch works by placing a small glucose sensor under the skin to measure your interstitial glucose, which is glucose in the body's tissues. Glucose readings are then sent directly to a compatible receiver or smartphone†, where up to 288 glucose readings are automatically taken per day. Putting on a diabetes patch is easy. With the G6 and 84% of users reported painless sensor insertion 1 and with the G7, 95% of participants reported on the questionnaire that sensor insertion felt painless. This makes it suitable for both children and adults.

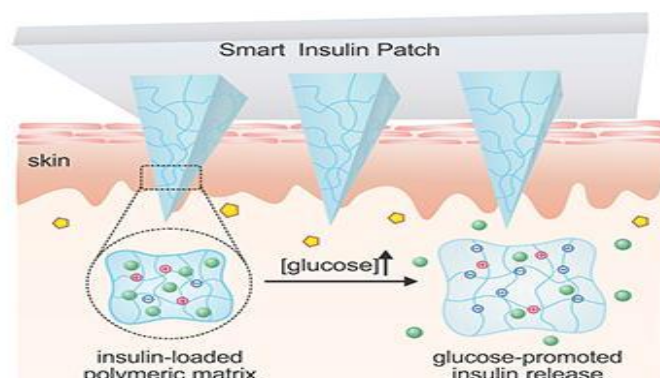
When applying the diabetes patch to your body, it is important to choose an area that will not be bumped or impacted frequently when you bend your body to ensure a comfortable position. Once applied, you press the adhesive patch onto your skin for up to 60 seconds for a secure hold.

To get the most out of each patch, make sure you rub the area to remove wrinkles and any chance of peeling once applied.

It is important for users to ensure that the skin is dry, that the room is not too humid, and that the sensor insertion site is cleaned twice: first with soap and water and then, once dry, with an alcohol wipe. Rear adhesive. The patch can be worn on the upper arm or back of the abdomen. The G6 can also be worn in the upper hips for children ages 2 – 17. With the G7, this additional insertion point is perfect for children ages 2 – 6.

Avoid wearing the sensor after a shower or bath as this will create excess moisture and the diabetes patch will not work as well. If you use extra adhesive, place it under the patch, away from where the needle is inserted, for a secure hold. If your skin is irritated or sensitive, you should work with your healthcare professional (HCP) to find a solution that works for you.





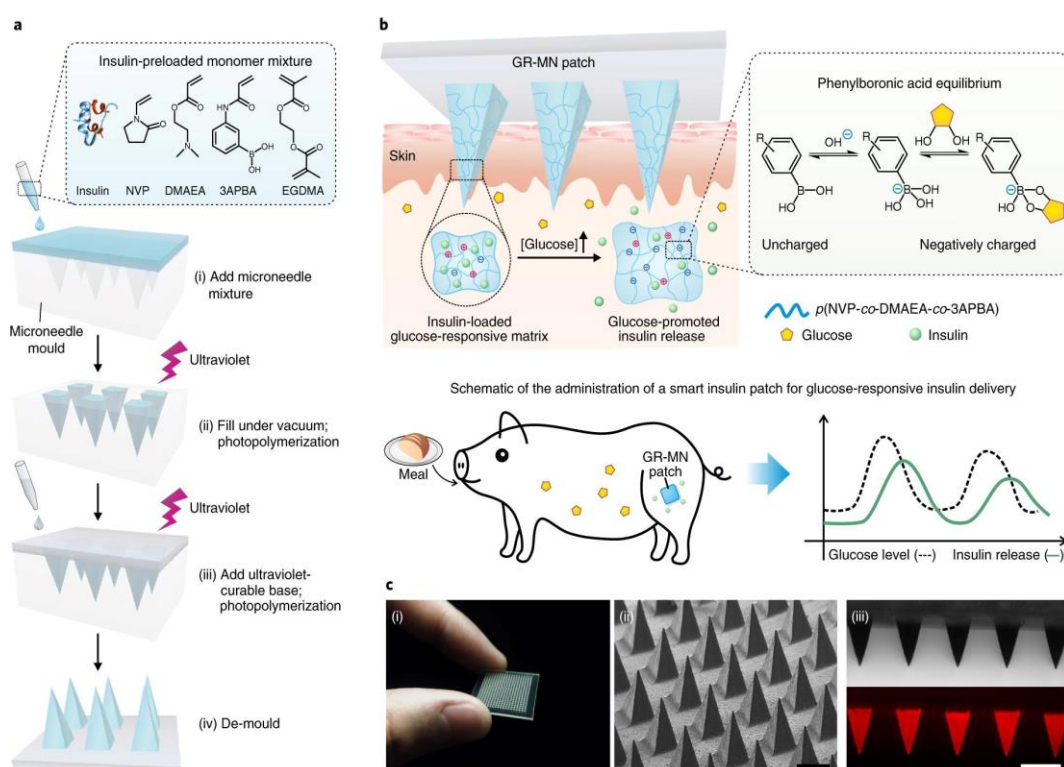
### Dig: Mechanism of glucose- responsive smart insulin patch

Insulin is a hormone produced naturally in the pancreas. It helps the body to regulate glucose, which comes from food intake and provides energy to the body. Insulin is the molecular key that helps move glucose from the bloodstream into cells for energy and storage. Diabetes occurs when a person's body does not naturally produce insulin (type 1 diabetes) or does not use the insulin that is produced efficiently (type 2). In either case, a regular dose of insulin is prescribed to manage the disease, which affects more than 400 million people worldwide.

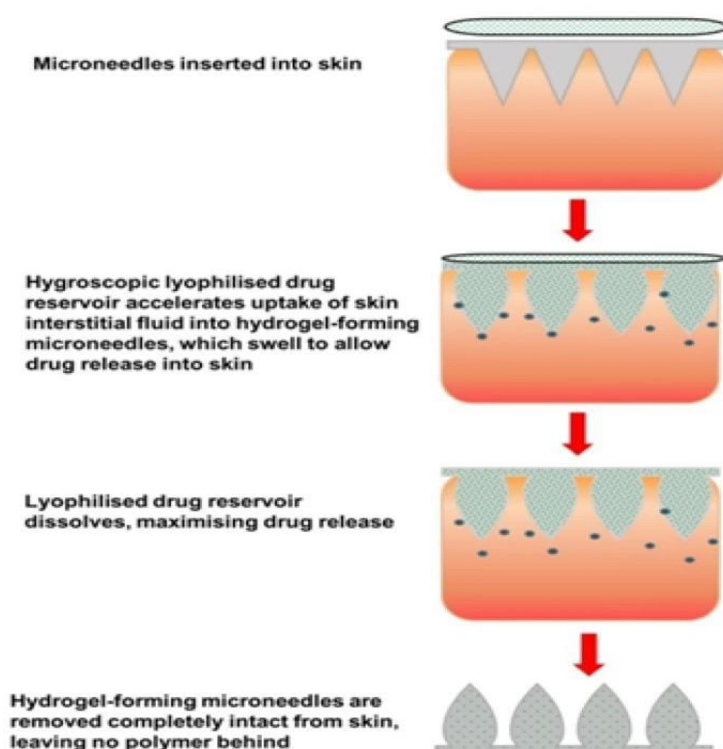
"The main goal is to improve the health and quality of life of people with diabetes," said study leader Zhen Gu, a professor of bioengineering at the UCLA Samueli School of Engineering. "This smart patch eliminates the need to constantly check blood sugar and then inject insulin as needed. It mimics the regulatory function of the pancreas, but is easy to use.

A smart patch monitors blood sugar (or glucose). It contains doses of insulin preloaded into very small microneedles, less than 1 millimeter in length, which quickly deliver the drug when blood sugar levels reach a certain threshold. When blood sugar normalizes, its insulin delivery also slows down.

Treatment for this disease has not changed much in most countries of the world over the decades. Diabetics will have their blood drawn using a device that measures glucose levels. They will then self-administer the required dose of insulin. Insulin can be injected with a device such as a needle and syringe, a pen, or delivered through an insulin pump, which is a portable cellphone-sized device attached to the body through a tube with a needle at the end.



### Dig: Diagrammatic Working of Diabetes Patches



### Dig: process of Hydrogel forming by microneedle

#### ❖ Glucose-responsive microneedle patches typically incorporate several key materials to achieve their functionality:

- Microneedle Materials** : Microneedles are commonly made from biocompatible materials such as:
  - ✓ **Silicon** : Offers mechanical strength and can be microfabricated with precision.
  - ✓ **Polymers** : Biodegradable polymers like polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), or polyvinylpyrrolidone (PVP) are often used due to their biocompatibility and ability to degrade safely in the body.
  - ✓ **Metal** : Stainless steel or titanium microneedles are durable and allow for precise fabrication.
- Glucose-Responsive Materials** : These materials change their properties based on glucose levels, enabling the patch to sense and respond to changes in blood glucose concentrations. Examples include :
  - ✓ **Enzymes** : Glucose oxidase (GOx) or glucose dehydrogenase (GDH) catalyze reactions that produce detectable signals (like color changes or electrical signals) corresponding to glucose levels.
  - ✓ **Hydrogels** : Responsive hydrogels can swell or change their permeability in response to glucose concentration changes, affecting drug release or signal generation.
- Insulin or Drug Reservoirs** : These reservoirs hold insulin or other drugs and can be formulated with glucose-responsive materials to control drug release based on glucose levels.
- Sensor Components** : Integrated sensors detect glucose levels. They may be based on optical, electrochemical, or other detection principles.
- Adhesive and Substrate Materials** : Biocompatible adhesives ensure the patch adheres comfortably to the skin without causing irritation. Substrates may include flexible materials that conform to the skin's contours.
- Electronics and Communication Components** : Some patches include electronic components for wireless transmission of data to external devices such as smartphones or monitors.
- Functional Coatings and Modifications** : Surface functionalization of microneedles or other components with glucose-responsive materials or coatings enhances their performance and sensitivity to glucose changes.

These materials collectively enable glucose-responsive microneedle patches to provide continuous or on-demand monitoring of glucose levels and precise insulin or drug delivery, aiming to improve management for individuals with diabetes.

❖ **Glucose-responsive microneedle patches integrate several advanced techniques to achieve their functionality. Here are some key techniques commonly used in their development:**

1. **Microfabrication** : Microneedles are typically fabricated using microfabrication techniques such as lithography, etching, or molding. These techniques allow for the precise fabrication of microneedles with controlled dimensions and shapes.
2. **Enzyme Immobilization** : Glucose-responsive patches often use enzymes like glucose oxidase (GOx) or glucose dehydrogenase (GDH) to detect glucose levels. Techniques such as enzyme immobilization onto the microneedle surface or within a hydrogel matrix can enhance enzyme stability and activity.
3. **Hydrogel Technology** : Hydrogels are used as matrices for enzyme immobilization or as components that change their swelling or permeability properties in response to glucose concentration changes. These hydrogels can be tailored to release insulin or other drugs in a glucose-responsive manner.
4. **Sensor Integration** : Microsensors, typically electrochemical or optical sensors, are integrated into the microneedle patch to detect glucose levels in the interstitial fluid. These sensors generate signals that correlate with glucose concentrations and can trigger drug release mechanisms.
5. **Smart Materials** : Materials that undergo structural or property changes in response to glucose levels (e.g., swelling, color change, conductivity change) are integrated into the patch design. These materials enable the patch to respond dynamically to glucose fluctuations.
6. **Drug Delivery Systems** : Techniques such as microfluidics or controlled release formulations are used to deliver insulin or other therapeutic agents in response to sensor signals. This ensures precise and timely drug administration based on real-time glucose levels.
7. **Biocompatible Adhesives** : Adhesives that are biocompatible and skin-friendly are used to ensure the patch adheres securely to the skin without causing irritation or discomfort.
8. **Wireless Communication** : Some advanced patches incorporate wireless communication technology to transmit glucose data to external devices such as smartphones or continuous glucose monitors (CGMs).

These techniques collectively enable glucose-responsive microneedle patches to provide accurate, real-time glucose monitoring and insulin delivery, enhancing the management of diabetes by offering convenient and responsive treatment options.

❖ **Function:-**

Glucose-responsive microneedle patches function uniquely to enhance diabetes treatment through their integrated monitoring and drug delivery capabilities:

1. **Continuous Glucose Monitoring** : Microneedles embedded with glucose sensors monitor interstitial fluid glucose levels continuously or at frequent intervals. This data provides real-time feedback on glucose fluctuations.
2. **Glucose Detection** : Sensors detect changes in glucose levels. This information is crucial for determining when insulin is needed.
3. **Insulin Delivery** : Upon detecting elevated glucose levels, the patch can release insulin through micro needles. This mimics the function of pancreatic beta cells, which release insulin in response to glucose.
4. **Responsive Mechanism** : Utilizes glucose-responsive materials or mechanisms (e.g., enzyme-based reactions, smart polymers) that trigger insulin release or adjust drug delivery rates based on glucose levels.
5. **Biocompatibility** : Designed with biocompatible materials to ensure the patch adheres comfortably to the skin and functions effectively without causing irritation.
6. **Integration and Convenience** : Integrates both glucose monitoring and insulin delivery into a single wearable device, reducing the need for separate devices and simplifying diabetes management.
7. **precision and Control** : Offers precise insulin dosing tailored to individual glucose levels, potentially improving blood glucose control and reducing the risk of hypo- or hyperglycemia.

These patches represent a significant advancement in diabetes care, aiming to provide more personalized and automated management options that enhance quality of life for individuals living with diabetes.

#### ❖ **Benefits :-**

Glucose-responsive microneedle patches offer several key benefits for diabetes treatment:

1. **Continuous Monitoring** : Provides continuous or frequent glucose monitoring without the need for frequent fingersticks, offering real-time insights into glucose levels.
2. **Precise Insulin Delivery** : Delivers insulin automatically in response to detected glucose levels, potentially improving blood glucose control and reducing the risk of hypo- or hyperglycemia.
3. **Convenience** : Integrates glucose monitoring and insulin delivery into a single wearable device, simplifying diabetes management and reducing the need for multiple devices.
4. **Reduced Burden** : Minimizes the daily burden of managing diabetes by automating aspects of glucose monitoring and insulin administration.
5. **Improved Quality of Life** : Enhances overall quality of life for individuals with diabetes by offering a more seamless and effective treatment option.

#### ❖ **Advantages and disadvantages of each type:-**

Here's a breakdown of the advantages and disadvantages of different types of glucose-responsive microneedle patches used for diabetes treatment:

- **Enzyme-Based Patches:**

##### **Advantages:**

- **High Specificity** : Enzymatic reactions are highly specific to glucose, providing accurate glucose sensing.
- **Natural Mechanism** : Mimics natural glucose sensing and insulin release processes.
- **Low Power Consumption** : Enzyme-based systems typically require low power for operation.

##### **Disadvantages:**

- **Enzyme Degradation** : Enzymes like glucose oxidase (GOx) or glucose dehydrogenase (GDH) can degrade over time, affecting patch longevity and accuracy.
- **Temperature Sensitivity** : Some enzymes are sensitive to temperature fluctuations, potentially affecting sensor reliability.
- **Response Time** : Enzyme-based systems may have slower response times compared to other technologies.
- **Smart Polymer-Based Patches:**

##### **Advantages:**

- **Responsive to Glucose Levels** : Smart polymers can change their properties (e.g., swelling, permeability) in response to glucose concentration changes, enabling precise insulin delivery.
- **Flexible Design** : Allows for customization of patch properties and responsiveness.
- **No External Power Needed** : Polymer-based systems may operate without external power sources, simplifying device design.

##### **Disadvantages:**

- **Complex Manufacturing** : Creating responsive polymer formulations and ensuring consistent performance can be challenging.
- **Limited Sensitivity Range** : Polymer responses may not cover the full range of glucose concentrations found in clinical settings.
- **Biocompatibility Concerns** : Some polymers may not be fully biocompatible, potentially causing irritation or allergic reactions.
- **Combined Glucose Monitoring and Insulin Delivery Systems:**

##### **Advantages:**

- **Closed-Loop Control** : Provides automated insulin delivery based on real-time glucose data, enhancing glucose control.
- **Patient Convenience** : Simplifies diabetes management by integrating monitoring and treatment into a single device.
- **Reduced Hypoglycemia Risk** : Closed-loop systems can adjust insulin delivery to prevent hypoglycemic episodes effectively.



**Disadvantages:**

- Complexity : Requires advanced sensor technology and algorithm development to maintain accurate glucose control.
- Cost : Integrated systems may be more expensive due to the complexity of components and technology.
- Regulatory Challenges : Obtaining regulatory approval for closed-loop systems involves rigorous testing and validation.
- Biocompatible Materials:

**Advantages:**

- Skin Compatibility : Materials like biocompatible polymers or metals ensure minimal skin irritation and comfortable wear.
- Longevity : Durable materials can withstand repeated use without degradation.
- Ease of Manufacturing : Well-established fabrication techniques exist for biocompatible materials.

**Disadvantages:**

- Limited Sensing Capability : Materials may lack integrated sensing capabilities, requiring additional sensors for glucose monitoring.
- Size and Design Constraints : Microneedle size and design may be limited by material properties, affecting device performance.
- Cost Considerations : High-quality biocompatible materials can be costly, impacting overall device affordability.
- Wireless Communication and Monitoring:

**Advantages:**

- Remote Monitoring : Enables healthcare providers or caregivers to monitor glucose levels and treatment remotely.
- Real-Time Feedback : Wireless communication provides immediate feedback on glucose trends and insulin delivery status.
- Data Accessibility : Facilitates data storage and analysis for long-term diabetes management.

**Disadvantages:**

- Complexity : Integration of wireless technology adds complexity to device design and operation.
- Power Requirements : Requires power for wireless transmission, affecting device size and battery life.
- Privacy and Security Concerns : Data transmission and storage require robust security measures to protect patient information.

Each type of glucose-responsive microneedle patch has its strengths and challenges, reflecting ongoing advancements in technology and innovation aimed at improving diabetes management. The choice of patch type often depends on factors such as patient needs, device usability, and clinical requirements.

## II. CONCLUSION

Glucose-responsive microneedle patches represent a promising advance in diabetes management, offering a sophisticated approach to insulin delivery and glucose monitoring. These innovative devices leverage the capabilities of bioresponsive materials and state-of-the-art technology to provide more patient-friendly and effective solutions for controlling blood glucose levels. By combining real-time glucose sensing with automated insulin release, microneedle patches can enhance therapeutic outcomes and improve patient compliance. However, further research is needed to address challenges related to long-term stability, product scalability, and patient acceptability. Continued development and clinical validation of these technologies will be critical to realizing their full potential and integrating them into standard diabetes care practices.

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