Microneedle-Based Glucose Sensor Platform

Subjects: Health Care Sciences & Services

Contributor: Jian Ju, Lin Li, Sagar Regmi, Xinyu Zhang, Shixing Tang

Significant advanced have been made in exploiting microneedle-based (MN-based) diabetes devices for minimally invasive wearable biosensors and for continuous glucose monitoring. Within this emerging class of skin-worn MN-based sensors, the ISF can be utilized as a rich biomarker source to diagnose diabetes. While initial work of MN devices focused on ISF extraction, the research trend has been oriented toward developing in vivo glucose sensors coupled with optical or electrochemical (EC) instrumentation.

Keywords: microneedle ; materials ; continuous glucose monitoring ; wearable biosensor ; electrochemical ; surface-enhanced Raman spectroscopy

1. Introduction

Diabetes mellitus is increasingly recognized as a serious worldwide public health concern; looking back at the growth rate of patients over the past 40 years, it can be expected to double by 2030 compared to that in 2015 [1][2]. One of the main roadblocks to disease control requires sensitive and reliable point-of-care testing (POCT) technology and should be able to provide quantitative results for disease diagnostics and monitoring [3]. Tight glycemic control is widely accepted for the diagnosis and monitoring of diabetes. Up to now, many types of techniques have been developed to measure blood glucose in all stages of treatment and disease management of diabetic patients [4][5][6]. Most of the above methods require the frequent withdrawal of fresh blood from the fingertip, which creates pain and is inconvenient with the potential risk for cross-contamination. Moreover, it cannot keep up with the demand for the real-time monitoring of blood glucose where the frequency of puncture is necessary daily, and the physiological signals which are missed may delay the medical treatment in time. Wearable sensors can alert the user regarding health abnormalities and are actively being developed by scientific researchers and medical diagnostics companies to achieve continuous monitoring of diseases [7]. Blood [8], sweat [9], saliva [10], and interstitial fluid (ISF) [11] are common detection samples in the design of wearable biosensors. In comparison with the other peripheral biofluids, the ISF contains abundant physiological information and exhibits a close correlation with blood samples due to the transcapillary exchange between blood and cells. Thus, the ISF can be utilized as a biomarker source to design the wearable biosensor to diagnose diabetes [12].

In the past few decades, microneedle (MN) patches have attracted extensive attention for their unique advantages for the collection of ISF samples [13]. The MN patches in micron-scale sizes of less than 1500 μm in length are normally arranged in an array form with up to hundreds of pieces [14]. In comparison with the hypodermic needles, the penetration by MN through the superficial skin usually does not reach the nerves and blood vessels in the deeper layers of the dermis, thus enabling painless and blood-free ISF collection devices [15]. Such convenient and efficient extraction ISF process promotes the development of a variety of biosensors, such as blood glucose [16], electrolyte [17], pH [18], drug metabolism [19], etc., [20]. When the MN device is indwelled under the skin, it opens a test window on the skin after being combined with optical, electrical, and other detection technologies to achieve real-time monitoring of the biological target components in the ISF [20]. Since non-invasive biosensing systems remain an elusive goal to date, the MN may be an ideal device to fabricate minimally invasive wearable biosensors at this stage of development. Innovative fabrication techniques MNs have been developed so far with various materials such as silicon, glass, ceramic, metal, polymers, carbohydrate etc., [21]. To realize particular functional requirements, people have also prepared microneedles of different shapes such as solid MN, hollow MN, dissolving MN, swellable MN, and coated MN [22]. Nevertheless, the research of wearable glucose biosensors faces considerable challenges. On the one hand, the strong mechanical strength, biocompatibility, complex manufacturing, and difficult integration with the test technologies are perceived as the four main obstacles to the development of MN wearable glucose sensors. On the other hand, the skin is sensitive, and it is easy to cause skin eruption by allergic reactions when the MN indwelling in the skin, the leaking of tissue fluid, and sweating cause interference with the detection sensitivity of wearable sensors. Therefore, there is still an urgent need that the MN-based wearable biosensor to be worn on the skin for a long time without discomfort and would provide timely feedback to patients' diagnosed information.

2. Overview of Fabrication of MN

From the start of work in 1976, many strategies have been developed for the preparation of MN, such as lithography, molds, etching [23], and three-dimensional printing [24]. The MNs can be classified into different groups based on materials, shape, and application orientation. The different materials that were selected so far for the preparation of the MN are silicon, glass, ceramic, metal, polymers, and carbohydrates. Based on their working principle, MNs are currently manufactured as solid, hollow, dissolvable, and swellable.

2.1. Materials for MN Fabrication

2.1.1. Metals

Metal is the most common material for the preparation of the MN due to its ease of fabrication. Among them, stainless steel and titanium have attracted much attention because of their good mechanical strength and controllable structure [25]. Chen's lab has developed a simple, rapid, and inexpensive strategy to fabricate hollow metal MN arrays using chemically etched silica needles as templates. In addition to that, some noble metals such as gold and silver are usually applied in MN to improve the performance of the sensor or drug delivery [26]. Liu's group reported a strategy for preparing the stainless-steel MN (Admin Patch 1200, AdminMed, Sunnyvale, CA, USA), which is coated with silver (Ag) to detect analytes at a depth of more than 700 mm below the surface of a skin phantom [27]. The Ag layer in the Ag-coated stainless-steel MN is found to be effectively enhancing the Raman signal. However, the wide use of these metal and stainless-steel needles would yield sharp waste and the potential biohazardous of used MN without adequate sterilization [28].

2.1.2. Silicon

Silicon is a very important material for preparing non-metallic MN due to its excellent mechanical strength and shape plasticity [23][29]. Different lengths and shapes of silicon-based MN are reported by deep reactive ion etching and photolithography methods [30]. Yan and Gale used a deep reactive ion etching technique to fabricate solid silicon MN arrays where the needle densities ranged from 400 to 11,900 needles/cm [31][32]. Such silicon-based MN exhibited better performance for diagnosis and drug delivery. However, some part of silicon-based MN is easy to break under the skin, which causes potential biological risks [33]. Moreover, the expensive instrument to prepare MN is a key factor that limits its wide application [34].

2.1.3. Polymer

Some very promising technology is focused on polymers MN since they are biocompatible, biodegradable, mechanically strong for skin insertion, and easy to manufacture. The most common method for producing polymer MN is the reverse mold method, as shown in **Figure 1**B. A wide variety of polymers including poly (methyl methacrylate) (PMMA) [35], poly (lactic-co-glycolic acid) (PLGA) [36], polyglycolic acid (PGA) [37], cyclic-olefin copolymer, poly (vinylpyrrolidone) (PVP) [38], poly (vinyl alcohol) (PVA) [39], methacrylate hyaluronic acid (MHA) [15] and SU-8 [40] are reported for MN preparation. Different from metals and silicon-based materials, polymers can be prepared by dissolving and swellable MN, which has unique advantages in the application of transdermal delivery and body fluid extraction.

Dissolving polymer MN have a unique application in the drug delivery field, which can dissolve within minutes or days and completely reabsorb in the skin, resulting in no biohazardous sharps [41]. Dissolving polymer MN gives a new way to improve the drug or biomolecular loading rate and accurately control the loading dose in comparison with the solid MN [37][42][43]. The preparation process of dissolving polymer MN is relatively simple and needs a two-stage mild fabrication process; the polymer is filled into the MN mold, then using a long centrifugation time to overcome the constraints of surface tension and solution viscosity [44][45][46]. It is much safer compared with metals and silicon MNs.

The swellable MN has gained significant interest because they swell by absorbing ISF under the skin, and the MN body is maintained without dissolving [47][48]. Such swelling behavior of the MN provides a new strategy for drug delivery and body fluid extraction [49]. Karp's group first discusses the change of shape, such as swellable tip interlocking with tissue. In this process, the cone-shaped needles can be inserted into the tissue in a dry (stiff) state; once the needle tips are in contact with the water in the tissue, the swollen needle tip localized in the tissue [50]. Xu's lab developed a swellable MN platform based on meth-acrylated hyaluronic acid (MHA) crosslinked by ultraviolet (UV) exposure that can rapidly and efficiently extract ISF, which greatly facilitates the subsequent offline timely analysis of metabolites [15]. In comparison with the dissolving polymer, swellable MNs exhibited strong potential application in the precise extraction of body fluid field.

2.1.4. Temperature-Dependent Materials

Carbohydrate-based materials are typical temperature-dependent materials, and they can be employed to make MN by micro-molding in high processing temperatures and drawing lithography, including the chitosan [51], sugar [52], galactose [53], polysaccharide [54], and galactose [55] which are widely used in the fabrication of MN. The carbohydrate-based MNs usually have a fundamental part in wellness management, which provides stimulating revolutions in drug delivery [22][56]. It must be pointed out that carbohydrates with an approval history in US Food and Drug Administration (US FDA) and classified as “generally recognized as safe” (GRAS) [57][58]. Xu’s lab first prepared a cry-MN (cryonics) patch. The patch was fabricated by step-by-step cryogenic in predesigned MN molds containing pre-suspended cells. The cryonic MNs can easily pierce the skin and deliver loaded living cells into the skin. This work provides new ideas for improving MN technology to intervene in the higher-level precision of the medical field.

2.2. Shape of MN

2.2.1. Solid

Solid is the most common shape of MN, and it is easy to prepare and usually has strong mechanical strength [59]. Solid MNs are usually used to create micro holes in the skin. The solid MNs are mostly applied to create microchannels in porcine. Different from other needles, the MN tip depth of solid MN does not reach the pain receptor. Thus, this process could be painless and improve patient compliance [60]. The microchannels created by the solid MN provide a simple way to diffuse drugs and extract ISF. The solid MN are regarded as devices so far for cosmetology, vaccination, drug delivery, etc., [33][46][61][62][63]. However, the solid MN bears limitations for drug delivery and ISF extraction due to the low drug loading rate and low efficiency of extracting body fluids. Therefore, hollow and coating MN has been successively developed to solve the above problems.

2.2.2. Coated MN

The coated MNs are based on solid MNs, macromolecules [64], small molecules, vaccines [65], or micron-size particles [53] that have close contact with the body of the needle [66]. In order to successfully create coatings on MN, different coating methods have been reported, such as dip coating [66], immersion coating [67], inkjet Printing [68], drop coating [69], and layer-by-layer coating [70]. Among them, the dip-coating method is the most utilized, but it has the problem of inherently suffering from poor drug delivery efficiencies. Therefore, if the dip-coating approach is used for layer-by-layer coatings, higher drug delivery efficiencies could be achieved [71][72]. More importantly, such coated MN gives the MN new functions, such as significantly improving its optical performance and expanding the application of the microneedle in the field of biosensing [28]. Van Duyne’s Lab used the active gold nanorods coated on the MN array surface to design a pH-sensitive biosensor; this sensor can quantitate pH over a range of 5 to 9 and can detect pH levels in an agar gel skin phantom and human skin in situ [73].

2.2.3. Hollow MN

The hollow MN has been developed because it allows aqueous drugs to flow through the lumen and into the skin, leading to faster rates of drug delivery than solid MN, which relies on the diffusion of drugs in the skin [74][75]. It must be noted that hollow needle fabrication is significantly difficult, and those possessing a high aspect ratio lack the internal support structure common to solid needles [76]. In addition, the less mechanical strength and non-uniform insertion of the hollow MN may cause transverse bending and limit their potential for drug delivery and extracting biological fluids through the skin. However, embedding open channels on hollow MN is a novel approach, providing a passage through the skin for light, which provides a new idea for collecting light signals under the skin. Liu’s lab proposed a hollow agarose MN with the pipette tip as the hollow mold and adopted Tollen’s method to form the thin silver layer as the SERS-active film hollow MN-SERS device, expanding the application of microneedles in the field of biosensing [28].

3. Microneedle Used for Glucose Monitoring

In the early stages, MN has mainly been used for the extraction of ISF or blood, on which the glucose level was measured by offline analysis technology. ISF can readily be extracted from the micro-hole created by MN; the concentration of glucose in the ISF is similar to it in the blood sample due to the energy transfer between blood and ISF [77][78]. Despite the good correlation, glucose monitoring in ISF is challenging due to its diffusion gap from capillaries to skin [79]. This provides a new way for the future development of wearable biosensors that can be worn for a long time.

3.1. Colorimetric-MN Glucose Sensor

E.V. Mukerjee et al. reported the fabrication of a silicon MN array used for the ISF extraction from the skin in 2004, each needle of the 20 × 20 MN array has a 200–350 μm tall needle shaft along with a base diameter of 120 μm on 300 μm

centers. However, there exists an initial 20–30 min latent time that is required to generate ISF that is enough to fill the bore hole of the MN. Then, then the color change from clear to deep blue shows that there is around 80 to 120 mg/dL in the extracted fluid [80]. In 2017, a novel MN sensing concept was developed by Xu et al. where they designed and fabricated a novel swellable MN platform based on the meth acrylated hyaluronic acid (MeHA); the obtained MN can rapidly and efficiently extract ISF from the skin, extract ≈1.4 mg ISF within 1 min. The extracted skin ISF can be recovered from the MN patch by centrifugation for the subsequent offline colorimetric glucose analysis. This proof-of-concept research opens a new avenue for the progress of MN-based microdevices, which has the potential application of sampling ISF as well as detection of minimally invasive metabolites. Kim et al. designed and fabricated a platform with porous MN on a paper substrate (PMP) for the quick analysis of absorbed samples. The paper-based sensors, as well as porous MNs, have a perpendicular through-whole fluidic channel: where the absorbed sample via MN flows to the sensor. The MN, which is biodegradable, has interconnected pores of 5–10 μm in diameter. The colorimetric method is used to indicate the glucose concentration by the TMB dye oxidization, and blue color development occurs in the presence of hydrogen peroxide [81].

The Gu' lab designed a glucose-responsive colloidal crystal (GCC) patch for minimally invasive, uncomplicated as well as naked-eye recognizable glucose colorimetric monitoring. To realize the application of this material in situ detection of glucose, they developed a secondary modification strategy that integrated the GCC with MN. Such core-shell MN structure by the assembly of the soft GCC on hard MN can be used to maintain the stimulus-responsive property of the GCC as well as support sufficient mechanical strength of MN to prick the skin. The skin showed very less inflammation after GCC-MN insertion in comparison to the untreated skin, which clearly proves the biosafety of the GCC-MN patch [16].

Xu and Li et al. reported an ingenious colorimetric dermal tattoo biosensor, which was manufactured by an MN patch for parallelly detecting the multiple health-related biomarkers ex vivo as well as in vivo. Then these MN patches transfer the reagents of colorimetric reaction into the dermis with very less invasion, which can form dermal tattoo biosensors. This biosensor reveals a change in color with respect to differences in pH, glucose, uric acid, as well as the temperature of the body. These alterations can be read by naked eyes for qualitative detection as well as captured using the camera of a smartphone. Such kind of colorimetric dermal tattoo biosensor is very helpful not only in health management but also in monitoring the disease.

3.2. Electrochemical-MN Glucose Sensors

The electrochemical-MN (EC-MN) glucose biosensor perfectly combines the MN with electrochemical detection technologies, which produces a series of glucose biosensors with excellent performance. The EC sensor is widely used for the development of glucose biosensors, comprising enzymatic and non-enzymatic sensors as shown in **Table 1**. The concept of enzyme-based glucose electrochemical sensors is dependent to monitors the oxygen consumption according to the enzyme-catalyzed reaction. However, the non-enzymatic EC glucose sensors are depended on the direct electrochemical oxidation of glucose [82]. The combination of MN patch technology paves another avenue for the development of a novel device for the in vitro and in vivo measurement of glucose in the ISF.

Table 1. Comparison between the different electrochemical-MN performances for the detection of glucose.

MN Description	Type Sensor	Analytical Technique	Analytical Parameters	Application	Ref.
Solid, Hollow/PPD/GOx	**Enzyme EC**	**Amperometric**	**Linear range: 0–14 mM LOD: 0.1 mM**	**None**	[83]
Solid, Au/GOx	**Enzyme EC**	**Amperometric**	**Linear range: 0–25 mM LOD: 0.1 mM**	**ISF**	[84]
Hollow/carbon paste/GOx/TTF	**Enzyme EC**	**power density**	**Linear range: 5–25 mM LOD: 0.1 mM**	**Artificial ISF**	[85]
Solid/PEDOT/GOx	**Enzyme EC**	**Amperometric**	**Linear range: up to 396 mg/dL (dry 7 days)**	**None**	[86]
PVDF-Nf/GOx	**Enzyme EC**	**Amperometric**	**Linear range: 0–20 mM LOD: 0.1 mM**	**Mice**	[87]
Au/MPA/GOx	**Enzyme EC**	**Cyclic voltammetry**	**Linear range: 0–400 mg/dL**	**ISF**	[88]
Solid/Au/FcCOOH/GOx	**Enzyme EC**	**Amperometric**	**Linear range: 2–13.5 mM**	**None**	[89]
Hollow/Pt/GOx	**Enzyme EC**	**Amperometric**	**up to 500 mg/dL**	**Volunteer**	[90]

MN Description	Type Sensor	Analytical Technique	Analytical Parameters	Application	Ref.
Solid/FAD-GDH/FcSH/h-PG/Au	Enzyme EC	Amperometric	Linear range: 0.1–10 mM	Artificial ISF	[91]
AuMN/pTCA-GOx	Enzyme EC	Amperometric	Linear range: 0.05–20 mM	Volunteers	[92]
Solid/Au/OPPy/AuNPs/GOx/Nf	Enzyme EC	Amperometric	Linear range: Up to 2.6 mM LOD: 0.04 mM	None	[93]
Solid/Silk/polyols/GOD	Enzyme EC	Amperometric	Linear range: 1.7–10.4 mM	None	[94]
Solid/Au/GOD	Enzyme EC	Amperometric	Linear range: 3–24 mM LOD:0.048 mM	Mice	[26]
Solid/Au-Si-MNA/Fc-PAMAM/GOx	Enzyme EC	Amperometric	Linear range: 3.6–6.0 mM	Mice	[95]
Solid/CNTs/Pt NPs	Non-Enzyme EC	Amperometric	Linear range: 3–20.0 mM	None	[96]
Solid/Pt black	Non-Enzyme EC	Amperometric	Linear range: up to 36 mM LOD: 0.05 mM	Rabbit	[97]
Solid/Au/Pt black/Nf	Non-Enzyme EC	Amperometric	Linear range: 1–40 mM LOD: 0.023 mM	blood serum	[98]
Solid/MN/Au/Pt black/Nf	Non-Enzyme EC	Amperometric	Linear range: 1–20 mM	Rat	[99]
Solid/Pt	Non-Enzyme EC	Amperometric	MARD = 9%, 96.6% in Zone A and B(CGM)	volunteer	[100]
Solid/MAP/GOx	Enzyme EC	Amperometric	Linear range: 100–400 mg/dL	Beagle volunteer	[101]
Solid/Au/GOx	Enzyme EC	Amperometric	Linear range: 1–40 mM	rat volunteer	[102]
Solid/Pt/PPD/GOx-Chitosan/PVC	Enzyme EC	Amperometric	Linear range: 0–40 mM	volunteer	[103]

Table Abbreviation, poly(o-phenylenediamine) (PPD), Glucose oxidase (GOx), tetrathiafulvalene (TTF), poly(3,4-ethylenedioxythiophene) (PEDOT), Nafion (Nf), Polyvinylidene fluoride (PVDF), 3-Mercaptopropionic acid (MPA), ferrocene monocarboxylic acid (FcCOOH), flavin adenine dinucleotide glucose dehydrogenase (FAD-GDH), terthiophene carboxylic acid (TCA), overoxidized polypyrrole (OPPy), glucose oxidase (GOD), MN array (MNA), ferrocene cored poly(amidoamine), dendrimers (Fc-PAMAM), Multi-walled carbon nanotubes (MWCNTs), mussel adhesive protein (MAP), poly-o-phenylenediamine (PPD), polyvinyl chloride (PVC).

References

1. Stanley, S.A. Peripheral nerve modulation to treat metabolic disease. Nat. Rev. Endocrinol. 2018, 14, 193–194.
2. Zhou, B.; Lu, Y.; Hajifathalian, K.; Bentham, J.; Di Cesare, M.; Danaei, G.; Bixby, H.; Cowan, M.J.; Ali, M.K.; Taddei, C. Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 44 million participant s. Lancet 2016, 387, 1513–1530.
3. Guo, L.; Chen, S.; Yu, Y.-L.; Wang, J.-H. A Smartphone Optical Device for Point-of-Care Testing of Glucose and Choles terol Using Ag NPs/UiO-66-NH2-Based Ratiometric Fluorescent Probe. Anal. Chem. 2021, 93, 16240–16247.
4. Pickup, J.C.; Hussain, F.; Evans, N.D.; Rolinski, O.J.; Birch, D.J. Fluorescence-based glucose sensors. Biosens. Bioele ctron. 2005, 20, 2555–2565.
5. Li, M.; Bo, X.; Mu, Z.; Zhang, Y.; Guo, L. Electrodeposition of nickel oxide and platinum nanoparticles on electrochemic ally reduced graphene oxide film as a nonenzymatic glucose sensor. Sens. Actuators B Chem. 2014, 192, 261–268.
6. Berger, A.J.; Itzkan, I.; Feld, M.S. Feasibility of measuring blood glucose concentration by near-infrared Raman spectro scopy. Spectrochim. Acta Part A Mol. Biomol. Spectrosc. 1997, 53, 287–292.
7. Kim, J.; Campbell, A.S.; Wang, J. Wearable non-invasive epidermal glucose sensors: A review. Talanta 2018, 177, 163 –170.
8. Garg, S.K.; Potts, R.O.; Ackerman, N.R.; Fermi, S.J.; Tamada, J.A.; Chase, H.P. Correlation of fingerstick blood glucos e measurements with GlucoWatch biographer glucose results in young subjects with type 1 diabetes. Diabetes Care 19

99, 22, 1708–1714.

9. Xiao, J.; Liu, Y.; Su, L.; Zhao, D.; Zhao, L.; Zhang, X. Microfluidic chip-based wearable colorimetric sensor for simple an d facile detection of sweat glucose. Anal. Chem. 2019, 91, 14803–14807.
10. Soni, A.; Jha, S.K. Smartphone based non-invasive salivary glucose biosensor. Anal. Chim. Acta 2017, 996, 54–63.
11. Abraham, A.A.; Fei, R.; Coté, G.L.; Grunlan, M.A. Self-cleaning membrane to extend the lifetime of an implanted glucos e biosensor. ACS Appl. Mater. Interfaces 2013, 5, 12832–12838.
12. Kim, S.; Lee, M.S.; Yang, H.S.; Jung, J.H. Enhanced extraction of skin interstitial fluid using a 3D printed device enablin g tilted microneedle penetration. Sci. Rep. 2021, 11, 14018.
13. Zhu, J.; Zhou, X.; Kim, H.J.; Qu, M.; Jiang, X.; Lee, K.; Ren, L.; Wu, Q.; Wang, C.; Zhu, X. Gelatin methacryloyl micron eedle patches for minimally invasive extraction of skin interstitial fluid. Small 2020, 16, 1905910.
14. Ahmad, N.N.; Ghazali, N.N.N.; Wong, Y.H. Concept Design of Transdermal Microneedles for Diagnosis and Drug Deliv ery: A Review. Adv. Eng. Mater. 2021, 23, 2100503.
15. Chang, H.; Zheng, M.; Yu, X.; Than, A.; Seeni, R.Z.; Kang, R.; Tian, J.; Khanh, D.P.; Liu, L.; Chen, P. A swellable micron eedle patch to rapidly extract skin interstitial fluid for timely metabolic analysis. Adv. Mater. 2017, 29, 1702243.
16. Zeng, Y.; Wang, J.; Wang, Z.; Chen, G.; Yu, J.; Li, S.; Li, Q.; Li, H.; Wen, D.; Gu, Z. Colloidal crystal microneedle patch f or glucose monitoring. Nano Today 2020, 35, 100984.
17. Min, J.; Sempionatto, J.R.; Teymourian, H.; Wang, J.; Gao, W. Wearable electrochemical biosensors in North America. Biosens. Bioelectron. 2021, 172, 112750.
18. García-Guzmán, J.J.; Pérez-Ràfols, C.; Cuartero, M.; Crespo, G.A. Toward in vivo transdermal pH sensing with a valid ated microneedle membrane electrode. ACS Sens. 2021, 6, 1129–1137.
19. Kiang, T.K.; Ranamukhaarachchi, S.A.; Ensom, M.H. Revolutionizing therapeutic drug monitoring with the use of interst itial fluid and microneedles technology. Pharmaceutics 2017, 9, 43.
20. Teymourian, H.; Tehrani, F.; Mahato, K.; Wang, J. Lab under the skin: Microneedle based wearable devices. Adv. Healt hc. Mater. 2021, 10, 2002255.
21. Erdem, Ö.; Eş, I.; Akceoglu, G.A.; Saylan, Y.; Inci, F. Recent Advances in Microneedle-Based Sensors for Sampling, Di agnosis and Monitoring of Chronic Diseases. Biosensors 2021, 11, 296.
22. Xie, L.; Zeng, H.; Sun, J.; Qian, W. Engineering microneedles for therapy and diagnosis: A survey. Micromachines 202 0, 11, 271.
23. Ji, J.; Tay, F.E.; Miao, J. Microfabricated hollow microneedle array using ICP etcher. J. Phys. Conf. Ser. 2006, 34, 187.
24. Henry, S.; McAllister, D.V.; Allen, M.G.; Prausnitz, M.R. Microfabricated microneedles: A novel approach to transdermal drug delivery. J. Pharm. Sci. 1998, 87, 922–925.
25. Zhu, M.; Li, H.; Chen, X.; Tang, Y.; Lu, M.; Chen, Y. Silica needle template fabrication of metal hollow microneedle array s. J. Micromech. Microeng. 2009, 19, 115010.
26. Liu, Y.; Yu, Q.; Luo, X.; Yang, L.; Cui, Y. Continuous monitoring of diabetes with an integrated microneedle biosensing d evice through 3D printing. Microsyst. Nanoeng. 2021, 7, 75.
27. Yuen, C.; Liu, Q. Towards in vivo intradermal surface enhanced Raman scattering (SERS) measurements: Silver coate d microneedle based SERS probe. J. Biophotonics 2014, 7, 683–689.
28. Yuen, C.; Liu, Q. Hollow agarose microneedle with silver coating for intradermal surface-enhanced Raman measureme nts: A skin-mimicking phantom study. J. Biomed. Opt. 2015, 20, 061102.
29. Wilke, N.; Hibert, C.; O'Brien, J.; Morrissey, A. Silicon microneedle electrode array with temperature monitoring for elect roporation. Sens. Actuators A Phys. 2005, 123, 319–325.
30. Chen, B.; Wei, J.; Tay, F.E.; Wong, Y.T.; Iliescu, C. Silicon microneedle array with biodegradable tips for transdermal dru g delivery. Microsyst. Technol. 2008, 14, 1015–1019.
31. Jiang, X.; Lillehoj, P.B. Microneedle-based skin patch for blood-free rapid diagnostic testing. Microsyst. Nanoeng. 2020, 6, 96.
32. Yan, G.; Warner, K.S.; Zhang, J.; Sharma, S.; Gale, B.K. Evaluation needle length and density of microneedle arrays in the pretreatment of skin for transdermal drug delivery. Int. J. Pharm. 2010, 391, 7–12.
33. Liu, S.; Jin, M.-N.; Quan, Y.-S.; Kamiyama, F.; Katsumi, H.; Sakane, T.; Yamamoto, A. The development and characteris tics of novel microneedle arrays fabricated from hyaluronic acid, and their application in the transdermal delivery of insu lin. J. Control. Release 2012, 161, 933–941.

34. Larrañeta, E.; Stewart, S.; Fallows, S.J.; Birkhäuer, L.L.; McCrudden, M.T.; Woolfson, A.D.; Donnelly, R.F. A facile system to evaluate in vitro drug release from dissolving microneedle arrays. Int. J. Pharm. 2016, 497, 62–69.

35. Jin, F.; Zheng, M.-L.; Liu, Z.-H.; Fan, Y.-M.; Xu, K.; Zhao, Z.-S.; Duan, X.-M. Layer-by-layer assembled PMMA-SH/CdSe–Au nanocomposite thin films and the optical limiting property. RSC Adv. 2016, 6, 25401–25408.

36. Ke, C.-J.; Lin, Y.-J.; Hu, Y.-C.; Chiang, W.-L.; Chen, K.-J.; Yang, W.-C.; Liu, H.-L.; Fu, C.-C.; Sung, H.-W. Multidrug release based on microneedle arrays filled with pH-responsive PLGA hollow microspheres. Biomaterials 2012, 33, 5156–5165.

37. Chen, M.-C.; Ling, M.-H.; Kusuma, S.J. Poly-γ-glutamic acid microneedles with a supporting structure design as a potential tool for transdermal delivery of insulin. Acta Biomater. 2015, 24, 106–116.

38. Yang, S.-J.; Jeong, J.-O.; Lim, Y.-M.; Park, J.-S. Synthesis and characterization of PVP microneedle patch using metal bioelectrodes for novel drug delivery system. Mater. Des. 2021, 201, 109485.

39. Nguyen, H.X.; Bozorg, B.D.; Kim, Y.; Wieber, A.; Birk, G.; Lubda, D.; Banga, A.K. Poly (vinyl alcohol) microneedles: Fabrication, characterization, and application for transdermal drug delivery of doxorubicin. Eur. J. Pharm. Biopharm. 2018, 129, 88–103.

40. Xiang, Z.; Wang, H.; Pant, A.; Pastorin, G.; Lee, C. Development of vertical SU-8 microtubes integrated with dissolvable tips for transdermal drug delivery. Biomicrofluidics 2013, 7, 026502.

41. Sullivan, S.P.; Koutsonanos, D.G.; del Pilar Martin, M.; Lee, J.W.; Zarnitsyn, V.; Choi, S.-O.; Murthy, N.; Compans, R.W.; Skountzou, I.; Prausnitz, M.R. Dissolving polymer microneedle patches for influenza vaccination. Nat. Med. 2010, 16, 915–920.

42. Matsuo, K.; Yokota, Y.; Zhai, Y.; Quan, Y.-S.; Kamiyama, F.; Mukai, Y.; Okada, N.; Nakagawa, S. A low-invasive and effective transcutaneous immunization system using a novel dissolving microneedle array for soluble and particulate antigens. J. Control. Release 2012, 161, 10–17.

43. Ling, M.-H.; Chen, M.-C. Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats. Acta Biomater. 2013, 9, 8952–8961.

44. Lee, I.-C.; He, J.-S.; Tsai, M.-T.; Lin, K.-C. Fabrication of a novel partially dissolving polymer microneedle patch for transdermal drug delivery. J. Mater. Chem. B 2015, 3, 276–285.

45. Park, Y.; Park, J.; Chu, G.S.; Kim, K.S.; Sung, J.H.; Kim, B. Transdermal delivery of cosmetic ingredients using dissolving polymer microneedle arrays. Biotechnol. Bioprocess Eng. 2015, 20, 543–549.

46. Putri, H.E.; Utami, R.N.; Wahyudin, E.; Oktaviani, W.W.; Mudjahid, M.; Permana, A.D. Dissolving Microneedle Formulation of Ceftriaxone: Effect of Polymer Concentrations on Characterisation and Ex Vivo Permeation Study. J. Pharm. Innov. 2021, 16, 1–13.

47. Yadav, P.R.; Dobson, L.J.; Pattanayek, S.K.; Das, D.B. Swellable microneedles based transdermal drug delivery: Mathematical model development and numerical experiments. Chem. Eng. Sci. 2022, 247, 117005.

48. Brazel, C.S.; Peppas, N.A. Mechanisms of solute and drug transport in relaxing, swellable, hydrophilic glassy polymers. Polymer 1999, 40, 3383–3398.

49. Chen, Z.; Li, H.; Bian, Y.; Wang, Z.; Chen, G.; Zhang, X.; Miao, Y.; Wen, D.; Wang, J.; Wan, G. Bioorthogonal catalytic patch. Nat. Nanotechnol. 2021, 16, 933–941.

50. Yang, S.Y.; O'Cearbhaill, E.D.; Sisk, G.C.; Park, K.M.; Cho, W.K.; Villiger, M.; Bouma, B.E.; Pomahac, B.; Karp, J.M. A bio-inspired swellable microneedle adhesive for mechanical interlocking with tissue. Nat. Commun. 2013, 4, 1702.

51. Chen, M.-C.; Ling, M.-H.; Lai, K.-Y.; Pramudityo, E. Chitosan microneedle patches for sustained transdermal delivery of macromolecules. Biomacromolecules 2012, 13, 4022–4031.

52. Loizidou, E.Z.; Williams, N.A.; Barrow, D.A.; Eaton, M.J.; McCrory, J.; Evans, S.L.; Allender, C.J. Structural characterisation and transdermal delivery studies on sugar microneedles: Experimental and finite element modelling analyses. Eur. J. Pharm. Biopharm. 2015, 89, 224–231.

53. Donnelly, R.F.; Morrow, D.I.; Singh, T.R.; Migalska, K.; McCarron, P.A.; O'Mahony, C.; Woolfson, A.D. Processing difficulties and instability of carbohydrate microneedle arrays. Drug Dev. Ind. Pharm. 2009, 35, 1242–1254.

54. Pere, C.P.P.; Economidou, S.N.; Lall, G.; Ziraud, C.; Boateng, J.S.; Alexander, B.D.; Lamprou, D.A.; Douroumis, D. 3D printed microneedles for insulin skin delivery. Int. J. Pharm. 2018, 544, 425–432.

55. Koyani, R.D. Biopolymers for microneedle synthesis: From then to now. Biomanuf. Rev. 2019, 4, 1.

56. Bhadale, R.S.; Londhe, V.Y. A systematic review of carbohydrate-based microneedles: Current status and future prospects. J. Mater. Sci. Mater. Med. 2021, 32, 89.

57. Lee, J.W.; Park, J.-H.; Prausnitz, M.R. Dissolving microneedles for transdermal drug delivery. Biomaterials 2008, 29, 2113–2124.

58. Wu, Q.-X.; Lin, D.-Q.; Yao, S.-J. Design of chitosan and its water soluble derivatives-based drug carriers with polyelectrolyte complexes. Mar. Drugs 2014, 12, 6236–6253.

59. Choi, S.O.; Kim, Y.C.; Lee, J.W.; Park, J.H.; Prausnitz, M.R.; Allen, M.G. Intracellular protein delivery and gene transfection by electroporation using a microneedle electrode array. Small 2012, 8, 1081–1091.

60. Chen, B.Z.; Liu, J.L.; Li, Q.Y.; Wang, Z.N.; Zhang, X.P.; Shen, C.B.; Cui, Y.; Guo, X.D. Safety evaluation of solid polymer microneedles in human volunteers at different application sites. ACS Appl. Bio Mater. 2019, 2, 5616–5625.

61. Boks, M.A.; Unger, W.W.; Engels, S.; Ambrosini, M.; van Kooyk, Y.; Luttge, R. Controlled release of a model vaccine by nanoporous ceramic microneedle arrays. Int. J. Pharm. 2015, 491, 375–383.

62. Lee, B.Y.; Bartsch, S.M.; Mvundura, M.; Jarrahian, C.; Zapf, K.M.; Marinan, K.; Wateska, A.R.; Snyder, B.; Swaminathan, S.; Jacoby, E. An economic model assessing the value of microneedle patch delivery of the seasonal influenza vaccine. Vaccine 2015, 33, 4727–4736.

63. Khan, H.; Mehta, P.; Msallam, H.; Armitage, D.; Ahmad, Z. Smart microneedle coatings for controlled delivery and biomedical analysis. J. Drug Target. 2014, 22, 790–795.

64. Cormier, M.; Johnson, B.; Ameri, M.; Nyam, K.; Libiran, L.; Zhang, D.D.; Daddona, P. Transdermal delivery of desmopressin using a coated microneedle array patch system. J. Control. Release 2004, 97, 503–511.

65. Quan, F.-S.; Kim, Y.-C.; Yoo, D.-G.; Compans, R.W.; Prausnitz, M.R.; Kang, S.-M. Stabilization of influenza vaccine enhances protection by microneedle delivery in the mouse skin. PLoS ONE 2009, 4, e7152.

66. Gill, H.S.; Prausnitz, M.R. Coated microneedles for transdermal delivery. J. Control. Release 2007, 117, 227–237.

67. Matriano, J.A.; Cormier, M.; Johnson, J.; Young, W.A.; Buttery, M.; Nyam, K.; Daddona, P.E. Macroflux® microprojection array patch technology: A new and efficient approach for intracutaneous immunization. Pharm. Res. 2002, 19, 63–70.

68. Uddin, M.J.; Scoutaris, N.; Klepetsanis, P.; Chowdhry, B.; Prausnitz, M.R.; Douroumis, D. Inkjet printing of transdermal microneedles for the delivery of anticancer agents. Int. J. Pharm. 2015, 494, 593–602.

69. Chen, X.; Prow, T.W.; Crichton, M.L.; Jenkins, D.W.; Roberts, M.S.; Frazer, I.H.; Fernando, G.J.; Kendall, M.A. Dry-coated microprojection array patches for targeted delivery of immunotherapeutics to the skin. J. Control. Release 2009, 139, 212–220.

70. van der Maaden, K.; Sekerdag, E.; Schipper, P.; Kersten, G.; Jiskoot, W.; Bouwstra, J. Layer-by-layer assembly of inactivated poliovirus and N-trimethyl chitosan on pH-sensitive microneedles for dermal vaccination. Langmuir 2015, 31, 8654–8660.

71. Ingrole, R.S.; Gill, H.S. Microneedle coating methods: A review with a perspective. J. Pharmacol. Exp. Ther. 2019, 370, 555–569.

72. Schipper, P.; van der Maaden, K.; Groeneveld, V.; Ruigrok, M.; Romeijn, S.; Uleman, S.; Oomens, C.; Kersten, G.; Jiskoot, W.; Bouwstra, J. Diphtheria toxoid and N-trimethyl chitosan layer-by-layer coated pH-sensitive microneedles induce potent immune responses upon dermal vaccination in mice. J. Control. Release 2017, 262, 28–36.

73. Park, J.E.; Yonet-Tanyeri, N.; Vander Ende, E.; Henry, A.-I.; Perez White, B.E.; Mrksich, M.; Van Duyne, R.P. Plasmonic microneedle arrays for in situ sensing with surface-enhanced Raman spectroscopy (SERS). Nano Lett. 2019, 19, 6862–6868.

74. Wang, P.-C.; Paik, S.-J.; Chen, S.; Rajaraman, S.; Kim, S.-H.; Allen, M.G. Fabrication and characterization of polymer hollow microneedle array using UV lithography into micromolds. J. Microelectromech. Syst. 2013, 22, 1041–1053.

75. Wang, P.-C.; Paik, S.-J.; Kim, S.-H.; Allen, M.G. Hypodermic-needle-like hollow polymer microneedle array: Fabrication and characterization. J. Microelectromech. Syst. 2014, 23, 991–998.

76. McConville, A.; Hegarty, C.; Davis, J. Mini-review: Assessing the potential impact of microneedle technologies on home healthcare applications. Medicines 2018, 5, 50.

77. Wang, Z.; Luan, J.; Seth, A.; Liu, L.; You, M.; Gupta, P.; Rathi, P.; Wang, Y.; Cao, S.; Jiang, Q. Microneedle patch for the ultrasensitive quantification of protein biomarkers in interstitial fluid. Nat. Biomed. Eng. 2021, 5, 64–76.

78. Ventrelli, L.; Marsilio Strambini, L.; Barillaro, G. Microneedles for transdermal biosensing: Current picture and future direction. Adv. Healthc. Mater. 2015, 4, 2606–2640.

79. Shi, T.; Li, D.; Li, G.; Zhang, Y.; Xu, K.; Lu, L. Modeling and measurement of correlation between blood and interstitial glucose changes. J. Diabetes Res. 2016, 2016, 4596316.

80. Mukerjee, E.; Collins, S.; Isseroff, R.R.; Smith, R. Microneedle array for transdermal biological fluid extraction and in sit u analysis. Sens. Actuators A Phys. 2004, 114, 267–275.

81. Lee, H.; Bonfante, G.; Sasaki, Y.; Takama, N.; Minami, T.; Kim, B. Porous microneedles on a paper for screening test of prediabetes. Med. Devices Sens. 2020, 3, e10109.

82. Hassan, M.H.; Vyas, C.; Grieve, B.; Bartolo, P. Recent advances in enzymatic and non-enzymatic electrochemical gluc ose sensing. Sensors 2021, 21, 4672.

83. Windmiller, J.R.; Valdés-Ramírez, G.; Zhou, N.; Zhou, M.; Miller, P.R.; Jin, C.; Brozik, S.M.; Polsky, R.; Katz, E.; Naraya n, R. Bicomponent microneedle array biosensor for minimally-invasive glutamate monitoring. Electroanalysis 2011, 23, 2302–2309.

84. Trzebinski, J.; Sharma, S.; Moniz, A.R.-B.; Michelakis, K.; Zhang, Y.; Cass, A.E. Microfluidic device to investigate factor s affecting performance in biosensors designed for transdermal applications. Lab Chip 2012, 12, 348–352.

85. Valdés-Ramírez, G.; Li, Y.-C.; Kim, J.; Jia, W.; Bandodkar, A.J.; Nuñez-Flores, R.; Miller, P.R.; Wu, S.-Y.; Narayan, R.; Windmiller, J.R. Microneedle-based self-powered glucose sensor. Electrochem. Commun. 2014, 47, 58–62.

86. Invernale, M.A.; Tang, B.C.; York, R.L.; Le, L.; Hou, D.Y.; Anderson, D.G. Microneedle electrodes toward an amperomet ric glucose-sensing smart patch. Adv. Healthc. Mater. 2014, 3, 338–342.

87. Chen, D.; Wang, C.; Chen, W.; Chen, Y.; Zhang, J.X. PVDF-Nafion nanomembranes coated microneedles for in vivo tra nscutaneous implantable glucose sensing. Biosens. Bioelectron. 2015, 74, 1047–1052.

88. Hwa, K.-Y.; Subramani, B.; Chang, P.-W.; Chien, M.; Huang, J.-T. Transdermal microneedle array-based sensor for real time continuous glucose monitoring. Int. J. Electrochem. Sci 2015, 10, 2455–2466.

89. Barrett, C.; Dawson, K.; O'Mahony, C.; O'Riordan, A. Development of low cost rapid fabrication of sharp polymer micro needles for in vivo glucose biosensing applications. ECS J. Solid State Sci. Technol. 2015, 4, S3053.

90. Ribet, F.; Stemme, G.; Roxhed, N. Real-time intradermal continuous glucose monitoring using a minimally invasive micr oneedle-based system. Biomed. Microdevices 2018, 20, 101.

91. Bollella, P.; Sharma, S.; Cass, A.E.; Tasca, F.; Antiochia, R. Minimally invasive glucose monitoring using a highly porou s gold microneedles-based biosensor: Characterization and application in artificial interstitial fluid. Catalysts 2019, 9, 58 0.

92. Kim, K.B.; Lee, W.-C.; Cho, C.-H.; Park, D.-S.; Cho, S.J.; Shim, Y.-B. Continuous glucose monitoring using a micronee dle array sensor coupled with a wireless signal transmitter. Sens. Actuators B Chem. 2019, 281, 14–21.

93. Zhang, B.L.; Yang, Y.; Zhao, Z.Q.; Guo, X.D. A gold nanoparticles deposited polymer microneedle enzymatic biosensor for glucose sensing. Electrochim. Acta 2020, 358, 136917.

94. Zhao, L.; Wen, Z.; Jiang, F.; Zheng, Z.; Lu, S. Silk/polyols/GOD microneedle based electrochemical biosensor for conti nuous glucose monitoring. RSC Adv. 2020, 10, 6163–6171.

95. Dervisevic, M.; Alba, M.; Yan, L.; Senel, M.; Gengenbach, T.R.; Prieto-Simon, B.; Voelcker, N.H. Transdermal electroch emical monitoring of glucose via high-density silicon microneedle array patch. Adv. Funct. Mater. 2022, 32, 2009850.

96. Yoon, Y.; Lee, G.S.; Yoo, K.; Lee, J.-B. Fabrication of a Microneedle/CNT Hierarchical Micro/Nano Surface Electrochem ical Sensor and Its In-Vitro Glucose Sensing Characterization. Sensors 2013, 13, 16672–16681.

97. Lee, S.J.; Yoon, H.S.; Xuan, X.; Park, J.Y.; Paik, S.-J.; Allen, M.G. A patch type non-enzymatic biosensor based on 3D SUS micro-needle electrode array for minimally invasive continuous glucose monitoring. Sens. Actuators B Chem. 201 6, 222, 1144–1151.

98. Chinnadayyala, S.R.; Park, I.; Cho, S. Nonenzymatic determination of glucose at near neutral pH values based on the use of nafion and platinum black coated microneedle electrode array. Microchim. Acta 2018, 185, 250.

99. Chinnadayyala, S.R.; Satti, A.T.; Kim, D.; Cho, S. Minimally invasive and continuous glucose monitoring sensor based on non-enzymatic porous platinum black-coated gold microneedles. Electrochim. Acta 2021, 369, 137691.

100. Sharma, S.; El-Laboudi, A.; Reddy, M.; Jugnee, N.; Sivasubramaniyam, S.; El Sharkawy, M.; Georgiou, P.; Johnston, D.; Oliver, N.; Cass, A.E. A pilot study in humans of microneedle sensor arrays for continuous glucose monitoring. Anal. Methods 2018, 10, 2088–2095.

101. Kim, K.B.; Choi, H.; Jung, H.J.; Oh, Y.-J.; Cho, C.-H.; Min, J.H.; Yoon, S.; Kim, J.; Cho, S.J.; Cha, H.J. Mussel-inspired enzyme immobilization and dual real-time compensation algorithms for durable and accurate continuous glucose monit oring. Biosens. Bioelectron. 2019, 143, 111622.

102. Li, X.; Huang, X.; Mo, J.; Wang, H.; Huang, Q.; Yang, C.; Zhang, T.; Chen, H.J.; Hang, T.; Liu, F. A Fully Integrated Clos ed-Loop System Based on Mesoporous Microneedles-Iontophoresis for Diabetes Treatment. Adv. Sci. 2021, 8, 210082 7.

103. Tehrani, F.; Teymourian, H.; Wuerstle, B.; Kavner, J.; Patel, R.; Furmidge, A.; Aghavali, R.; Hosseini-Toudeshki, H.; Brown, C.; Zhang, F. An integrated wearable microneedle array for the continuous monitoring of multiple biomarkers in interstitial fluid. Nat. Biomed. Eng. 2022, 6, 1–11.