Brief Description and Application of Microneedle Biosensors

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Abstract. In recent years, tremendous advances have been made in microneedle (MN)-based biosensors. MN biosensors have been used as devices for developing non-invasive, continuous monitoring of patient health status due to their painless, non-blood contact characteristics. The development of biosensors based on an integrated microneedle platform for the detection of biomarkers in interstitial fluid is covered in this article. The combination of microneedle platforms with biosensors continues to create new opportunities for non-invasive detection and ongoing monitoring. The classification of MN microneedles and multiple MN biosensors for identifying various bodily fluid components, such as blood glucose, antibiotics, lactate, etc., are presented in this study. It reviews this next generation MN integrated circuit platform and explains the various directions of current MN integrated circuit platform development. These have been combined with electrochemical biosensor integration for quantitative detection of various metabolites, electrolytes, and other substances known to be present in interdermal tissue fluids. Furthermore, this paper explores some of the major issues and potential solutions for this new MN sensing technology.

Keywords: Microneedle; biosensor; interstitial fluid; glucose; minimally invasive sensors.

1. Introduction

Due to their distinctive benefits in gathering ISF samples, microneedle (MN) patches have developed into a research hotspot for many experimenters in recent years [1]. Common samples included in MN biosensor designs include blood, sweat, saliva, and interstitial fluid (ISF) [2]. Because to the cross-capillary exchange between blood and cells, ISF has a strong connection with blood samples and carries a lot of physiological information when compared to other peripheral biofluids [3]. ISF can therefore be a biomarker for the development of biosensors [4].

MN patches that are micro-sized and less than 1500 m long are typically grouped in arrays of up to several hundred patches [5]. The penetration of MN into the surface layers of the skin typically does not reach the nerves and blood vessels in the deep dermis, in contrast to hypodermic needles. This enables the use of painless and bloodless ISF collecting devices [6]. The construction of several biosensors, including those for the detection of blood glucose, antibiotics, lactate, ATP, and other substances, has been made easier by this practical and effective method for extracting ISF. ISF biological target components can be monitored in real-time by creating a response channel in the skin, the MN device is placed beneath the skin where it is paired with optical and electrical detection techniques [4]. Due to the fact that non-invasive biosensing devices have so far remained a pipe dream, MN offers a strong development path for the creation of microinvasive biosensors. In the subsequent paper, the author will first classify MNs, describe the various MN types' detection techniques, then concentrate on how MNs are used to identify various biomarkers, and lastly, this study will provide a summary of the current situation and MNs' prospects for the future.

2. Mechanism

Since the project's inception in 1976, numerous methods for creating microneedles have been developed. Based on their shape, the microneedle biosensors that have been created to date can be divided into three categories: solid MNs, coated MNs, and hollow MNs.

2.1. Solid MN

The most prevalent shape for MNs is a solid, which is simple to create and typically has a high mechanical strength. In order to create micropores in the skin, solid MNs are frequently utilized. The majority of solid MN applications are for generating body microchannels. Unlike other needles, solid MNs' MN tip depth does not pierce the pain receptors. The technique might therefore be painless and increase patient cooperation. Drug diffusion and ISF extraction are made simple by the microchannels made by solid MN. Solid MNs have up till now been thought of as tools for cosmetology, immunization, medicine delivery, etc. However, due to low drug loading rates and poor bodily fluid extraction efficiency, solid MNs have limits in both drug delivery and ISF extraction. In order to overcome the aforementioned problems, hollow and coated MNs have been continuously developed.

2.2. Coated MN

Vaccines, macromolecules, tiny molecules, micron-sized particles, or solid MNs that are in intimate contact with the needle body are all examples of coated MNs. Inkjet printing, layer-by-layer coating, drop coating, dip coating, immersion coating, and layer-by-layer coating are just a few of the coating methods that have been successfully used to construct coatings on MNs, according to reports. The dip coating technique is the most popular among them, although it has its own issues with ineffective medication delivery. Thus, using the dip coating approach can result in a greater medication delivery efficiency. More significantly, this coated MN gives MN additional powers, including dramatically improving its optical properties and expanding the usage of microneedles in biosensing.

2.3. Hollow MN

When compared to solid MNs, which rely on drug diffusion through the skin, hollow MNs deliver drugs more quickly because they allow aqueous drug solutions to enter the skin through the lumen. It is significant to highlight that hollow needles are particularly challenging to produce, and they lack the internal support system found in solid needles, while those with high aspect ratios do. Moreover, hollow MNs' limited mechanical strength and unequal insertion may cause lateral bending, limiting its effectiveness for medication administration and biofluid extraction through the skin. Yet, a revolutionary method for creating a passage for light to travel through the skin is to implant open channels in hollow MNs. This notion offers a fresh perspective on how to gather light signals below the skin.

3. Application

3.1. Glucose Detection

Microneedle sensors, which can be separated into sensors that utilize enzymes and sensors that do not require enzymes, are more commonly employed for glucose detection. Electrochemical methods are typically used for this purpose. Enzyme-containing sensors measure glucose levels by spotting glucose-enzyme reaction products. On the other hand, enzyme-free sensors result in the direct oxidation of glucose at the electrode [7].

Yiqun Liu et al. reported in 2021 a novel integrated microneedle biosensor device fabricated with a combination of 3D printing process and electroplating process as shown in figure 1, which can be applied for continuous monitoring of subcutaneous glucose levels [7]. Glucose in the interstitial fluid reacts with glucose oxidase on a working electric shock to produce H_2O_2, which generates a current response signal. The microneedle biosensor's dual electrode structure is composed of an Ag/AgCl counter electrode/reference electrode and an Au working electrode coated with Prussian blue. The microneedle surface is coated with Au or Ag/AgCl, and each electrode uses a particular number of them. The biosensor device's linear detection range can be increased by adding a Prussian blue coating, and there is a good linear correlation between the sensor readings from the manufactured microneedle

biosensor device and the readings from commercial blood glucose meters. Yet for the time being, more research is required to clarify the microneedle shape and the variables affecting skin thickness in the continuous monitoring of blood glucose.

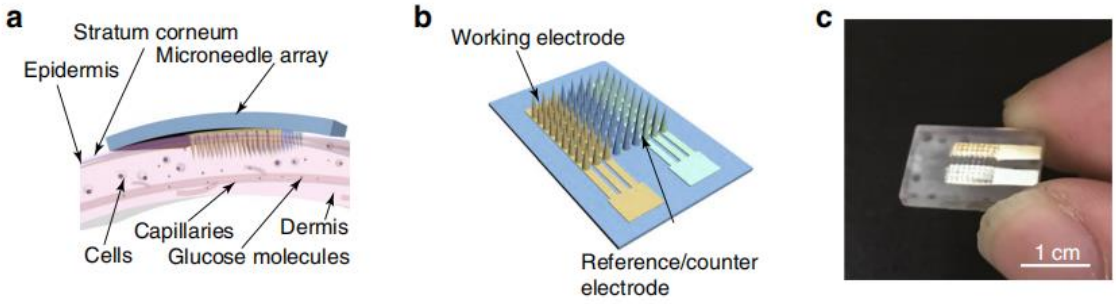

Fig. 1 a) A schematic representation of the microneedle array placed within the skin's dermis and interstitial fluid. b) A conceptual representation of the microneedle array. c) An image taken with a camera of the electrochemical **sensor** with microneedles [7].

Lee et al. first reported a MN-based three-electrode integration and production of a non-enzymatic electrochemical sensor [8]. Working electrode and counter electrode were made by employing SU-8 shade masks to deposit iron catalysts. The working electrode was created by electrodeposition of Pt nanoparticles onto a variety of multi-walled carbon nanotubes (MWCNTs) grown on a variety of silicon nanotubes. The silicon MN arrays were covered with silver using a shade mask, then chlorinated to provide Ag/AgCl as a reference electrode [8]. The suggested glucose biosensor increases the electroactive surface area for non-enzymatic electrochemical in vitro monitoring of glucose levels by combining potential transdermal MN arrays made from body fluids with platinum-based nanoparticles embedded in carbon nanotube arrays. The calibration curve for hydrogen peroxide and the detecting current has a slope of 0.2555±0.0277 A/mM and a coefficient of 0.9828. The sensor's hydrogen peroxide detection limit in phosphate-buffered saline (PBS) is 1.60 M. These findings suggest that the sensor can detect hydrogen peroxide quickly and sensitively, allowing it to react to changes in blood glucose more precisely and sensitively [7].

3.2. Antibiotic Detection

In 1974, a method for detecting penicillin was first reported, which involved coating a glass pH electrode with penicillinase.

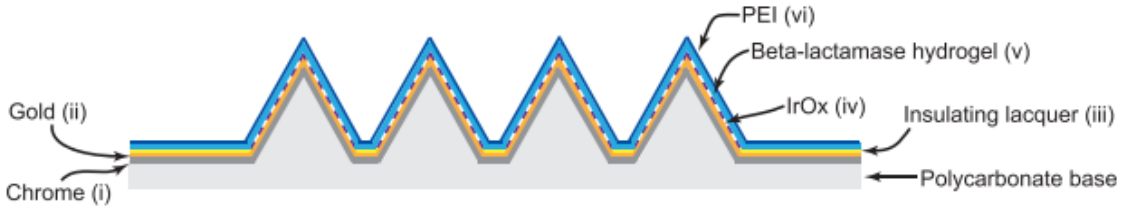

Fig. 2 A cross section of functioning electrode microneedles in a schematic shows each layer. Prior to applying gold through e-beam evaporation, chromium (i) is first sputter-coated onto the poly(carbonate) substrate (ii). Just the spikes are conducting since the base of the arrays is coated in an insulating lacquer (iii). When a continuous voltage of +0.6 V is provided in comparison to an Ag|AgCl reference electrode, iridium oxide (iv) is produced on the gold electrode. The iridium oxide layer (v) is covered with a layer of hydrogel containing -lactamase, and when it has dried, PEI (vi) is added for mechanical stability [9]

Shara et al. reported on a minimally invasive microneedle-based biosensor to track levels of -lactam antibiotics in 2019 (see figure 2) [9]. The gadget detects local pH changes brought on by -lactamase hydrolysis of -lactam antibiotics using an iridium oxide pH detecting layer [9]. The use of iridium oxide to replace the glass pH electrode in the previous method resulted in a sensor with better stability, shorter response time, more rapid response, and lower impedance. The base of the microneedle array is insulated with silver epoxy, and once the silver epoxy has dried, it is covered with an insulating varnish, leaving the tips of the microneedles visible. Each electrode received approximately 10 L of insulating varnish through a wide-bore needle syringe. Using cyclic voltammetry in a ferrocene monocarboxylic acid solution, each electrode was put to the test to see whether the silver epoxy had adequately insulated it. After doing in vivo sensing tests after the sensor had been sterilized with gamma radiation, it was found that the sensor's sensitivity was good and that the functional layer had held during the test. The sensor was initially shown to track the concentration of antibiotics in vivo by testing on volunteers [9].

However, the concentration of antibiotics in the intercellular fluid was low and reached the detection limit of the sensor, and the sensor needs to be further improved in the future, or it can be combined with other biomarkers to improve the sensitivity of the detection. Real-time detection of antibiotics can be applied in combination with control systems for real-time personalized drug delivery through changing antibiotic concentrations in vivo.

3.3. Lactate Detection

Hollow microneedle arrays filled with modified carbon fibers and pastes can be used to create electrochemical sensors that respond to H_2O_2, lactate, and ascorbic acid in a highly selective and sensitive manner (AA). The fabrication of MN array (MNA)-based enzyme sensors for the detection of organophosphorus nerve poisons and the continuous monitoring of alcohol is possible using this two-component design.

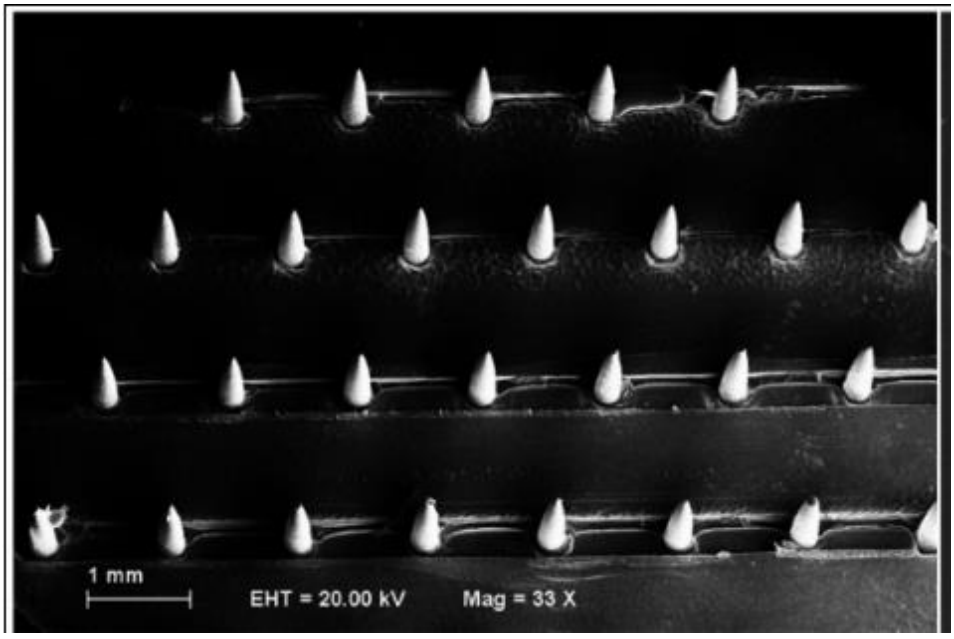

Fig. 3 Consistently generated conical microneedles using micromolding [10]

As shown in figure 3, Skaria et al in 2019 prepared a solid MNA sensor using PLA/f-MWCNT composite by microforming technique for monitoring electrochemical changes in the skin to assess the amount of ascorbic acid. The unmodified non-conjugated polymeric microneedles still showed good sensitivity to electrochemical activity over a wide range of detection. At a detection limit of 180 μM, ascorbic acid produced a linear current response in these mna after being electrochemically characterized by differential pulse voltammetry (DPV) [10].

3.4. Adenosine Triphosphate (ATP) Detection

Cellular ATP is not only a high-energy compound, but is also involved in neuronal signaling, and release assays are important due to its signaling function.

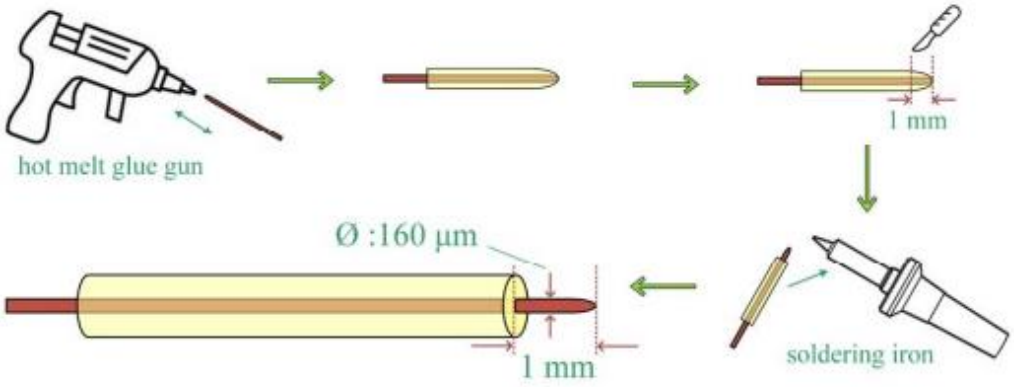

Fig. 4 Schematic representation of the fabrication steps for micro-needle tip electrodes. Finally, 160 m in diameter and 1 mm in length micro-**needle** tip electrodes were produced [11]

Figure 4 illustrates a simple method devised by Qin and Zhu et al. to make a three-dimensional platinum nanoflower-decorated microneedle tip electrode that increases the electrode surface area while preserving enzyme activity [11]. By immobilizing glucose oxidase and hexokinase jointly on the surface of the three-dimensional Pt nanoflower-decorated microneedle tip, a two-enzyme ATP biosensor was created [11]. With a sensitivity of 0.840 nA M, this easily made ATP biosensor can be used to measure cellular ATP release in real time, 5 M, S/N = 3, and a lower limit of detection of 10^{-1} mm^{-2} on ATP.

4. Conclusion

Wearable devices are still having trouble getting real-time molecular data from ISF. This review details the contribution of MN integrated biosensors for the minimally invasive detection of biomarkers present in ISF, which has a high potential to replace blood as the body fluid being monitored and is known to have concentrations that are comparable to some biomarkers in blood. Notwithstanding numerous obstacles, significant progress has been made in recent years in the synthesis of microneedles for wide-ranging table applications. With the development of more bio-friendly materials, MNs may now be created in a range of morphologies to meet therapeutic needs. However, there is still a lot of work to be done to achieve accurate control and reproducible MN preparation in terms of size, shape, content, and structure. The fields of biology, medicine, chemistry, physics, electronics, and materials science must all contribute to this endeavor.

This paper provides an overview of the detection of several biomarkers using MN biosensors. It is apparent that the electrochemical analysis of ISF remains at the core of existing MN biosensors, with functional MN being unquestionably the most essential component of the many MN sensors stated above. The focus of upcoming research will be on developing new, functional MN electrodes. Further research on the molecular perfusion time from blood to skin ISF as well as the make-up of transdermal fluid in people will be necessary for the development of transdermal sensors. The development of integrated microneedle sensors has not yet reached a degree of maturity, so future work on MN sensors can focus on improving the stability of enzymes on electrodes, calibrating sensing data for errors, and extending the test time window. As a result, microneedle sensors are being developed in the direction of intelligence, miniaturization, wearability, and data visualization. These devices offer opportunities for the future development of real-time monitoring of patients' health status and personalized development of healthcare programs.

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