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A SYSTEMATIC REVIEW ON MICRONEEDLE AS PROMISING DRUG DELIVERY SYSTEM

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ABSTRACT

Recent advancements in transdermal drug delivery have generated interest in finding alternatives to traditional method like needle, creams, and patches. The outer layer of skin known as the stratum corneum, often hinders effective drug delivery, limiting its effectiveness. Microneedles offer a promising solution by creating tiny pathway through the skin, allowing drug to be deliver to the upper layers of the skin. This review cover the various potential uses of microneedle in the field of biomedicine and also discusses different type of microneedle, such as solid, dissolving, hydrogel, coated, and hollow ones which are made from specific material and methods. These microneedle are now being used in various area, such as delivering oligonucleotides, vaccine, insulin etc.

Keywords: Microneedle, Drug Delivery, Biosafety, Microneedling, Hydrogel

1. INTRODUCTION

In recent years, there has been a significant change in the pharmaceutical administration business due to the advancement of microneedle technology. There has been a lot of interest in how microneedles, which are tiny instruments made to puncture the epidermis of the skin, can change how drugs are delivered. This article aims to provide a comprehensive review of the latest advancements in microneedle technology, highlighting the revolutionary potential they hold for a variety of industries, including pharmaceuticals, healthcare, and diagnostics, as well as their vast range of applications. [1] Microneedles offer a less invasive way to administer medication when compared to more traditional methods like injections and oral administration. The ability of these minuscule needles to efficiently and painlessly pierce the epidermis opens up new pathways for the delivery of drugs, vaccines, and even diagnostic instruments. In exploring the intricacies of microneedle technology, this study seeks to elucidate the basic ideas that direct their design, fabrication, and functioning. [2]

Our analysis will be based on a thorough examination of recent literature, which includes significant discoveries and advancements in microneedle research. This review critically examines the advantages and disadvantages of various microneedle designs, materials, and fabrication techniques in an effort to provide readers with a comprehensive understanding of the state-of-the-art in this rapidly evolving field. We will also discuss the potential impact of microneedle technology on public health and patient adherence, emphasizing its potential to alleviate problems associated with conventional medication delivery methods. Through the lens of specific case studies, we will highlight efficient applications of microneedles in the delivery of medications with higher precision, less side effects, and improved therapeutic outcomes. As we explore the intricacies of microneedle technology, we hope to shed light on the current state of affairs as well as possible future directions. Through the integration of current information and the suggestion of future research routes, this study aims to contribute to the continuing discourse on microneedle technology and its revolutionary potential for drug delivery.

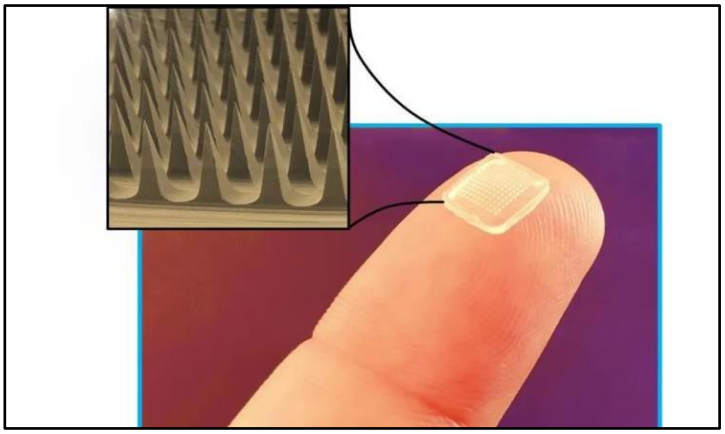

Fig 1: micro-needles are needle-like structures with microscale diameter and lengths up to one mm [3]

History

The remarkable history of microneedle technology is based on the fusion of advances in materials science and medical innovation. Although the idea of utilizing needles for medical purposes has been around for millennia, the modern form of microneedles arose as a unique technological advancement in the late 20th century.

Early Concepts and Development:

When researchers started looking into ways to improve transdermal drug delivery in the 1970s and 1980s, they came up with the idea of employing microneedles for drug delivery. Because of the skin's barrier qualities, traditional transdermal patches have trouble efficiently delivering several medications. Researchers and engineers realized that employing microneedles to make holes in the stratum corneum the skin's outermost layer could help improve drug absorption [4]

Pioneering Work:

In the 1990s, groundbreaking research on microneedle technology got underway. Mark Prausnitz and associates first presented the idea of using microneedles for medication administration in a landmark publication in 1998. In order to facilitate the delivery of medicinal chemicals through the skin's outer layer, an array of microneedles was designed to do so painlessly. [5]

2. FEATURES OF MN's

A promising technology, microneedles have a number of properties that make them appealing for use in medicine administration and other applications. Among the essential elements are:

2.1 Painless Penetration:

As compared to regular needles, microneedles allow for minimally invasive delivery and frequently cause little to no pain.

2.2 Drug Delivery Precision:

They offer targeted drug delivery, making it possible to administer treatments precisely.

2.3 Enhanced Patient Compliance:

Patient compliance could rise as a result of the decreased discomfort and anxiety related to microneedles, particularly for ongoing or regular treatments.

2.4 Avoidance of Need for Highly-trained Personnel:

Although microneedle application is straightforward and may not require highly specialized expertise, access to medical interventions may be increased.

2.5 Improved Stability of Some Drugs:

Certain medications can be designed with microneedles to increase their stability, making them ideal for distribution.

2.6 Reduced Risk of Needlestick Injuries:

By decreasing the possibility of needlestick accidents for medical personnel, microneedles improve safety in hospital environments.

2.7 Applications Beyond Drug Delivery:

Besides the delivery of drugs, microneedles are used in biosensing and diagnostics. [6,7]

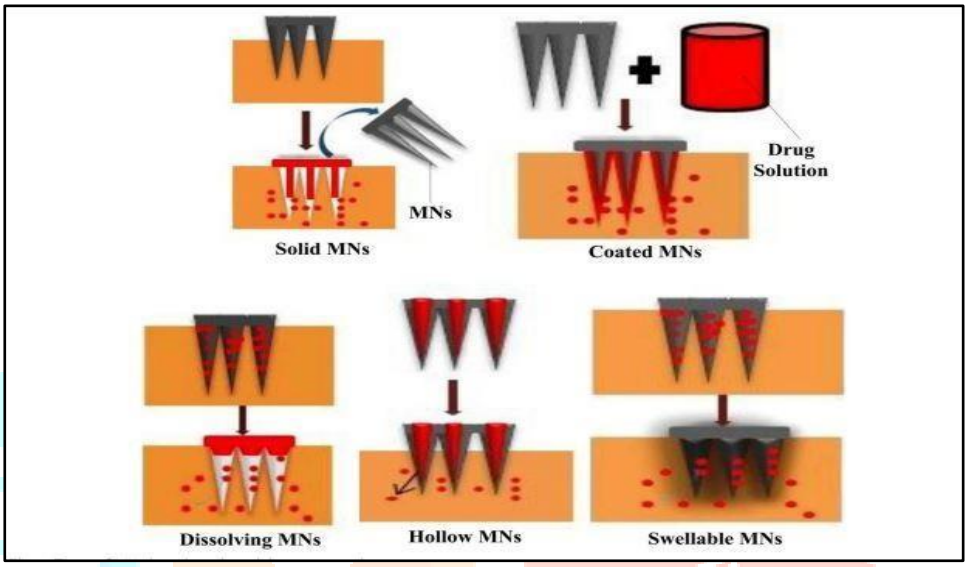

Fig 2: types of microneedles [8]

3. Types of MN's

Based on the fabrication strategy, MNs are divided into two groups: in-plane MNs and out-of- plane MNs. The MNs are categorized as solid, hollow, coated, dissolving, and hydrogel- forming depending on the drug delivery aspects. (Fig. 2)

3.1 Solid MNs

The aim of this kind of microneedle shape is to promote drug administration to the dermis, hence enhancing bioavailability and kinetic transport across the skin, by penetrating the stratum corneum. Solid microneedle delivery is a better option for vaccine distribution than intramuscular delivery because it has a stronger antibody response and lasts longer. Compared to hollow microneedles, solid microneedles are easier to make, have better mechanical qualities, and have sharper points. Furthermore, a solid microneedle can be made of a variety of materials, including silicon, metals, and polymers. [9]

3.2 Coated MNs

The "coat-and-poke approach" is used to administer the medication through the coated MNs. This method involves coating the MNs with the medication before inserting them into the skin. The medication coating on MNs that have been injected dissolves into the skin, and the MNs are then taken out. This method has the benefit of only requiring one step and having a straightforward delivery system; however, it has the drawback of only delivering a significantly lower amount of the medication. Sustained release is made possible by coated MNs with the medication entirely covering their surface. Effective research has been done on coated MNs for the delivery of DNA, genes, proteins, and peptides. Steel for siRNA is present in these non- invasive MNs. A number of critical factors need to be adjusted in these MN preparations: uniform coating, stability, MN coating technique (spraying or dip coating), and MN release. High viscosity and a decrease in surface area, as demonstrated by Gill and M. Prausnitz, may enhance these MNs' drug delivery efficacy. According to reports, MNs are effectively coated when they are submerged in solutions with opposing charges when layer coating. Piezoelectric inkjet printing was reported to be used for coating antifungals on MNs. [10]

3.3 Dissolving MNs

This kind of MN has drawn a lot of interest since it can be used with the "poke and release" principle, which makes dissolving microneedles a user-friendly feature. However, these needles are usually composed of polysaccharides or other polymers to dissolve the entire section of the MN. Typically, the process of dissolving MNs involves filling molds with polymeric solutions and allowing them to dry in a vacuum at room temperature. The medicinal ingredients are combined and dried together prior to the application of the polymeric solution. When the dissolving MN is applied, the therapeutic agents gradually penetrate the skin and break down the MN through a process of swelling or dehydration. The main benefit of this kind of MN is that it may administer the medication in a single application without causing blockage, which would prevent the microchannels from healing. [11]

3.4 Hollow MNs

Similarly to micron syringes, hollow MNs are typically used to administer liquid formulations via the skin's subcutaneous layer. These MNs are capable of administering higher dosages of the medication than solid MNs. The medication solution or dispersion is contained in an empty space inside these MNs. A particular medication can be injected into the skin via hollow microneedles that have been placed. Drug compounds can be continuously delivered via these hollow MNs by employing a variety of methods, including as diffusion, pressure, or electrical aid. Many different materials, such as silicon, metal, glass, ceramic, and polymers, can be used to create hollow MNs. High molecular weight molecules such as proteins, oligonucleotides, and antigens are typically better suited for this method. The likelihood of needle apertures clogging during skin piercing and flow resistance are the technique's main drawbacks. [12]

3.5 Hydrogel-forming MNs

The hydrogel microneedles are made of polymers with a high swelling index. Channels between the transdermal patch's drug reservoir and skin microcirculation form as a result of the polymers' swelling in the presence of interstitial fluid. The drug's distribution is sustained and rate-controlled by the swellable polymer. By altering the polymer's crosslinking, drug release can be regulated; consequently, the swelling capacity. Making hydrogel microneedles from more FDA-approved and biocompatible materials is typically simpler and less expensive. [13]

3.6 Microneedle Arrays For Biosensing

In order to facilitate the real-time monitoring of biomarkers and provide important insights into the physiological state of the body, one type of microneedle that is intended for both drug delivery and biosensing applications is the microneedle array.

Key Features:

- Biosensing Capability: Biosensing microneedle arrays have an ability to capture biomolecule-containing interstitial fluid for on-site analysis.
- Real-time Monitoring: They make it possible to monitor analytes on a regular or continuous basis, offering dynamic insights into physiological changes.
- Minimally Invasive: Similar to other microneedles, this kind provides a minimally invasive method that lessens discomfort and possible adverse effects. [14]

3.7 Microfabricated Microneedles

The portion of microneedles that are manufactured precisely through sophisticated microfabrication techniques are known as microfabricated microneedles. These microneedles provide a great deal of control over their features and dimensions, enabling customization according to particular applications. [15]

4. FORMULATION OF MN's

4.1 Material Empolyed

Materials that are required for the formulation of Microneedle are listed below.

4.1.1 Inorganic non-metallic materials

I. Ceramics

Compared to most polymers, the mechanical strength, high temperature stability, and moisture resistance of biocompatible ceramics are higher. Moreover, the ceramics' surface can improve molecular penetration by electrostatically interacting with biomolecules. In order to prepare ceramic microneedles, two common methods are used: dual-replicated PDMS production molds and ceramic micro-molding technology. The

former involves uniform filling of the mold and steps for drying, in which the solvent evaporates and forms a raw tape that causes microstructure defects.

S. Bystrova used ceramic sintering and micro-forming to create alumina ceramic microneedle arrays. They put a PDMS mold filled with slurry into a petri dish, sealed it with paraffin film, and subjected it to ultrasonic radiation for 30 minutes to degas the container and stop raw tape from forming. Upon testing at the micro-indentation station, the created ceramic microneedles showed no signs of damage. Since alumina is sintered at advanced temperature, it has thermal insecurity, the hybridization of pottery and polymers can introduce strong covalent bonds, and the cross-linking of organic and inorganic factors forms a three-dimensional network, thereby perfecting the chemical and thermal stability. Presently generally used microneedle ceramic accoutrements substantially include alumina and zirconia. [16,17]

II. Silicon

In the 1990s, silicon was used to construct the first Microneedle. Silicon has a crystalline structure and is anisotropic. Because of the way the atoms are arranged in the crystal lattice, it has different elastic moduli. Because silicon is pliable, it can be used to create microneedles in a variety of shapes and sizes. It can be mass-produced due to its enticing physical attributes and capacity for large-scale manufacturing. Due to its high cost and labor-intensive manufacturing techniques, silicon is rarely utilized in the preparation of microneedles. Furthermore, the majority of components' silicon is brittle and prone to breaking. Consequently, certain issues related to biocompatibility might surface. [18]

4.1.2 Metal

The excellent mechanical and physical qualities, low breaking point, great biocompatibility, and inexpensive cost of metal materials make them ideal for use as the structural building blocks of microneedles. It is possible to employ metal microneedles for solid-state, coated, hollow, and other types of microneedles. Ni, titanium, and stainless steel are among the metal microneedles. The non-degradable and rigid nature of the metal microneedles is an issue, though. [19]

I. Aluminum

Outlined a combination of micromachining, electrolyte polishing, and anodizing methods to prepare an aluminum microneedle array with the nanochannels on the surface, which had hundreds of times the specific surface area of a traditional template. The mechanical characteristics of aluminum microneedles can be enhanced and their drug-carrying capacity enhanced by integrating a dense network of needle-like nanotube thin film channels that span a broad surface area. Aluminum is a silver-white light metal with outstanding features like ductility, lightweight, and corrosion resistance. [20]

II. Titanium

Titanium is a silver-white transition metal that finds extensive usage in medicine. Its many good qualities include low density, strong resistance to acid and alkali, high strength, great temperature resistance, and stable chemical characteristics. Presented a titanium porous microneedle array made using enhanced metal injection molding (MIM) technology, which ensures the microneedles' biocompatibility and allows them too readily and fracture-free pass through human forearm skin. O. Khandan prepared the Ti microneedles with the complicated through holes using a titanium deep reactive ion etching technique, which he then used to the ocular drug delivery devices. [21]

III. Stainless steel

A specific kind of unique steel material that has exceptional mechanical qualities, corrosion resistance, and biocompatibility is stainless steel. Surgical implants are often made of stainless steel, particularly the ultra-low carbon grades AISI316L and AISI317L. As a result, stainless steel has emerged as the most popular metal microneedle material. There are several methods for preparing stainless steel microneedles, including femtosecond laser processing, electric discharge machining, electro-hydraulic atomization, and excimer and infrared laser processing. E. M. Cahill produced stainless steel microneedles with a high specific surface area and related porosity by an electrolytic polishing technique while maintaining mechanical integrity. These can significantly increase the stainless steel microneedles' ability to load drugs. A. Ullah coated the stainless steel microneedles' surface with a porous polymer to speed up the medication delivery process. The drug release of porous coating MNs for the administration of lidocaine was 25 times more than that of uncoated MNs. [22]

IV. Polymers

The polymer's facile formability, quick processing cycle, low cost, and abundant material diversity make it simple to produce on a wide scale, and the needle's durability is good. In addition, the polymer material may be both biocompatible and biodegradable, and studies on the molding process of polymer materials have gained significant importance in the field of medical microneedle production. [23]

V. Acrylate

Common properties shared by acrylic polymers include transparency, low toxicity, and ease of production, broad adhesion, water resistance, and durability. As a result, there are several medicinal applications for acrylic resin. Melt extrusion and molding techniques can be used to create acrylate microneedles. S.D. Gittard studied the process of microneedle penetration and mechanical failure mode by testing the shape of microneedles produced from acrylate-based polymer e-shell 200. [24]

VI. Polyvinyl Pyrrolidone (PVP)

PVP is a thermoplastic resin that is created by ethylene polymerization. Its benefits include strong electrical insulation, resilience to most acids and alkalis, and non-toxicity. D. P. Liu task was to create insulin-loaded soluble PVP microneedles using a two-step centrifugation and molding procedure. CaCO3 doped PVP microneedles have a high mechanical strength when compared to pure PVP microneedles. Furthermore, by altering its shape, its mechanical stability may also be improved. [25]

VII. Polycarbonate

(PC) PC is a high molecular polymer with a molecular chain that includes carbonate groups. This robust thermoplastic resin exhibits resistance to mild acids and alkalis, along with remarkable electrical characteristics, dimensional stability, fatigue resistance, and high strength and elasticity. Owing to the thermodynamic characteristics of polycarbonate (PC), hot embossing may be used to create PC microneedles. Palladium Nano powders in PC adhesive were utilized by A. McConville to create microneedles with a high mechanical strength. The surface-modified PC microneedles were created by K. Nair using micro-injection molding and plasma technology, which enhanced the PC materials' surface energy and roughness. [26]

VIII. Polylactide (PLA)

PLA is a polymer that is produced from starch raw materials (such as maize) by the polymerization of lactic acid. It possesses the best tensile strength and ductility, as well as good gloss and transparency, biocompatibility, degradability, and thermal stability.

The sharp PLA microneedles were produced by Y. C. Kim. using oxygen plasma etching, and mechanical testing revealed that the obelisk-shaped microneedles outperformed the pyramid-shaped microneedles in terms of mechanical strength. [27]

IX. Hydrogels

Hydrogels exhibit favorable mechanical characteristics and material permeability. It is quite difficult to have enough mechanical strength to pierce the skin when the hydrogel is dry. Following its penetration of the skin, it rapidly absorbs a little quantity of tissue fluid; this causes the swelling to become pliable and the internal network structure to open, acting as a conduit for the movement of materials. Osmotic pressure between tissue fluid and the hydrogel would cause tiny molecules to circulate and diffuse freely at the same time. As a result, the crosslinked hydrogel makes up the majority of the inflated microneedles. Soft lithography may be used to create hydrogel microneedles. S. kim produced the microneedles using X-linked HA nanoparticles. Because hydrogel is added, the microneedles can deliver medications continuously and be employed for a variety of purposes where a drug's prolonged release over many days is necessary. M. Bok. Studied using hyaluronic acid microneedles and an AC iontophoresis to increase the permeability of hydrogels and medications. [28,29]

X. Carboxymethylcellulose (CMC)

It is an anionic polymer molecule that is typically created by reacting natural cellulose with caustic alkali and monochloroacetic acid. It is a carboxymethylated derivative of cellulose. It is easily dissolved in water, hygroscopic, and non-toxic. With its superior biodegradability and biocompatibility, CMC can increase the mechanical strength of dissolving microneedles. Mold preparation is one way to prepare CMC microneedles. A soluble microneedle made of trehalose and CMC was created by J.H. Jeong. Trehalose speeds up the

microneedle's dissolving rate while CMC gives it mechanical strength. Administered as inserting microneedles with a good tolerance, human growth hormone. Manufactured CMC using hydrogel microneedles made of gelatin copolymer with ultrasonic technology to administer lidocaine. Applying microneedles boosted permeability by up to 17 times at 0.5 hours, with an average increase of up to four times. Less than 7 minutes was needed to achieve therapeutic levels of lidocaine. [30]

XI. Cellulose acetate phthalate (CAP)

The hydroxyl groups in the cellulose acetate molecule can be esterified with acetic acid to obtain CAP, a modified natural porous polymer. CAP is easy to process, selective, and water permeability. It is safe, non-allergic, and non-toxic when used topically over an extended period of time. But with strong oxidants and alkaline solutions, it is easily degraded. Because of its sensitivity to pH, CAP can be utilized to electrochemically regulate the release of drugs. When the local pH shifts as a result of a suitable reduction potential, it may expand or dissolve. Utilizing CAP as a polymer binder and Nano-particle carbon as a conducting material, conductive microneedles were created using a mold technique. The local pH on the electrode rises as a result of a hydrogen evolution process that takes place when power is introduced to the microneedle. The CAP polymer, which makes up the needle shape, would inflate as a result of the pH rise, regulating the release of the medicine. [31]

XII. Polyvinylalcohol (PVA)

PVA could serve as the primary material for the dissolving microneedles because of its exceptional heat degradation properties. 3D printing can be used to create PVA microneedles. A PVA microneedle patch was created by R.Y. He for use in point-of-care testing. Following the extraction of interstitial fluid from the hydrogel's high pore microstructure, PVA was heated and dissolved in a water bath. Target concentration in the solution was found, and the target biomarker was efficiently and rapidly retrieved from the microneedle patch. [32]

XIII. Polycaprolactone (PCL)

For its strong organic homopolymer compatibility, good biodegradability, and high biocompatibility, PCL has found extensive use in the domains of drug carrier, plasticizer, degradable plastics, nanofiber spinning, and forming and processing materials. PCL microneedles can be made using 3D printing, mold making, laser cutting, melt extrusion, and other techniques. PCL has a low melting point and good thermal ablation changes. It may be utilized as a substance in the soluble microneedles that releases the model medications when exposed to heat and light.Y. Zhang used lauric acid and PCL as arrows, polyethylene and PCL as a support base, and Cu7S4 nanoparticles as light-to-heat conversion factors. The detachable microneedle arrow was lodged in the skin after the microneedles were inserted and the support base was dissolved. After that, photo-thermal activated PCL under near-infrared light to ablate and release the loaded metformin medication. [33,34]

4.1 Method of Fabrication

Microneedles can be fabricated using various techniques, each offering unique advantages and suitability for specific applications. Here are some common fabrication methods for microneedles:

I. Micromolding:

Principle: Micromolding involves creating microneedles by molding a polymer into a microneedle-shaped cavity or mold.

Process: A master mold is created with the desired microneedle geometry, and the polymer is cast or injected into the mold. After solidification, the microneedles are demolded.

Materials: Polymers such as poly(lactic-co-glycolic acid) (PLGA), polyvinyl alcohol (PVA), or other biocompatible materials. [35]

II. Photolithography and Etching:

Principle: This method is commonly used for silicon or metal microneedles. It involves using photolithography to define patterns on a substrate, followed by etching to create the microneedle structures.

Process: A photoresist is applied to a substrate, exposed to light through a mask, and developed to create a pattern. The substrate is then etched to form the microneedle structures.

Materials: Silicon, metals (e.g., stainless steel), or other etchable materials [36]

III. Laser Ablation:

Principle: Laser ablation involves using a laser to remove material and create microneedles directly on a substrate.

Process: A laser is focused on the material, and controlled ablation forms the microneedles. This method allows for precision and customization.

Materials: Various materials, including polymers, metals, and ceramics.[37]

IV. 3D Printing:

Principle: Additive manufacturing techniques, such as 3D printing, enable layer-by-layer construction of microneedles, offering flexibility in design and customization.

Process: A 3D printer deposits material layer by layer to build up the microneedle structures according to a computer-generated design.

Materials: Polymers, ceramics, and other printable materials.[38]

V. Drawing Lithography:

Principle: Drawing lithography involves pulling a heated, microneedle-shaped capillary through a polymer solution, creating solidified microneedles.

Process: The capillary is coated with a polymer solution, and as it is pulled through the solution, the polymer solidifies into microneedles.

Materials: Polymers that can be dissolved in a solvent. [39]

VI. Electrodeposition:

Principle: Electrodeposition involves depositing material onto an electrode to form microneedles.

Process: An electrode is submerged in a solution containing the material, and electroplating or electrophoretic deposition forms the microneedles on the electrode.

Materials: Metals or conductive materials. [40]

VII. Replica Molding:

Principle: Similar to micromolding, replica molding involves creating a mold from a master template, but it is often used for microneedles with more intricate designs.

Process: A master template is used to create a negative mold, and then the microneedles are molded using this negative mold.

Materials: Polymers and other moldable materials.

The choice of fabrication method depends on factors such as the material properties, desired microneedle design, scalability, and intended application. Researchers and engineers often select the method that best suits the specific requirements of their microneedle-based devices. [41]

5. APPLICATION OF MN's

5.1 Bio-sensing Applications MN's

I. Glucose Biosensor

Microneedles have emerged as a promising technology for glucose biosensing, offering a minimally invasive approach to continuous glucose monitoring. These tiny needles, penetrating the skin to access interstitial fluid, facilitate real-time tracking of glucose levels

Minimally Invasive: Monitoring: Microneedle-based biosensors overcome some of the drawbacks of conventionally invasive techniques by enabling frequent glucose monitoring with little discomfort.

Continuous Glucose Monitoring: Electrochemical sensors built into microneedles provide continuous monitoring and accurate, real-time glucose testing.

Enhanced Patient Adherence: Because microneedle-based biosensors offer a more convenient and unobtrusive way to monitor blood glucose, they improve patient adherence.

Wireless Connectivity for Remote Monitoring: By combining wireless transmission capabilities with microneedles, it is possible to monitor glucose levels remotely, which helps to provide more individualized diabetic care. [42].

II. Lactate biosensor:

At first, the accumulation of lactate may result in soreness and exhaustion. If treatment is not received, the body will continue to get more acidic and may develop dangerous illnesses. Miller used dynamic light micro-stereolithography to create a hollow microneedle sensor. Functionalized the microneedles with

electrodeposited Au multi-walled carbon nanometers and electropolymerized mediators such methylene blue to increase the stability of the lactic acid sensor in interstitial fluid with an anti-interference capability. According to P Bolella the sensor demonstrated exceptional performance in both artificial interstitial fluid and human serum.[43]

III. Alcohol biosensor:

Numerous disorders of the liver, brain, heart, pancreatic, and cancer can be brought on by alcohol. Three hollow microneedles were used to create a microneedle-based subcutaneous alcohol detecting device by Vinu Mohan. Alcohol oxidase was immobilized on a platinum wire that can detect the alcohol concentration in artificial interstitial fluid and mouse isolated skin models, and two platinum and one silver wire were inserted into each hollow as the electrodes.[44]

IV. Beta-lactam biosensor

Strong bactericidal action, little toxicity, a broad range of applications, and superior clinical efficacy characterize beta-lactam antibiotics. By electroplating iridium oxide on the microneedle platinum surface and immobilizing β-lactamase with a hydrogel, T.M.Rawson created a beta-lactam microneedle sensor. For open circuit potential and data analysis to determine the beta-lactam concentration, the hill potential equation and logarithmic plot were utilized [45]

5.2 Biomedical Application

I. Oligonucleotide delivery:

Short RNA or DNA molecules are called oligonucleotides. It is challenging to transport oligonucleotides to their intracellular location of action. As a result, several methods for improving the delivery were found. The microneedle method was tried to deliver 20- merphosphorothioated oligodeoxynucleotide. The poke with patch method was explored to deliver oligonucleotides using solid microneedles composed of titanium or stainless steel. Compared to unbroken skin, it was discovered that a greater quantity of medication reached the site of action. The combination of iontophoresis and microneedle technique produced superior outcomes compared to iontophoresis used alone. [46,47]

II. Vaccine therapy:

A biological preparation is a vaccination. It offers active acquired immunity against a certain illness. A vaccine is a form of disease-causing microorganism that has been destroyed or rendered weaker, along with one of its toxins or surface proteins. Vaccine therapy boosts the body's immune system and offers defense against microorganisms in the future. It has been discovered that the microneedle method works well for vaccination therapy. [49] The DNA vaccination was administered with a microneedle. Compared to standard injections, the observed immune responses were significantly better. Additionally, an attempt was made to create a microneedle patch that might be used to administer the influenza vaccination. When employing hollow microneedles to give the medicine instead of intramuscular injection, a lower dose is needed. A study was conducted on the use of hollow microneedles for the administration of rabies and anthrax vaccines N. Ogai synthesized hollow microneedles using poly-glycolic acid to improve the intradermal vaccination's effectiveness. Enhanced immunity is provided by the drug's precise administration in the upper dermis. When using intradermal vaccination with microneedles on the fifteenth day following immunization, the antibody titers were considerably higher than when using subcutaneous injection. Additionally, the use of dissolving microneedles for intradermal immunization was studied.[48]

III. Peptide delivery:

Although transdermal delivery eliminates this, less peptide is able to get through the skin. Insufficient peptide penetration through the skin can be addressed by peptide delivery using microneedles. Vasopressin is a powerful peptide hormone; desmopressin is a synthetic version of it. It is meant to take the position of low vasopressin levels. This drug is used to treat hemophilia A, diabetes insipidus, and bedwetting in young children. A study on the use of microneedles to deliver desmopressin revealed that this method was safer and more effective than previous delivery methods. A high molecular weight, water-insoluble cyclic peptide called cyclosporine A is used to treat a variety of skin conditions. By using a molding method, dissolving microneedles containing cyclosporine that were 600μm long and 250μm wide were created. Pressing fabricated microneedles containing 10% cyclosporine A into the skin of a pig for 60 minutes revealed that approximately 65% of the microneedle dissolved, delivering 34 ± 6.5μg of medication. In one work, S. Liu created microneedles based on polyethylene glycol diacrylate and filled them with GAP-26, a gap junction

blocker, to deliver peptides through the swelling effect. The enhanced peptide loading through the proposed microneedles was validated by the reduction in keloid fibroblast proliferation and collagen I expression [49,50]

IV. Hormone Delivery:

One peptide hormone is insulin. The purpose of the medicine is to reduce elevated blood sugar levels. It has been discovered that administering insulin via microneedle reduces blood glucose levels more effectively. Solid microneedles were created by Q.Y Li. who then investigated how insulin delivery affected the blood glucose levels of diabetic mice. The outcomes showed that the blood glucose level had dropped to 29% of its starting level at 5 hours, confirming the enhanced skin permeability of insulin when applied with a microneedle. Studied microneedles combined with β-cell capsules from pancreas, which sense blood glucose and release insulin. However, the effectiveness of the patch was found to be lacking.

Therefore, a microneedle matrix comprising synthetic glucose signal amplifiers (GSAs) was created. This matrix was made up of Nano vesicles that included the enzymes glucoamylase, α-amylase, and glucose oxidase. These amplifiers demonstrated that the β-cell capsules secreted insulin. In comparison to traditional injection therapy, the results of a clinical research on parathyroid hormone (I-34) coated microneedles showed a 3 times shorter Tmax and a 2 times shorter apparent T1/2 . These studies demonstrated the effective use of microneedles in hormone treatment. Furthermore, by using the appropriate polymers, they can also be altered for long-term action. Furthermore, the distribution of different hormones using iontophoresis in conjunction with microneedles might be investigated. [51,52]

V. Cosmetics:

The use of microneedles in cosmetics is becoming more and more popular, particularly for treating scars and imperfections on the skin. The microneedle method was tried to deliver several active substances for cosmetics, such as retinyl retinoate, eflornithine, and ascorbic acid. Phosphatidylcholine liposomes, or Nano liposomes, exhibited enhanced lipid solubility upon incorporation of melanin. When using an e-roller, it was discovered that the amount of pigment that penetrated deeply close to the hair structures was greater. The use of microneedles for improved delivery of origin, pal-KTTKS, and melanostatin has also been studied. [53,54]

VI. Lidocaine Delivery:

Lidocaine serves as a local anesthetic agent. When using a microneedle to administer lidocaine, patients report more compliance since it produces less discomfort than a hypodermic injection. The microneedle tips were coated with lidocaine. In just two minutes, these microneedles demonstrated improved drug delivery and consistent in vitro skin penetration. Therefore, for quick and painless local anesthesia, microneedles might be utilized. When compared to the topical formulation, microneedles coated with PEG-lidocaine dispersions demonstrated enhanced drug delivery in a 3-minute examination. [55]

VII. Pain therapy:

Moulds made of polydimethylsiloxane were used to create polymeric microneedles filled with meloxicam. In around 60 minutes, the in-vitro penetration studies demonstrated a 100% drug release. An enhanced transdermal flow of 1.60μg/cm2/hr was noted, and the drug deposition was reported to be 63.37%. In comparison to a medication solution without any, the penetration rose 2.58 times. Treatment for neuropathic pain is typically challenging. The current therapies have certain negative effects and are unable to sufficiently relieve pain. The use of dissolvable microneedles to alleviate neuropathic pain has been investigated. These demonstrated good specificity against the receptors and released a peptide antagonist that was selective for the calcitonin gene-related peptide (CGRP). There were no adverse effects or skin irritations from the analgesic microneedle patch. After 20 minutes of treatment, around 75% of the microneedles dissolved. The efficient administration of medications using microneedles has created enormous prospects for the pain management sectors. [56]

VIII. Ocular Delivery:

Targeting medication administration can be used to address a number of posterior segment conditions. Nanoparticles were delivered through the suprachoroidal space using iontophoresis. It was discovered that the particles localized at the injection site in the absence of iontophoresis. More than 30% of the nanoparticles were able to reach the posterior portion of the eye when paired with microneedles. [57]

IX. Cancer therapy:

Worldwide, cancer affects a large number of individuals each year, and cancer therapy presents numerous difficulties. For the delivery of several anticancer medications, microneedles have been studied. Anti-PD-1 (aPD1) was studied as a potential treatment for melanoma using self- degradable microneedles that delivered the drug continuously. Microneedles were used to deliver pH-sensitive dextran nanoparticles laden with glucose oxidase and anti-PD-1. To treat basal cell carcinoma, a topical cream containing 5-fluorouracil is used. When the cream was given to skin that had received solid microneedle treatment, the permeability of 5-fluorouracil was increased by up to 4.5 times. Further evidence of enhanced effectiveness with microneedles was provided by a significant suppression of tumor growth. S. Bhatnagar looked at using microneedles to administer gemcitabine and tamoxifen, two chemotherapy drugs, to treat breast cancer. The adverse effects of these medications could be lessened with localized administration. The application of polymeric microneedles for localized anticancer drug delivery and skin cancer research has also been studied. [58]

5.3 Other applications:

I. Blood extraction:

Solid microneedles are typically used to puncture the stratum corneum in order to obtain interstitial fluid, which is subsequently extracted using a vacuum chamber. The capillary blood collection apparatus developed by T.M. Blicharz. Consists of a microfluidic system, a storage vacuum, and a solid microneedle patch. According to clinical tests, the discomfort experienced during the device-assisted blood collection procedure is substantially less than that of a venipuncture. C. G. Li and colleagues devised a blood collection device combining an elastic self- recovering actuator and microneedles to address the dynamic challenge of blood collection by microneedles. In order to provide elastic energy that would power the blood extraction and distribution, the elastic self-restoring actuator was applied externally. It didn't need an external power source [59]

II. Interstitial fluid extraction:

Interstitial fluid is a valuable sample resource with potential use in health monitoring since it contains a large number of target biomarkers associated with health and disease. The following are some methods for removing interstitial fluids.

Diffusion-based interstitial fluid collection into hydrogel microneedles:

The hydrogel's phase transition properties enable the microneedles to become stiff when dried, facilitating their simple absorption into the skin. In addition, the hydrogel's highly porous architecture offers a good swelling capacity for interstitial fluid extraction.

R.Y. He, used polyvinyl alcohol and chitosan as the building blocks to create hydrogel microneedle patches. The large pore structure of the hydrogel was used to provide good swelling and adsorption performance for the interstitial fluid extraction process. The heat- breaking characteristics of vinyl alcohol enable the targeted biomarkers to be recovered quickly. The device successfully measured the glucose levels in rabbit skin throughout the day. An osmotic fluid-driven hydrogel microneedle patch was introduced, according to M. Zheng, and it can collect interstitial fluid three times faster than the platform that is currently in use. [60]

6. MICRONEEDLE BIOSAFETY & TOXICITY:

Ensuring Safe and Effective Transdermal Drug Delivery

Transdermal medication delivery has found a potential ally in microneedle technology, which provides a less intrusive way to deliver therapeutic molecules. These tiny needles allow for the easier delivery of medications, immunizations, and other bioactive substances by penetrating the stratum corneum, the skin's outermost layer. Although microneedles have many benefits over traditional needle injections, including better patient compliance and a lower risk of infection, their widespread use depends critically on maintaining biosafety.

Biosafety Concerns and Mitigation Strategies:

1. Skin Irritation and Allergic Reactions: Microneedles can irritate the skin or create allergic responses. To allay these worries, biocompatible materials—like medical-grade polymers— have been used extensively. Studies on the immune system's reaction to different microneedle formulations have highlighted the significance of choosing skin-friendly materials.[61]

2. Infection Risk: To reduce the risk of infection, sterility must be maintained both during the creation and use of microneedles. The danger of contamination can be decreased by using aseptic production techniques and adding antimicrobial agents to the materials used to make microneedles. Disposable, one-time use microneedle devices can also help reduce the risk of infection.[62]

3. Mechanical Injury: The skin may sustain mechanical damage if microneedle patches are placed or removed incorrectly. In order to reduce the danger of trauma, research has concentrated on refining the geometry and length of microneedles. To protect patient safety, proper user instruction and removal and application directions must be followed.[63]

4. Biodegradability and Environmental Impact: Growing concern has been raised about the environmental impact of microneedle waste, so researchers are looking into biodegradable materials for the fabrication of microneedles in an effort to address this problem. One eco- friendly alternative being looked into is biopolymer-based microneedles, which would ensure that the disposal of used microneedles has as little of an impact on the environment as possible. In order to quick up the transition of this technology from the lab to clinical application, microneedle biosafety is an important factor that needs to be taken into consideration. In order to solve biosafety problems and ensure the safe and successful use of microneedle-based transdermal drug delivery systems, breakthroughs in material science, manufacturing methods, and user-friendly design are needed. [64]

7. FUTURE PROSPECT

In terms of the future, microneedle-based medicine delivery holds enormous promise. Research is still being conducted to address issues including scalability, cost-effectiveness, and regulatory concerns in order to further improve the design and fabrication processes. Developments in nanotechnology and materials science will probably help create next- generation microneedles with better drug loading capacities, mechanical qualities, and biocompatibility. The potential for real-time medication release and therapeutic response monitoring is presented by the integration of smart technologies, such as feedback systems and microneedle-based sensors. This could further advance the idea of personalized medicine by resulting in the creation of closed-loop systems that modify drug delivery in response to specific patient needs.

CONCLUSION

To sum up, the review into microneedles as a viable medication delivery method has revealed a wide range of prospects to transform the medical industry. The potential of microneedles as an innovative technology is highlighted by their unique qualities, which include their minimally invasive nature, increased drug bioavailability, and capacity to overcome different obstacles associated with current drug delivery systems. A great deal of research and development work in this field has yielded important insights into the manufacture, design, and use of drug delivery systems based on microneedles. When it comes to delivering a variety of therapeutic agents, such as small compounds, biologics, and vaccines, microneedles provide an adaptable platform.

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