

Polymeric Microneedles for Health Care Monitoring: An Emerging Trend

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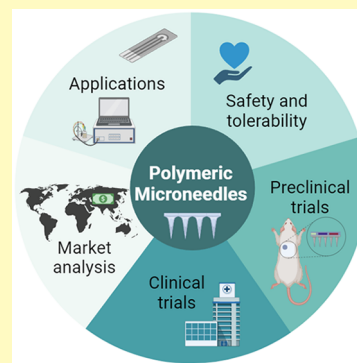
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ABSTRACT: Bioanalyte collection by blood draw is a painful process, prone to needle phobia and injuries. Microneedles can be engineered to penetrate the epidermal skin barrier and collect analytes from the interstitial fluid, arising as a safe, painless, and effective alternative to hypodermic needles. Although there are plenty of reviews on the various types of microneedles and their use as drug delivery systems, there is a lack of systematization on the application of polymeric microneedles for diagnosis. In this review, we focus on the current state of the art of this field, while providing information on safety, preclinical and clinical trials, and market distribution, to outline what we believe will be the future of health monitoring.



KEYWORDS: microneedle, healthcare, monitoring, biomarkers, analyte, biosensor, interstitial fluid, bioreceptor

Even after 100 years of invention, microneedles (MNs) still attract genuine interest from industries and academics.¹ The first patent for solid and hollow MNs was filed in 1971.² Following this, in 1973, a patent for drug-coated MNs was filed,³ and, in 1998, the concept of silicon microfabricated MNs for drug delivery was reported.⁴ The first reports on the delivery of vaccines, macromolecules, nanoparticles, and genetic materials happened in 2001 and 2002.^{5,6}

Traditionally, biomolecules are collected from blood, using painful hypodermic needles, which cause stress/anxiety, and are prone to needle stick injuries.^{7,8} The advancement in MN technology has led to the exploration of dermal interstitial fluid (ISF) as an alternative source of biomarkers. The skin is typically composed of the *stratum corneum*, epidermis, and dermis. Even though the epidermis contains a small amount of ISF, most of the ISF is contained in the dermis.⁹ ISF is composed of peptides, proteins, electrolytes, water, and other nutrients that can be used for continuous health monitoring and diagnostics. Furthermore, the use of ISF in diagnostics is amplified by the large skin area and total volume of ISF available (which is 3 times higher than blood).⁷ To reach the ISF, MNs should have a height of ~ 500 – $900\ \mu\text{m}$, depending on the skin type, ethnicity, and age of the person. In addition, the diameter/width and the tip diameter of the MNs should be optimized to reduce insertion pain.^{10–12}

The use of MN arrays for ISF collection and analysis started with hollow glass MNs to draw glucose. The results obtained compared with blood glucose levels and fell under the clinical acceptance range.^{13,14} Since then, swellable, solid, hydrogel,

and sponge-forming MNs have been demonstrated to collect/draw ISF, along with hollow MNs.^{14–19} Broadly the use of MNs for diagnostics can be split into two categories: (i) MNs used to collect biomarkers from the ISF, which will then be analyzed outside the MN array using traditional benchtop methods;^{20–22} (ii) sensing element(s) integrated into the MN arrays and used to detect biomarkers *in situ* using electrochemical or optical approaches.^{23–26}

MNs for sensing applications can be produced from a variety of materials, such as silicon, metals or polymers.^{27–29} However, polymeric MNs have been recently attracting attention in the fabrication of monitoring devices because of their enhanced biocompatibility, advantageous mechanical properties, easy, low-cost and reproducible manufacture, ability to quickly draw ISF, and large variety of physicochemical properties.^{30–32}

During the last decades, several MN reviews have been published to cover the wide depth and breadth of MN technology in the drug delivery and cosmetics sectors.^{33–40} Different review articles have also been published covering the developments in ISF sampling, MN-based sensors/wearables, and wearable electrochemical sensors.^{27,41–48} Although there are plenty reviews focused on the application of polymeric

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MNs for drug delivery applications,^{49–57} there are only a few covering the use of polymeric MNs for health monitoring.^{30,58} As such, we devised this review to summarize the work that has been recently published on this topic and provide an outlook on the role of polymeric MNs in diagnostics and its potential for the future of the healthcare market. We start with a discussion of the types of MNs and their fabrication approaches and then present a detailed overview of the recent work published on the use of MNs for diagnostics. In this overview, we cover aspects related to the type of polymers used to fabricate the MNs, the analysis method and the analyte(s) targeted. We later discuss the safety and efficacy of MN-based devices and the main findings collected in preclinical and clinical trials. We further analyze the market distribution and economic importance of MN-based devices. Lastly, we provide a glimpse of the future trends in MNs for diagnosis and highlight the obstacles to overcome to introduce MN-based sensing devices in the clinic.

■ TYPES OF MICRONEEDLES FOR MONITORING APPROACHES AND THEIR MANUFACTURING

There are different types of MNs reported in literature, however for monitoring approaches only solid, hollow, coated, and swellable are utilized (Figure 1). These MNs can be made

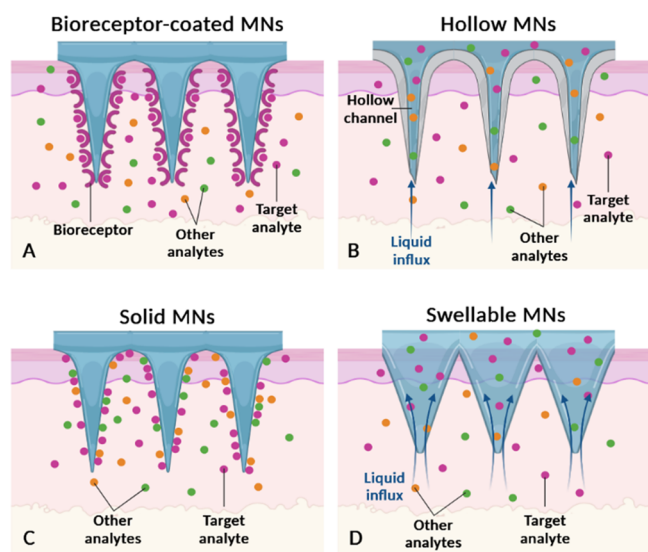


Figure 1. Types of polymeric microneedles and their analyte collection strategies. (A) Microneedles coated with a layer of bioreceptors; (B) hollow microneedles; (C) solid microneedles; and (D) swellable microneedles. Adapted with permission from Sil *et al.*⁶¹ Copyright 2024 Elsevier.

of varied materials, including silicon, metals, biomaterials, and polymers.^{27–29} The choice of MN fabrication process depends on the materials used, critical dimensions required, and functionalities. MN fabrication can be divided based on the type of MN into different categories, each having its advantages and disadvantages. Only a few fabrication processes are referred (for a more thorough reading, please see the review articles^{59,60}).

Solid Microneedles. Solid MNs are the simplest type of MNs, formed by solid micron-sized projections made of only one material. The first solid MNs fabricated for ISF collection contained planar arrays of five MNs and were made using 316 stainless steel. These MNs had a 10- μ m diameter tip and their

lengths varied from 250 to 650 μ m. The developed MNs were used to collect ISF from 21 human participants for $\sim$ 20 min, using a vacuum pump for suction. The collected ISF was used to analyze several clinical biomarkers and the results were comparable with typical blood sample analysis.^{62,63} However, due to the complications of vacuum setup and time-consuming procedures, the use of metal MNs for ISF collection has not attained much attention and has shifted to polymers [e.g., polylactic acid (PLA), polyglycolic acid (PGA)] due to their skin compatibility.¹⁵ Unlike metal MNs, solid polymeric MNs can draw fluid by capillarity, bypassing the need for vacuum pumps.

Solid MNs can be produced from molds, using for example soft lithography, micromolding,⁶⁴ hot embossing⁶⁵ and injection molding⁶⁶ techniques. These are primarily pattern transfer techniques, where the material is applied into existing molds to create MNs. They are ideal for mass production and consistent scalable fabrication. However, they have limited design flexibility, which does not allow the fabrication of complex geometries.

Solid MNs can also be directly created from the substrates using chemical etching,⁶⁷ lithography,⁶⁸ or deep reactive ion etching,⁶⁹ yielding structures that have precise geometry, high-aspect-ratio, and can be scaled for mass production. For these processes, a wide range of substrate materials can be used, including silicon, metals, and polymers. However, these techniques may result in rough surface finishes. In addition, they require specialized equipment, the process is often complex and demands expertise for operation. MNs can also be created using photolithography,⁷⁰ femtosecond laser processing,⁷¹ and electrical discharge machining (EDM).⁷² These processes create precise, complex, intricate and customized MN designs. However, they once again require specialized equipment and expertise for operation. Moreover, complex designs are time-consuming, and only certain substrates can be used. Finally, 3D printing,⁷³ an additive manufacturing technique, has been used to build MNs layer-by-layer from digital designs. This technique is suitable for rapid prototyping and customization of complex geometries from a variety of available resins, but is limited by its resolution (lower compared to traditional MN fabrication techniques), and lower mechanical strength. There are also biocompatibility issues because of the limited medical-grade resins available, and often, there are postprocessing steps that might be needed to achieve the desired surface finish.

Hollow Microneedles. Hollow MNs are miniaturized versions of hypodermic needles, which use their inner channels to collect fluid. They have been fabricated from a variety of materials, such as metals (e.g., stainless steel, nickel, titanium), polymers (e.g., polydimethylsiloxane, poly(methyl methacrylate)), silicon, and ceramics (silicon carbide, alumina), and used for detecting bioanalytes. For example, silicon micro-fabricated hollow MNs were designed and fabricated with a height of 250–350 μ m, to draw ISF and measure glucose.¹⁷ In another study, ultrafine stainless steel MNs were purchased and assembled in a 3D-printed structure to extract ISF (up to 16 μ L) and analyze transcriptome and proteome signatures.⁷⁴ Even though hollow MNs have been used to prove the concept of ISF collection, the possibility of needle blockage is a concern.

There are different approaches to fabricate hollow MNs, including lithography with etching, EDM, laser processing, and 3D printing, which have been briefly detailed above for the

fabricating of solid MNs. Besides these, drawing lithography has been used for the fabrication of hollow MNs.⁷⁵ Drawing lithography deposits material through a fine nozzle onto a substrate, drawing MNs with controllable dimensions and shapes. However, this technique is unsuitable for mass production and has limitations regarding the materials that can be used and the geometries that can be drawn. Metal electroplating⁷⁶ is also used to fabricate hollow metal MNs. This fabrication method involves electroplating a conductive material onto a template, followed by etching of the template material to create the desired MNs.

Coated Microneedles. MNs with a coating containing an active material are used to deliver a broad range of active materials (e.g., proteins, peptides, small molecules, DNAs, viruses). This type of MNs carries a lower concentration of active material because this is placed only on the surface of the MNs and not on the core. Nonetheless, the active materials are delivered very rapidly to the skin. Coated MNs have been used in biosensing applications, for example, to sample ISF for the detection of illicit drugs (using polydimethylsiloxane (PDMS) MNs coated with ligand-modified gold nanorods)⁷⁷ or to directly monitor glucose levels (using polyimide MNs coated with glucose-detecting enzymes).⁷⁸

Coating of microneedles is commonly performed by dip coating,⁷⁹ spin coating,⁸⁰ and electrodeposition.²⁸ These processes create a thin film in the surfaces to impart specific properties or functionalities. This is suitable for a range of functional coatings, the process is straightforward and the achieved MNs have uniform coating thickness and surface coverage. Nonetheless, there is limited thickness control, the optimization of the coating thickness may require several iterations, and not all coating materials are compatible with the fabrication method or the MN substrate.

Swellable Microneedles. The advancement in polymer engineering, concerning mechanical robustness upon insertion and ability to hold fluid through swelling or capillary action, has been supporting the development of swellable MNs. Swellable MNs expand after contact with fluids, due to the diffusion of water into the matrix of the needle material. Mostly, polymer-based materials are used to develop swellable MNs. For example, gelatin methacryloyl-based MNs have been developed that swelled from 293% to 423% upon contact with the ISF, depending on the concentration of polymer and UV cross-linking time used.⁸¹ Swellable MNs can usually collect higher amounts of fluid in a shorter period, as exemplified by methacrylated hyaluronic acid (MeHA) MNs, which were able to collect $\sim 1.4 \mu\text{L}$ of ISF in ~ 1 min and $\sim 2.3 \mu\text{L}$ in ~ 10 min on mice skin.³¹ MeHA and chondroitin sulfate, were shown to collect $\sim 1\text{--}2 \mu\text{L}$ of ISF.^{31,82} Hydrogel polymers, such as poly(vinyl alcohol), chitosan, polyvinylpyrrolidone, and gelatin methacryloyl facilitated the collection of $\sim 3\text{--}20 \mu\text{L}$ of ISF.^{83–85}

Swellable MNs are typically fabricated by casting/molding swellable polymers into PDMS master molds with an inverse geometry of the MNs. Casting is followed by a solidification step to form the MNs, which can then be peeled from these molds.^{73,86} Some polymers may further require cross-linking to improve mechanical strength, control the swelling behavior, or enhance MN stability.⁸⁷

Sensor-Integrated Microneedles. Sensor-integrated MNs need a slightly different manufacturing approach due to the requirements of colorimetric, fluorescent, or electrochemical measurements. For example, it is necessary to ensure

that the quantity of biomarker-sensing material in the MNs is smaller than the amount of material that gives mechanical robustness. Likewise, for electrochemical sensors, gold, silver, and platinum electrodes need to be incorporated into the system (generally, by sputtering, metal evaporation, or printing),^{28,88–90} and then connected to the source meter via an ion-conductive interface or matrix.⁴⁵ The incorporation of the sensing material can be done on the backside of the MN array or along the MN tips.^{84,91}

■ MICRONEEDLE SAFETY AND TOLERABILITY

MNs are generally regarded as a safe and less painful alternative to conventional sampling methods because of their ability to penetrate the skin without contacting blood vessels and nerve fibers.^{92,93} The first observation in humans of painless MN insertion was made by Kaushik *et al.*, in 2001.⁹⁴ Since then, various publications have corroborated this observation. Haq *et al.* stated that MN application produced more “pressing” and “heavy” sensations, whereas hypodermic needles triggered more “sharp” and “stabbing” feelings.⁹⁵ Van Damme *et al.* found that the “prick–pain” associated with their MN device, MicronJet, was significantly lower than that of intramuscular injections.⁹⁶ The participants involved in a study by Frew *et al.* reported a positive experience with MNs and the majority preferred them over hypodermic needles.⁹⁷

One of the main safety concerns around MNs regards their ability to elicit skin irritation, i.e., a reversible inflammatory reaction of the skin.⁹⁸ However, this concern has been debunked by numerous articles. Bal *et al.* published a study stating that the irritation caused by MNs of different lengths and geometries was minimal and short-lived, resolving in less than 2 h.⁹⁸ Van Damme *et al.* and Hoesly *et al.* reported that the skin reactions caused by their respective MN devices were mild and transient.^{96,99} Moreover, Hoesly *et al.* stated that the reactions were characterized by self-contained, barely perceptible erythema that rapidly disappeared without the need for external intervention.⁹⁹ Likewise, the MNs used in a study by Rouphael *et al.* were well-tolerated, causing only mild pruritus, tenderness, and erythema.¹⁰⁰

The other main concern surrounding MNs is the possibility of opening a pathway for pathogen entry upon MN removal.¹⁰¹ Nevertheless, Haq *et al.* demonstrated that the skin disruption caused by MNs is transient, repairing itself in less than 24 h. They also showed that MNs create smaller channels that heal faster than the ones created by hypodermic needles, which lowers the risk of pathogen exposure.⁹⁵ Additionally, standard disinfection before MN application can further help mitigate this risk.¹⁰¹ Lastly, it is worth mentioning that the small dimension of MNs can decrease needle phobia in patients while fighting needle stick injuries in healthcare workers.^{92,101} Overall, MNs can have a significant impact on patient compliance by presenting themselves as a bypass to the pain and fear of injection associated with conventional hypodermic needles.^{101,102}

■ CURRENT TRENDS USING POLYMERIC MICRONEEDLES FOR MONITORING

Various MN-based sensing devices have been produced based on silicon, metallic or polymeric MNs. Silicon and metals are the classical options for MN production and offer several attractive features related to their rigidity and multiple fabrication methods. However, their utility is hampered by

their expensive and laborious fabrication processes, which often require multiple processing steps in a clean room environment. In addition, silicon MNs are brittle and carry an added risk of fracturing upon skin insertion. Lately, polymers have been attracting a great deal of attention as alternatives to these conventional materials.^{103,104} The main techniques applied for polymeric MN production (photolithography, replica molding, 3D printing, and micromachining) are inexpensive and less cumbersome compared to the techniques used to fabricate silicon and metal MNs. Moreover, these techniques require shorter processing cycles and are suitable for large-scale production.^{59,104} The low-cost aspect of polymeric MNs becomes even more pronounced when considering that some of their fabrication techniques allow mold reuse³² and the raw material used for fabrication, i.e. polymers, is already more affordable than metals or silicon.¹⁰⁴ In addition, polymers have the advantage of being easily formable and offering a wide material variety,⁵⁹ both natural and synthetic, some of which with enhanced eco-friendly and biocompatibility features.^{30,58} Due to their unique and vast inherent physicochemical properties, polymers are often preferred for applications where specific surface characteristics are required.¹⁰⁵ Furthermore, polymeric MNs have a lower risk of breaking upon insertion than silicon MNs due to their softer nature which allows a higher needle flexibility and a better adaptation to the curved nature of the skin.^{30,45} The mechanical properties of polymeric MNs can also be tuned by adjusting their concentration, molecular weight, and cross-linking density.¹⁰⁶ Overall, polymeric MNs are gathering the attention of the scientific community⁵⁸ and are increasingly being used for the fabrication of health monitoring devices because of their biocompatibility, facile and low-cost production, advantageous mechanical properties, and possibility of extracting large amounts of fluid in a short timespan.^{30–32} Thus, we have decided to focus only on polymeric MNs moving forward.

In this section, we layout the information published in the past 5 years about polymeric MN-based devices for monitoring to provide an overview of the polymers, detection approaches and analytes being explored for health-related applications. To facilitate reading, we have divided them into (i) ISF collecting devices, and (ii) biosensor integrated health monitoring devices (Figure 2).

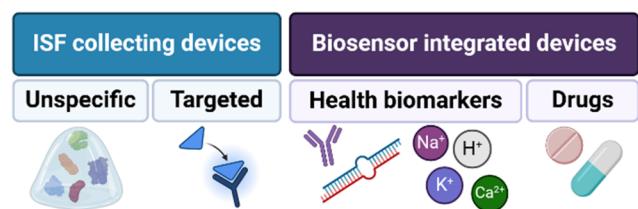


Figure 2. Types of polymeric microneedle-based health monitoring devices.

ISF Collecting Devices. Polymeric MNs are a minimally invasive, low-cost, and painless alternative to clinically available methods used to collect ISF analytes, such as suction blisters, reverse iontophoresis, and microdialysis.^{92,107,108} In addition, they allow the extraction of large quantities of ISF for analysis, and show improved biocompatibility and mechanical properties.^{30–32} Sample collection devices present in the literature aim to collect biomolecules for posterior benchtop analysis,

and can be divided into two categories: (i) those that extract a portion of the whole ISF, which is later processed to separate and analyze specific analytes, and (ii) those that are modified with target-specific moieties (Figure 1A). These bioreceptor-modified MNs have the advantage of capturing exclusively the biomarker of interest, which avoids postprocessing steps, simplifies biodetection and makes this process more efficient.^{30,61,109} Among untargeted MNs, analyte collection can be made through (i) hollow channels (Figure 1B), (ii) nonspecific surface adsorption (Figure 1C), or (iii) swelling of the polymeric matrix (Figure 1D).⁶¹ In the past 5 years, a total of 9 articles reporting MN-based sampling devices have been published (Table 1). Whole ISF collecting are characterized by the development of MNs that entrap a panoply of bioanalytes via swelling.^{108,110–112} Analyte-specific devices report bioreceptor-modified swellable MNs for the collection of nucleic acids¹¹³ and articles reporting bioreceptor-modified solid MNs for collecting proteins.^{77,109,114,115} In every case, captured bioanalytes are posteriorly analyzed using standard benchtop techniques, such as immunofluorescence, spectroscopy, or colorimetric assays.

Huang *et al.* cross-linked acrylic acid (AA) with gelatin methacrylate (GelMA) in various proportions to produce GelMA-AA MNs capable of collecting breast cancer biomarkers from the ISF (carcinoembryonic antigen, CEA, and glycoantigen CA15–3). They found that both the GelMA/AA ratio and the cross-linking density play a crucial role in the swelling and mechanical properties of the MN patches. When using an optimal mixture of 1% GelMA + 30% AA, the MNs were able to penetrate the skin without causing nerve damage or pain. Furthermore, they were able to capture CEA and CA15–3 in a mice model, which were later quantified by immunofluorescence (ELISA).¹⁰⁸

Takeuchi *et al.* produced porous PDMS MNs coated with hyaluronic acid (HA) to draw ISF glucose based on the mechanical compression of the PDMS matrix. By optimizing the porosity ratio, they were able to create MNs (with 60% porosity) that successfully penetrated the skin and extracted ISF at a rate of 0.46 $\mu\text{L}/\text{min}$ *in vivo*. Moreover, the successful extraction of glucose was confirmed through the change of color of a glucose test paper placed on the backside of the MNs.¹¹¹

Hsieh *et al.* developed controllable-swelling MNs that, when combined with paper-based colorimetric sensing or surface-enhanced Raman scattering (SERS), provided ultrasensitive biomolecular recognition of cefazolin, nicotine, paraquat, and methylene blue. The MNs, made of a mixture of poly(ethylene glycol) diacrylate and MeHA, could rapidly and reliably extract ISF from the skin. Moreover, in a proof-of-concept in human volunteers, the system effectively detected nicotine levels in ISF, highlighting its potential for personalized medicine.¹¹²

Fonseca *et al.* fabricated gelatin methacryloyl MNs that were able to collect urea in the ISF (detected through UV–vis spectroscopy). The MNs exhibited high water uptake ability, reaching equilibrium within 20 min, indicating their potential for ISF extraction. MNs showed noncytotoxic behavior toward human keratinocyte cells, confirming their safety for dermal application. Moreover, the MNs successfully penetrated human abdominal skin *ex vivo* and quantified urea from model agarose hydrogels, demonstrating the potential for real-time urea monitoring.¹¹⁰

Table 1. Summary of the MN-Based Sample Collection Devices Published in the Last 5 Years

Type of MN	MN composition	Method of analysis	Target analyte	Reference
Swellable	Acrylic acid incorporated into gelatin methacrylate	Immunofluorescence (ELISA)	Breast cancer biomarkers	Huang <i>et al.</i> ¹⁰⁸
	Porous polydimethylsiloxane (PDMS) coated with hyaluronic acid (HA)	Colorimetry–glucose test paper	Glucose	Takeuchi <i>et al.</i> ¹¹¹
	Mixture of poly(ethylene glycol) diacrylate and methacrylated hyaluronic acid (MeHA)	Colorimetry or surface-enhanced Raman spectroscopy	Cefazolin, nicotine, paraquat, and methylene blue	Hsieh <i>et al.</i> ¹¹²
	Gelatin methacryloyl	UV–vis spectroscopy	Urea	Fonseca <i>et al.</i> ¹¹⁰
Swellable and bioreceptor-modified	Poly-L-lactide coated with alginate	Fluorescence	Cancer-associated RNAs	Al Sulaiman <i>et al.</i> ¹¹³
Bioreceptor modified	Mixture of poly(ethylene glycol) diacrylate and poly(ethylene glycol)	Immunofluorescence	Inflammatory cytokines (TNF- α , IL-1 β , and IL-6)	Zhang <i>et al.</i> ¹⁷⁴
	Polystyrene	Immunofluorescence (p-FLISA)	Pro-inflammatory cytokine (IL-6)	Wang <i>et al.</i> ¹⁰⁹
	Polydimethylsiloxane (PDMS)	Surface-enhanced Raman spectroscopy or mass spectroscopy	Fentanyl or alprazolam	Simas <i>et al.</i> ⁷⁷
	Trimethylolpropane ethoxylate triacrylate	Immunofluorescence or aptamer-based fluorescent quenching	Anemia biomarkers (hemoglobin, ferritin, folic acid, and vitamin B12)	Wu <i>et al.</i> ¹¹⁵

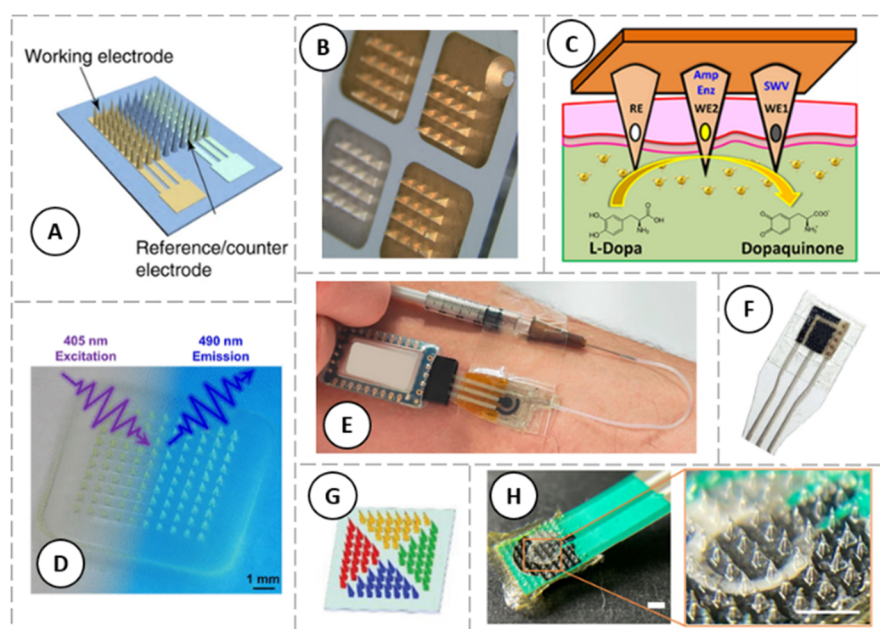


Figure 3. Representative examples of polymeric microneedle-based health monitoring devices. (A) Schematic illustration of a 3D-printed microneedle array produced using clear resin and sputtered with gold to form a conductive 3-electrode system. Adapted from Liu *et al.*²³ (B) Microneedle base used to produce a sensor to detect the concentration of antibiotics in interstitial fluid (ISF). Adapted from Rawson *et al.*¹²⁶ (C) Schematic representation of a microneedle sensor for L-Dopa monitoring in ISF. Adapted with permission from Goud *et al.*¹²⁷ Copyright 2019 American Chemical Society; (D) Image of a fluorescence-based biodegradable microneedle glucose sensor. Adapted from Sang *et al.*¹²⁸ (E) Image of the wearable glucose sensing patch on a human arm. Adapted with permission from Parrilla *et al.*¹²⁴ Copyright 2022 Elsevier; (F) Single-walled carbon nanotube modified microneedle sensor. Adapted with permission from Drăgan *et al.*¹²⁹ Copyright 2023 Elsevier; (G) Patterned microneedle array for fabricating colorimetric dermal tattoo biosensors. Adapted from He *et al.*²⁶ (H) Digital photo of a microneedle-glucose sensor and zoom-in image of microneedle structure before fluid extraction. Scale bar: 2 mm. Adapted from Zheng *et al.*⁹³

Al Sulaiman *et al.* presented poly-L-lactide MN patches coated with peptide nucleic acid probe-functionalized alginate for multiplex sampling of specific cancer-associated micro-RNAs from the ISF. The MNs could sample up to 6.5 μL of fluid in 2 min, with a sampling rate of 0.74 $\mu\text{L}/\text{min}$, outperforming existing sampling technologies. Moreover, they demonstrated high specificity and sensitivity in human skin biopsies, detecting target concentrations as low as 6 nM.¹¹³

Zhang *et al.* created MNs, made of a mixture of poly(ethylene glycol) diacrylate and poly(ethylene glycol), integrated with photonic crystal barcodes for the noninvasive

detection of ISF inflammatory cytokines. The photonic barcodes were decorated with specific probes and enabled biomarker enrichment and detection through immunofluorescence in a sepsis mouse model. These encoded MNs showed advantages over existing MNs for ISF detection, including simplified procedures, multiplex detection capability, and *in vivo* detection preserving the biological activity of targets.¹¹⁴

Wang *et al.* introduced a polystyrene MN patch functionalized with biorecognition elements to capture protein biomarkers selectively. The patches exhibited sufficient mechanical strength for skin penetration without yielding,

minimal invasiveness, and excellent biocompatibility. Furthermore, when combined with Plasmonic Fluor-Linked Immunosorbent Assay (p-FLISA), they were capable of local biomarker detection with high sensitivity in mice.¹⁰⁹

Simas et al. modified PDMS MNs with ligand-coated gold nanoparticles to detect potent drugs of abuse in the ISF. When combined with SERS or mass spectroscopy, this multimodal detection approach was able to distinguish between fentanyl, alprazolam, or mixtures thereof with high accuracy in human patient samples.⁷⁷

Wu et al. functionalized trimethylolpropane ethoxylate triacrylate MNs with antibodies to detect anemia biomarkers. When using immunofluorescence or aptamer-based fluorescent quenching, the MNs demonstrated high specificity and sensitivity and yielded results within 20 min. The sensitivities for ferritin, folic acid, and Vitamin B12 were significantly enhanced compared to conventional methods, achieving lower limits of detection (LODs) achieved. The integrated device maintained sensitivity for up to 21 days of storage without significant degradation, suggesting practical usability and stability.¹¹⁵

Overall, the research collectively demonstrates that MNs have great feasibility, efficacy and versatility for minimally invasive ISF sampling, offering potential applications in biomarker monitoring, and disease diagnosis. The articles focused various aspects, including optimization, fabrication techniques, mechanical properties, fluid extraction performance, and sensing capabilities. The key factors influencing the performance and efficacy of MN devices for ISF collection account: 1) composition and fabrication optimization to guarantee controlled swelling performance or ISF extraction, mechanical strength, and skin penetration efficiency; 2) porosity, pore size, and surface coatings play critical roles in fluid extraction rate and biosensing performance; 3) integration with sensing platforms allows for the detection of specific biomarkers, including proteins, nucleic acids, and small molecules, with high sensitivity and selectivity. Techniques such as plasmonic fluorimetry and SERS enable ultrasensitive detection even at low concentrations; 4) *ex vivo* and *in vivo* evaluations confirm successful skin penetration and reliable ISF extraction.

Targeted Disease and Health Monitoring *in Situ*.

Unlike previously mentioned devices, biosensor integrated devices allow precise *in situ* analyte analysis.⁶¹ These devices can target a wide range of biomolecules and can even be inserted into closed-loop systems, such as the ones used in diabetic patients to simultaneously measure glucose levels and administer the corresponding dose of insulin.¹¹⁶ Disease biomarker detecting tools have been used for instance to monitor diabetes progression, nasopharyngeal carcinoma, and chronic kidney disease. Recently published MN-based monitoring devices can be grouped based on their sensing principle into optical and electrochemical sensors.⁶¹ Electrochemical sensors are more common due to their cheap, easily reproducible and upscalable manufacture. However, they present some limitations, mainly related to their need for external energy sources.¹¹⁷ Figure 3 contains a few representative examples of both electrochemical and optical polymeric MN-based sensors used for health and disease monitoring. Glucose monitoring plays a significant role in monitoring diseases (e.g., diabetes mellitus¹¹⁸ and prediabetes¹¹⁹ and gestational diabetes¹²⁰), and health conditions (e.g., insulinoma,¹²¹ metabolic syndrome,¹²² and Cushing's

syndrome¹²³). Among recently published MN-based biosensors, glucose monitoring devices are the most common and the only ones reported to have been incorporated into a closed-loop system. *Parrilla et al.* developed their glucose sensing device based on a polyether ether ketone MN array connected to an enzymatic biosensor. The ISF is actively drawn from the skin using a syringe and immediately contacts with a carbon screen-printed electrode modified with glucose oxidase (GOx) to detect glucose.¹²⁴ *Zheng et al.* produced an osmolyte-powered hydrogel MN patch made up of maltose and MeHA to extract the ISF via *in situ* swelling. The extracted ISF then contacts with a gold-based electrochemical biosensor modified with GOx to detect glucose levels.¹⁸ *Sharifuzzaman et al.* opted for the direct modification of the surface of polyimide MNs with a glucose-detecting enzyme (glucose dehydrogenase, in this case). The MNs were then connected to a custom 3-electrode system which produced the electrochemical readout of the device.⁷⁸ *Liu et al.* 3D-printed a MN array using clear resin, which was sputtered with gold to form a conductive 3-electrode system. This was further modified with GOx to form a system capable of detecting glucose in the ISF.²³ Similarly, *Barrett et al.* electrodeposited platinum onto the surface of Norland Optical Adhesive NOA68 MNs, which were then modified with GOx to detect glucose.¹²⁵ *Dervisevic and Voelcker* opted for OrmoComp photoresist coated with a thin layer of gold to produce MN arrays, which were then modified with GOx to enable glucose detection. This electrochemical system had the particularity of possessing microcavities that protect the sensing layer from damage upon insertion/removal.¹³⁰ *Zhao et al.* decided on silk and D-sorbitol MNs modified with GOx and pierced with platinum/silver wires to create a glucose monitoring biosensor.¹³¹ *Luo et al.* developed a system capable of simultaneously detecting glucose and administering the corresponding dose of insulin. This system is formed by hollow chitosan MNs. The inner layer functions as an insulin injector and the outer layer, where GOx is immobilized, serves as a glucose sensor. The whole system is controlled by an electrochemical electrode and the insulin is delivered with the help of a small electroosmotic pump.¹¹⁶

Conversely, *Sang et al.*, *Zeng et al.*, *Li et al.* and *Wu et al.* chose nonelectrochemical approaches for glucose detection. *Sang et al.* went for a fluorescent-based MN sensor. Glucose-responsive fluorescent monomers were added to silk fibroin MNs to produce a patch that, when excited with violet light, turned proportionally blue according to the glucose levels present on the extracted ISF.¹²⁸ *Zeng et al.* went for a colorimetric biosensor based on colloidal crystal MNs. Clear resin MNs were infused with glucose-responsive colloidal crystals that proportionally shifted from blue to green upon contact with the glucose present in the ISF.¹³² *Li et al.* created swellable MeHA MNs modified with GOx-like gold nanoparticles to detect glucose based on colorimetric changes.¹³³ *Wu et al.* fabricated hollow MNs and coupled them with a glucose paper strip to produce a colorimetric sensor for glucose detection.¹³⁴

Glucose monitoring has also been performed alongside other bioanalytes through multianalyte MN-based devices. *Dai et al.* developed an electrochemical wearable patch based on MeHA MNs to monitor glucose and lactate levels.¹³⁵ *He et al.* reported a colorimetric dermal tattoo biosensor made of HA MNs to monitor glucose, pH, uric acid, and temperature.²⁶

Overall, the MN monitoring devices developed for glucose monitoring were capable of extracting ISF containing glucose without causing significant damage or pain. Furthermore, these devices exhibited minimal inflammation after insertion into the skin, ensuring their suitability for long-term use. They showed accurate and continuous monitoring of glucose, offering convenient and rapid monitoring of levels without the need for additional processing steps. The studies have all reported extended linear ranges of glucose detection, suitable for monitoring diabetic patients, along with high sensitivity and selectivity against common interferents. *In vivo* experiments on animal models, including diabetic rabbits and mice, demonstrated the reliability, accuracy, and correlation with conventional blood glucose meters, validating the effectiveness of MN-based glucose monitoring devices. Some of these studies explored multiplexed detection capabilities, enabling simultaneous monitoring of multiple biomarkers (e.g., glucose, insulin, pH, uric acid, and temperature), expanding the potential applications of MN-based biosensors. In addition, one of the papers¹²⁴ showed that a microfluidic setup significantly improved the sensing performance of MNs, enhancing glucose transport and detection efficiency, whereas another article¹²⁸ developed a user-friendly interface, including a smartphone app, which facilitated practical use of MN-based glucose monitoring devices, enhancing accessibility and convenience for users.

To monitor nasopharyngeal carcinoma, Yang *et al.* reported a device to detect Epstein–Barr virus (EBV) cell-free DNA, a newly found biomarker for this disease, based on poly(methyl vinyl ether-*alt*-maleic acid) hydrogel MNs, a reverse iontophoresis Au-carbon nanotube membrane and a flexible electrochemical sensor. The device demonstrated good conductivity and efficient capture of EBV. *In vivo* studies showed that early and accurate detection of nasopharyngeal carcinoma tumors is possible, surpassing other sampling methods.¹³⁶ Likewise, Zheng *et al.* developed a multianalyte electrochemical MN sensor array for diagnosing early chronic kidney disease (CKD). Their study combined HA and MeHA to create MNs for ISF extraction. MeHA lacked strength, so non-cross-linked HA was added for reinforcement. HA-MeHA MNs exhibited improved porosity and mechanical strength, enhancing ISF adsorption. The MN patch featured four electrodes for simultaneous sensing of phosphate, uric acid, creatinine, and urea, and showed sensitivity and specificity in physiological conditions. *In vivo* tests demonstrated multiplexed biomarker detection in ISF, with biomarker levels correlating with CKD progression.¹³⁷ Together, these devices have proven effective for the monitoring of pressing healthcare conditions and we expect that, in the future, similar devices will arise that monitor other disease biomarkers, like C-reactive protein which is overexpressed in several immune-system diseases, including lupus and Crohn's disease.^{138–140}

In situ monitoring has also been directed at osmolytes, such as sodium, calcium, and potassium, involved in different electrolyte imbalance disorders (e.g., hypernatremia,¹⁴¹ hypercalcemia,¹⁴² and hypokalemia¹⁴³), and responsible for kidney diseases (acute kidney injury, CKD, and, renal dysfunction).^{144–146} Omar *et al.* produced polystyrene MNs coupled with an electrochemical sensor to detect sodium, calcium, potassium, and pH from ISF. This wearable device integrated the sensors, an energy-harvesting system, and an IOT technology. The system harnessed energy from body motion and sunlight (Triboelectric Nanogenerator coupled with a

solar cell) charging, the battery necessary for sensing. The four sensors exhibited excellent electrical and sensing performance for each analyte, and demonstrated high sensitivity, selectivity, repeatability, and stability over time. Furthermore, real-data on multiple biomarkers was transmitted to a smartphone app, enhancing the convenience of monitoring.¹⁴⁷

The monitoring of pH is useful to track metabolic acidosis as changes in pH serve as predictors of the onset of circulatory shock.¹⁴⁸ Dervisevic *et al.* fabricated OrmoComp MNs coated with a thin layer of gold and modified with polyaniline to monitor pH changes in ISF. The working and reference electrodes were fabricated using high-density polymeric MN arrays and a polyethylene naphtholate film. The insulating OrmoComp layer prevented electropolymerization. The sensor exhibited high sensitivity, minimal interference from various ions found in ISF, high reproducibility, accurate monitoring and immediate responses of pH changes in *ex vivo* models.³²

Alcohol consumption is directly linked to many diseases (e.g., alcohol use disorder and liver diseases) and associated with increased risks of cardiovascular diseases and certain cancers (e.g., liver, colon, and esophagus). Furthermore, alcohol can contribute to the development of mental health disorders (e.g., depression and anxiety). Zheng *et al.* developed swelling MeHA MNs adhered to an electrochemical test strip to detect alcohol. To resolve the stretch incompatibility between the expandable MeHA MNs and the waterproofing electrochemical sensor, a chitosan layer was added between the two substrates. The fabricated MN device was able to extract ISF in less than 1 min and to provide accurate real-time alcohol measurements in an *in vitro* skin model, within a 0–20 mM linearity range. Overall, this work demonstrated the fabrication of a low-cost and convenient MN-based monitoring platform that could easily be adapted to other bioanalytes, like glucose.⁹³

Glutathione has been suggested as a biomarker for mitochondrial disease.¹⁴⁹ Zhao *et al.* created a colorimetric biosensor for glutathione detection based on swelling MNs, made of a poly(vinyl alcohol) (PVA) and sodium alginate hydrogel. The hydrogel MNs achieved a swellable ratio of 150% and were able to rapidly extract ISF (6.4 mg in 15 min). The device was able to accurately detect glutathione *in vitro* (with a limit of detection of 0.36 μ M) and *in vivo* in a rat model. Moreover, the results obtained *in vivo* were comparable to the ones obtained for blood using a commercial kit. This platform represents an alternative to currently available test kits for glutathione, which are expensive and nonreusable,¹⁵⁰ and we believe it holds great promise for the application to other metabolic diseases, such as hemochromatosis, which is characterized by high levels of ferritin.¹⁵¹

MN-based monitoring devices can also be used to detect various substances, from medicines to illicit drugs. Goud *et al.* created two systems to monitor the ISF concentration of medications for treating Parkinson's disease, one for levodopa and one for apomorphine. For the levodopa sensor, three Eshell 200 acrylate-based hollow MNs were produced and filled with unmodified carbon paste, tyrosinase-containing carbon paste, or a silver wire. Electrical contacts were then established to obtain an enzymatic and nonenzymatic sensor capable of detecting levodopa *in vitro* and *ex vivo* (in mice skin), within a linear detection range of 50 to 200 μ M.¹⁵² For the apomorphine sensor, four resin-based hollow MNs filled with unmodified carbon paste, rhodium nanoparticle containing carbon paste, or a silver wire were used to form a

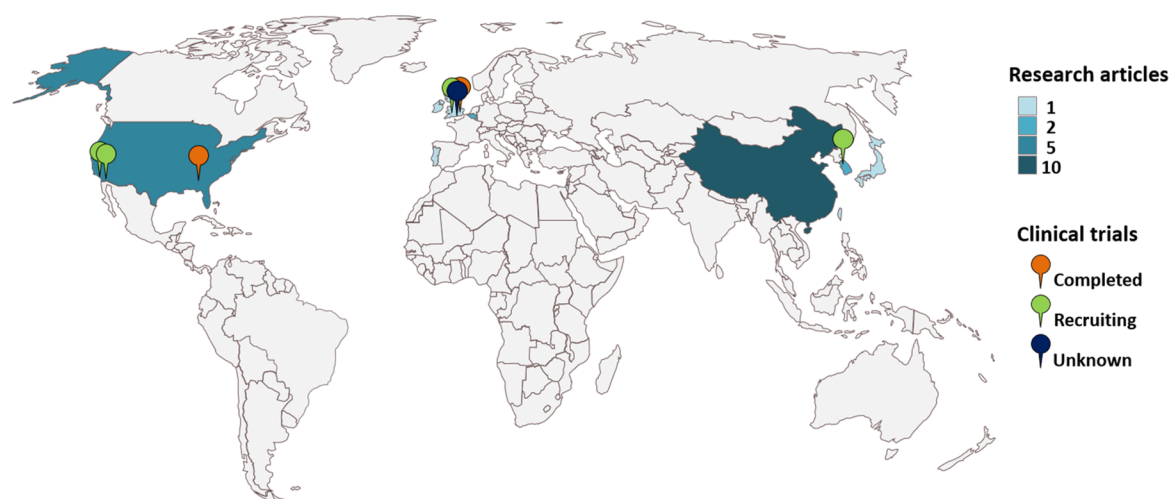


Figure 4. Geographical distribution of clinical trials involving microneedle-based health monitoring devices.

nonenzymatic sensor capable of detecting this medication. The sensor detected apomorphine *in vitro* with a limit of detection of $0.6\ \mu\text{M}$ (using square-wave voltammetry) or $0.75\ \mu\text{M}$ (using chronoamperometry). Moreover, the device showed good stability and antibiofouling properties against artificial ISF.¹²⁷ Rawson *et al.* engineered a sensor to detect the concentration of phenoxymethylpenicillin (PK), a common antibiotic, through the modification of metalized polycarbonate MN arrays with β -lactamase. The sensor was tested on 10 healthy human volunteers and showed to be capable of detecting phenoxymethylpenicillin with a limit of detection of $0.17\ \text{mg/L}$. Furthermore, the pharmacokinetic results obtained using the MN sensor were comparable to the ones obtained using microdialysis.¹²⁶ Lastly, Drăgan *et al.* produced polyether ether ketone hollow MNs filled with silver or graphite paste and then modified with single-walled carbon nanotubes to detect 3,4-methylenedioxymethamphetamine (MDMA), an illicit drug. The sensor detected MDMA in artificial ISF within a linear range of 1 to $50\ \mu\text{M}$ and a limit of detection of $0.75\ \mu\text{M}$.¹²⁹ Overall, these devices showed excellent analytical performance, with high sensitivity and selectivity for their target analytes. Furthermore, the incorporation of the levodopa monitoring device¹⁵² with a portable wireless electroanalyzer demonstrated the ability of these medication monitoring devices to provide timely individualized feedback on the appropriate dosing regimen. In the future, we expect to see the extension of drug monitoring MN-based devices toward other analytes, both for rapid illicit drug screenings and for continuous monitoring of long-term dose-sensitive medications.

In conclusion, recently published MN-based biosensing devices have shown potential for the sensitive and selective analysis of a myriad of analytes *in situ*, from small biomolecules like alcohol to complex synthetic drugs like MDMA. The incorporation of some of these devices with wireless data transmission platforms further demonstrated their real-life applicability, helping users to make informed, data-based decisions about their health.

PRECLINICAL TESTING

MNs have been tested in different *in vitro*, *ex vivo*, and *in vivo* animal models. Many authors use *ex vivo* models for insertion tests and to assess skin irritation,^{134,135} but excised animal skin has also been used, for instance, to test the ability of MNs to

collect ISF. For instance, Zheng *et al.* tested the capacity of their osmolyte-composited swellable MNs to draw ISF *ex vivo* (in pig skin) and showed they were able to collect approximately $8\ \mu\text{L}$ of ISF. The authors also tested these MNs *in vivo* (in mice), which collected a sufficient volume ($\sim 4\ \mu\text{L}$) for the straightforward analysis of glucose via a MN-integrated electronic sensor.¹⁸ In another work, a MN-based diagnostic device built by adhering a MN patch to an electrochemical strip was tested *in vitro* (in a hydrogel model), and the results were comparable to blood glucose ranges for normal and diabetic status. However, the experiments *in vivo* resulted in a smaller electrochemical signal, which could still be correlated to blood glucose levels.⁹³ MNs fabricated using a glucose-responsive polymer blend with conductive carbon nanotubes (sensing composite material) were also tested to draw ISF from rats (healthy and induced to have type 1 diabetes). The glucose concentrations measured with this device were comparable to blood samples analyzed using a glucometer, even after the MNs were worn for half a day. However, this MN array still needs to be paired with a separate reader or integrated with an electronic circuit to enable wireless data transmission to simplify personalized glucose monitoring.¹⁵³ Moreover, gold nanoparticle swellable colorimetric MNs for glucose detection were validated for ISF extraction in female SD diabetic and healthy rats for 20 min. Color changes of the collected MN patch were analyzed using a smartphone camera and ImageJ software, and the concentrations of glucose in ISF obtained were consistent with blood glucose levels.¹³³ Lastly, male NU/J athymic nude mice were used to assess the efficacy of a wearable sensor patch incorporating hydrogel MNs to measure in real-time both glucose and lactate concentrations in ISF. The sensor patch provided comparable measurements of glucose and lactate levels, particularly of glucose.¹³⁵ Given this information, we believe that these integrated sensing platforms, combining MNs and advanced electrochemical sensing circuits, may soon contribute to improving disease management and overall health monitoring.

Overall, the preclinical validation experiments have shown promising ISF collection and biomarker detection.

CLINICAL TRIALS

Ongoing and recruiting clinical trials will be briefly discussed (Figure 4). Taking into account the small number, all clinical trials, regardless of the material they are made of, are included in this section. To date, only two trials aiming for sample collection with MNs are listed at <https://clinicaltrials.gov>. There is one clinical trial recruiting participants with house dust mite allergic rhinitis (NCT05922176). Samples (RNA) will be collected with a minimally invasive technique, using a MN patch (no information is provided regarding the MN material used) as an alternative to skin biopsy and blood collection methods. This study will involve screening potential biomarkers to assess the response to immunotherapy, and to explore their utility as indicators for predicting the prognosis of immunotherapy in allergic diseases. The trial is recruiting participants aged 19 to 60 years, from all sexes, who have allergic rhinitis caused by the antigen of the American house dust mite, with moderate-severe persistent rhinitis, without any known skin diseases or allergic diseases. Samples will be collected from these participants before and after immunotherapy for transcriptomic profiling based on skin-extracted RNA samples for their comparison with normal skin samples.¹⁵⁴ Then, there is a completed clinical trial related to glucose monitoring (NCT02682056) that enrolled 15 pediatric participants (7–18 years old) with a diagnosis of diabetes. Testing was performed using MN patches made from biocompatible polymers or metal, to collect ISF or an intravenous catheter and lancet to draw blood. The mean age of the participants was 16.8 (80% were white, 1 black or African American and 2 unknown). The study comprised glucose monitoring during 4 h, and other data was simultaneously collected (e.g., apprehension level regarding the sample collection varying between not afraid to very afraid, and pain level assessment). Monitored glucose levels were comparable between all the approaches used during the study testing period. The participants reported less apprehension with the MN patch than with the intravenous catheter, but still higher apprehension than when Lancet was used. No adverse effects were observed in any of the study participants.¹⁵⁵

There is one clinical trial recruiting participants to use MNs (no information provided on the material of the hollow MNs that will be used) for levodopa monitoring (NCT04735627). In this trial, a levodopameter will be used in participants aged 48 to 85, which must meet the movement disorders society diagnostic criteria for clinically established Parkinson's disease (mild, moderate, or severe), must be taking instant release oral carbidopa/levodopa therapy and also either not be taking or be on stable doses of other antiparkinsonian medications (e.g., dopamine agonists, monoamine oxidase B inhibitors or catecholamine O-methyl transferase inhibitors). The participants will receive oral or intravenous administered medication and then the MN device will measure the levodopa levels in ISF. These levels will be compared to plasma levodopa levels measured using high-performance liquid chromatography. The goal of this clinical trial is to allow patients with Parkinson's disease to take proactive healthcare measures to maintain an optimal levodopa regimen.¹⁵⁶

A clinical trial using a MN-based sensing device to monitor antibiotic concentrations was completed in 2020 (NCT03847610). This trial tested a polycarbonate MN array structure metallized to produce four independent electrodes¹²⁶ for tracking phenoxymethylpenicillin concentrations in the

plasma of 10 participants (mean age 42, 70% male) and compared it against the current gold standard (microdialysis and blood sampling). Although the accuracy of the device was not reported, none of the participants observed any adverse effects.¹⁵⁷ Another clinical trial on closed-loop control of penicillin delivery is currently recruiting participants (NCT04053140). In this exploratory study, 20 healthy volunteers (>18 years old) will be enrolled and administered the drug. Three sets of tests will be conducted: 1) penicillin G 1200 mg administered every hour for collection of samples with a MN array, 2) penicillin G 2400 mg administered every 4 h for a MN array and closed-loop control delivery experiment, and 3) penicillin G 600 mg administered every hour for MN array and closed-loop control delivery studies. The polycarbonate MN biosensor metallized with chrome,¹⁴⁸ will be sited peripherally. In study experiments 2 and 3, the MN arrays inserted will be collected after the duration of the study and used to titrate the benzylpenicillin dosage according to the pharmacokinetics and pharmacodynamics target. The main aim is to study the feasibility of the penicillin MN biosensor technology linked with a closed-loop automated delivery of antibiotics.¹⁵⁸

A trial measuring methadone concentration on ISF using silicon microneedles¹⁵⁹ is recruiting participants (aged 18–70) taking methadone for chronic pain (at least one dose of 10 mg per week, taken as prescribed in the last 4 days before consent to participate) (NCT05981573). This pilot study aims to assess if a physician can 1) recognize the peak of methadone dose use *ex vivo* in a remote medication monitor and 2) determine the status of prescribed dose taking over time. The ISF collected sample will be assayed electrochemically and the results compared to methadone concentrations in the blood detected using liquid chromatography, mass spectroscopy, and differential pulse voltammetry.¹⁶⁰

There is also a clinical trial on lactate monitoring using MNs (no information on the MN material) in the clinicaltrials.org list (NCT04238611), however, its status is unknown, and the last update on the Web site was done in August 2021. This may be due to a delay in the recruiting of the participants. Therefore, although the status is presently unclear, we opted to include this trial in our review. The goal is to validate a MN-based device for the continuous measurement of lactate during exercise and compare its precision and accuracy with blood measurements. In addition, the acceptability in terms of pain, comfort, physical restriction, and skin sensation will be evaluated.¹⁶¹

The results of these trials will provide further knowledge on the future potential application of MN biosensing technologies in healthcare monitoring.

Clinical trials offer valuable insights into the potential applications of MN sensing technologies, and of their feasibility and efficacy in real-world clinical settings. Despite some trials being ongoing or having unknown statuses, their inclusion underscores the importance of exploring and validating MN-based technologies for continuous health monitoring.

MICRONEEDLE MARKET

The global market for MNs is witnessing continuous growth. In 2023, the market estimates were expected to reach USD 768.9 million up to USD 2.81 billion, with the compound annual growth rate (CAGR) varying between 6.83% (2023–2028), and 6.6% (2023–2033).^{162,163} The drivers for this

Table 2. Current List of Companies Commercializing Products Integrating Polymeric Microneedles

Company	Country	Products	Microneedle material
Raphas ¹⁷⁰	Korea	Microcone (8 Acropass beauty patches and 1 Therapass medical device)	Hyaluronic acid
MITI Systems ¹⁷¹		Eye patch, spot patch, and sMTS EGF Oil Scrub Essence	
CosMED Pharmaceuticals ¹⁷²	Japan	MicroHyal and gMJETTM	
Think-Lands ¹⁷³		Information not available	Polyglycolic acid
Micropoint Technologies ¹⁷⁴	Singapore	Micropoint Patch and MPatch	Polyurethane, polypropylene, polyethylene, polystyrene, poly(methyl methacrylate), polycarbonate, hyaluronic acid, polyvinylpyrrolidone, carboxymethyl cellulose, . . .
Vaxess ¹⁷⁵	USA	MIMIX patch	Silk fibroin proteins
LTS ¹⁷⁶	Germany	Microneedle Patch	Polymers, including polyvinylpyrrolidone and polyvinyl alcohol
Innoture ¹⁷⁷	England	Customizable coated, solid, or dissolvable microneedles	Polymers (more specific information not available)

market revenue growth are related to the innovative delivery of medicinal formulations. The global market is segmented by type of product, application, and region. Based on type, the market is segmented into patch, rollers, radiofrequency, and laser MNs, and based on MN needle material, the market segments into metal, glass, polymer, and silicon.¹⁶⁴ The solid MN segment dominates the market, witnessing an increase in the market of polymeric MNs due to the advancements in these systems as substitutes to conventional hypodermic injection for transdermal drug delivery.^{165,166} Based on application insights, the global market is segmented into skin rejuvenation, alopecia, sun damage, acne, scars, and spots. However, the increasing incidence of diabetes is driving the industry demand for minimally invasive and pain-free administration approaches. Moreover, technological advancements and the widespread adoption of smart devices, coupled with the integration of AI and data analytics, are also driving market growth.¹⁶⁵ The main players in the MN market include companies such as Becton, Dickinson and Co., Cynosure, Candela Corp, and Vaxess Technologies Inc.¹⁶⁷ In terms of market share, North America holds the highest share of this market. To date, there is no market estimate for MNs used in biosensing applications, but they are expected to be positioned in the same segment as polymeric MNs.

The global point-of-care diagnostics market was valued at USD 40.61 billion (2022) and is expected to expand at a CAGR of 6.5% from 2023 to 2030.¹⁶⁸ The drivers for this growth are the rising prevalence of target diseases, increase in funding from multiple sources, rapid disease identification, and monitoring with reduced barriers to care. In this POC market, we find kits for glucose monitoring, infectious disease testing, and urine analysis, among others. Major market players in the POC market are intensifying their efforts to incorporate cutting-edge technologies like AI in the production of diagnostic tests, aiming to enhance efficiency (e.g., lab-on-a-chip platforms, wearable technology, and innovations in smartphone-based technology).¹⁶⁹ MN-based sensing devices will soon have an impact on this market.

There are a few companies, predominantly in Asia, working with polymeric microneedles (Table 2). Most of these companies work with transdermal drug delivery products to replace the conventional injection approach or transdermal systems. These companies are pursuing their R&D with different medical-grade polymers (e.g., HA, polyglycolic acid, and poly(methyl methacrylate)). The materials being used by these companies account for nondegradable and biodegradable polymers. Although the companies identified in Table 2 mostly

work on drug delivery, we identified a few companies using polymeric MNs for skin care [Raphas (Korea), CosMED Pharmaceuticals (Japan), and MITI Systems (Korea)]. There are some commercially available HA-based MN products on the market for skin care (e.g., Microcone, MicroHyal, and gMJETTM), but the vast majority of companies commercialize products for drug delivery (e.g., MIMIX patch and MPatch), or fabricate tailored services for their customers (e.g., the company Innoture, England). In terms of IP, most companies have the MN composition, fabrication, and application(s) protected. There are other companies also in this space that work with alternative MN materials (e.g., stainless steel, titanium, and ceramics). These nonpolymeric MN devices are used for varied applications including skin care, drug delivery, blood collection devices, and metabolite monitoring. According to our research, we did not find any commercially available MN device focused on monitoring and diagnostics. However, we anticipate that a few products will become closer to the market once the clinical trials have finished.

■ FUTURE TRENDS AND CHALLENGES

Throughout this review, we have shown that there is a great deal of interest in polymeric MNs for health monitoring. Considerable work has been published demonstrating the safety and efficacy of polymeric MNs for ISF collection and analysis, and there are already two completed trials and several others ongoing using MNs for diagnostics. Moreover, there are eight companies fabricating products based on polymeric MNs and two companies commercializing MN-based devices for biosensing purposes. As such, and given that both the MNs and POC devices industries represent multibillion-dollar market sectors expected to sustain a growing trajectory in the next decade, we expect the introduction of MN-based devices in the market in the next few years. Furthermore, unlike MNs for drug delivery, MNs for diagnostics do not need to follow a combined product approval path to obtain regulatory approval. Instead, they can be marked as medical devices,¹⁷⁸ facilitating the approval process and reducing the time required to place these devices in the market. Future research in polymeric MN monitoring must continue to focus on advancing multiplexed analyte sensing systems to provide comprehensive health and disease monitoring, enhance diagnostic capabilities, and enable personalized healthcare. Additional effort is also expected on the integration of sensing components into polymeric MNs to enable more compact and portable devices for diagnostics. There is also a drive to develop wearable and patch-based systems for extended use.

We anticipate that most, if not all, future polymeric MN-based sensing devices will incorporate wireless communication and connectivity features, allowing for continuous data transmission to smartphones or cloud-based platforms, and enabling remote real-time data monitoring and feedback, which will empower users to make informed decisions about their health. Also, integration with artificial intelligence and machine learning algorithms is foreseen for advanced data analysis, and interpretation (e.g., pattern identification and trend prediction) for personalized data-based health recommendations. Research efforts are also expected to advance long-term monitoring, potentially incorporating implantable MNs for continuous biomarker surveillance, offering significant advantages for managing chronic diseases. Anticipated developments include a transition toward biocompatible, biodegradable materials, alongside progress in nanomaterials and functional polymers. Integration of smart materials and responsive sensors into MNs is envisioned to enable dynamic adjustments in response to physiological changes, thus enhancing monitoring accuracy and reliability. Moreover, it is imperative to continue enhancing sensing performance through design, surface chemistry, and sensor integration for improved sensitivity, selectivity, and response time.

Despite promising, polymeric MN-based monitoring is challenged by stability, durability, and reliability of the integrated sensors due to the mechanical stresses encountered during wear, including long-term wear. Furthermore, their long-term adherence to skin might change, which may cause discomfort, and even pain, if the patch becomes loose. Biofouling problems also need to be carefully addressed at the concept stage to minimize these events. Furthermore, there are several obstacles to the translation of academic MN monitoring research into marketable products. For instance, scaling up of the manufacturing process to produce MNs with consistent quality in large quantities. This will require investing in cost-effective scalable techniques, such as roll-to-roll manufacturing. This can be challenging, because the materials used in scalable processes, might not be the same ones used at the research level, which will demand search for alternative biocompatible materials, and several iterations to optimize the scalable manufactured devices. In addition, regulatory agencies, such as the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), may require adherence to Good Manufacturing Practices (GMP) guidelines to ensure that the devices are consistently produced and controlled according to quality standards. This will implicate considerable additional costs related, for example, to the establishment of GMP-compliant facilities and to an increase in operational costs. Besides, GMP compliance entails training of personnel on GMP principles throughout the organization, and thorough and complex documentation recording (e.g., standard operating procedures, batch records, quality control tests) which is resource-intensive. However, even if GMP compliance is not mandated, implementing quality management practices and adhering to relevant standards can help ensure the safety, reliability, and effectiveness of the devices. Finally, regulatory approval of the MN monitoring devices produced might also be a hurdle because this is a lengthy and complex process, which requires rigorous preclinical and clinical testing.

In conclusion, polymeric MN-based monitoring devices hold the promise of revolutionizing health diagnostics, providing rapid and minimally invasive testing beyond traditional

laboratory confines. In addition, further advancements in fabrication techniques, sensing capabilities, and clinical validation are expected to drive the translation of MN technology into practical clinical applications. This advancement has the potential to significantly enhance healthcare accessibility, particularly in remote or resource-limited regions.

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Notes

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VOCABULARY

AA, acrylic acid; CAGR, compound annual growth rate; CEA, carcinoembryonic antigen; CKD, chronic kidney disease; EBV, Epstein–Barr virus; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; GelMA, gelatin methacrylate; GMP, Good Manufacturing Practices; GOx, glucose oxidase; HA, hyaluronic acid; ISF, interstitial fluid; MeHA, methacrylated hyaluronic acid; MN, microneedle; PDMS, polydimethylsiloxane; SERS, surface-enhanced Raman scattering

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