Microneedles have emerged for transdermal monitoring of biomarkers, which are a miniaturized replica of hypodermic needles with length-scales of hundreds of micrometers, with a goal to achieve time-sensitive clinical information for routine point-of-care health monitoring. Transdermal biosensing via microneedles offers remarkable opportunities for moving biosensing technologies from research laboratories to real-field applications and enables development of easy-to-use point-of-care microdevices, minimally invasive, and with minimal-training features that are very attractive for both developed and emerging countries. This would eliminate the need for blood extraction using hypodermic needles and in turn, reduce the related problems such as infections in the patients, sample contaminations, and analysis artifacts. In this review, we provide a general overview of recent progress in microneedle-based sensing research, including: (a) in-vivo microneedle diagnostic systems for glucose monitoring with an emphasis on sensor construction and general health monitoring (b) in-vitro use of microneedle sensors. The main objective of the review is to provide a thorough and critical analysis of recent advances and developments in microneedle research field and to bridge the gap between microneedles and biosensors.

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Microneedles, which are a miniaturized replica of clinical hypodermic needles, are micron-size devices, which can physically disrupt the outer layer of the skin. The integration of microneedles in biosensors envisions a novel class of minimally invasive and painless biosensors for both in-vitro and in-vivo risk-free measurements of analytes of clinical interest. In the last two decades, microneedles have shown (in human volunteers) to increase compliance both toward skin puncture and operation procedures, even by non-technical personnel, along with application toward risk-free and (nearly) pain-free skin penetrations. Previous publications and reviews have described in detail various microneedle fabrication methods, principles behind microneedle designs, and extraction methods that involve the use of microneedles.

An increasing number of concepts have been published on the use of microneedles for in-vivo and in-vitro biosensing applications, aimed at low cost, pain-free, fast and reliable measurement of glucose in ISF and in blood serum samples. Although a couple of reviews published concerning the minimally invasive monitoring of glucose, did not focus on in-vivo and/or in-vitro enzyme and/or non-enzymatic glucose biosensing, there was room for review of microneedles based enzymatic and non-enzymatic minimally invasive CGM. Microneedles have fewer interactions than traditional hypodermic needles with the dermis, where Meissner’s corpuscles, Pacinian corpuscles, and large nerve endings reside; as such, microneedles produce little to no pain sensation. Microneedles thus provide a minimally invasive approach for creating artificial pores in the skin.

The aim of the study was to critically summarize (a) start-of-the-art developments on the use of microneedles for in-vivo (transdermal) and in-vitro biosensing applications, to bridge the gap between microneedles and biosensors, (b) recent progress in microneedle-based sensing research for CGM. The organization within provides the reader with a clear and logical path starting from enzymatic in-vivo and in-vitro glucose sensing, proceeding with non-enzymatic in-vivo and in-vitro glucose sensing and ends with tabulation of the discussed microneedle sensors for readers convenience.

Glucose Sensing with Microneedles

In their early stages, microneedles were mainly used for the extraction of extracellular fluids, either blood or ISF, in which the glucose content was measured either in-line by integrated biosensors or offline by standard commercial methods. Besides this, an increasing number of research works has been reported on the use of microneedles for in-vivo and in-vitro biosensing applications, to enable ISF flow through the microneedles and pass the integrated enzymatic electrochemical electrodes located beneath the microneedle array. ISF was extracted through 200-μm tall microneedles and mixed with a buffer solution. The needles were used to pierce the outermost layers of the skin on a finger and extract sample ISF from the epidermis. Capillary and evaporation forces were exploited to enable ISF flow through the microneedles and pass the integrated two-electrode enzyme-based glucose biosensor; the latter was placed in a shallow flow channel grooved into the Pyrex underneath the needle. An in-device enzyme immobilization on the sensor electrodes was carried out through the use of auxiliary flow channels. A preliminary experimental calibration of the glucose biosensor (not connected to the needles) at different glucose concentrations between 0 and 600 mg dL$^{-1}$ highlighted a linear response in the range of 0–160 mg dL$^{-1}$, with an optimal flow-rate of 25 μL min$^{-1}$. Regarding the whole microsystem, a significant variation of the biosensor current was measured after the needles were inserted into the skin, thus suggesting the successful sampling of ISF through the microneedles. The glucose biosensor showed a readily discernable signal at the outset of testing; however, the responsiveness of the sensor was not sustained over the course of testing. The limitations of the device were the fact that the device relied on movement of small volumes of interstitial fluid through channels within the device.

Mukherjee et al. created an array of 200 hollow silicon microneedles, in which the microneedle lumen was off-set from the tip; they demonstrated interstitial fluid extraction from the ear of a human subject via wicking. The microsystem consisted of a silicon/glass chip with dimensions of 2 cm × 1 cm × 0.1 cm. The silicon chip integrated an array of hollow microneedles intended for ISF extraction on the front side, and a reservoir for ISF collection and storage, connected to the needles through a net of fluidic microchannels, on the back-side. The microneedles were fabricated by means of a process combining deep reactive ion etching (DRIE), diamond blade circular sawing, and isotropic etching. Needles with different shapes were produced volcano-like, micro-hypodermic, and snake-fang, although only the snake-fang microneedles (20 × 20 array of needles featuring a shank...
Figure 1. Image of the microneedle arrays (A). Schematic representation of the sensor design (B). Response curve for amperometric sensors on platinum-coated steel microneedle electrodes (C) and the corresponding cytotoxicity data for 1, 3, and 7 days of storage in PBS, for platinum-coated steel microneedle sensors (D). Reproduced with permission from Ref35.

An amperometric glucose sensing smart patch has been reported using a conducting polymer, poly(3,4-ethylenedioxythiophene) (PEDOT), to entrap GOx directly on the surfaces of solid stainless-steel microneedle arrays (length of 680 μm and width of 250 μm) (Figure 1A).35 PEDOT provided a biocompatible environment to trap the active enzymes and allowed glucose to diffuse into the polymer matrix (Figure 1B). In addition, its electrical properties provided a low voltage signal transduction pathway. A particular advantage of this technique is the ability of the microneedles to collect sample directly from the interstitial fluid without complicated microfluidic components and/or separated sensor architectures. The microneedle-based biosensors were then tested in-vitro using a 2 mM solution of glucose in Phosphate buffered saline to make sequential glucose additions. Chronoamperometry was employed to monitor current changes over time, corresponding to each addition of glucose until a steady-state stable value was reached, the latter used to correlate current values to glucose concentration values. Pt-coated microneedles showed improved performance with respect to bare stainless-steel microneedles, with high linearity between 36 and 432 mg dL−1 of glucose, almost covering the physiological range 0–432 mg dL−1 of glucose for diabetic patients, and good S/N ratio (10.7) (Figure 1C). Investigation of the effects of various common interferents in human blood highlighted that glucose exhibited a far higher signal than any other analyte found in blood. Long-term stability of the microneedle-based glucose biosensors was also evaluated by storing the microneedles for 1, 3, and 7 days either in PBS (wet storage) or in an empty vial (dry storage), at room temperature prior to performing glucose detection (Figure 1D). The performance of the Pt-coated microneedle sensors was not significantly altered by either wet or dry storage conditions, still maintaining high linearity and S/N ratios, contrary to bare steel microneedle sensors that demonstrated relatively poor performance. The microneedle-based sensors were calibrated and performed within the physiological range of glucose; however, the microneedle-based sensors were tested in vivo; as such, it is currently unknown if shearing of the soft polymer coating on the exterior of the microneedle can occur during skin penetration.

Valdes-Ramirez et al. described a microneedle-based self-powered biofuel-cell (BFC) sensor for subdermal glucose monitoring. BFCs are very attractive for on-body applications, since they offer an approach to develop an autonomous energy supply (thus eliminating the need for external power source) for medical devices by harvesting energy from body fluids. With this aim, microneedle-based BFCs are found to be considerably promising as self-powered biosensors, capable of harvesting biochemical energy from subdermal fluids and providing power signals proportional to the concentration of the analyte of interest. The microneedle-based self-powered BFC glucose sensor was released through the integration of a BFC carbon-paste bioanode and cathode into a hollow microneedle array. The
bioanode was obtained by mixing carbon paste (87%) with the enzyme (10% GOx) and mediator (3% tetrathiafulvalene (TTF), whereas the cathode was obtained by mixing the carbon paste with Pt black (1:1 weight ratio). The prepared carbon paste-GOx-TTF bioanode and the carbon paste-Pt black cathode were finally intruded into six hollow microneedles of the array, with one row of three microneedles working as bioanode and one row as cathode. An Ag/AgCl reference electrode and a Pt wire counter electrode completed the three-electrode system for the electrochemical characterization. In vitro characterization of the microneedle-based BFC sensor for subdermal glucose monitoring was carried out by using artificial ISF with glucose concentration in the range 0–25 mM. Power density, as a function of concentration of glucose, showed a linear behavior over the whole range 0–25 mM, thus indicating the suitable glucose measurements addressing both hypoglycemia and hyperglycemia. In particular, a low power density of 0.4 μW cm⁻² was obtained for the blank solution (0 mM glucose), whereas higher power densities of 3–5 μW cm⁻² were observed over the normal glucose range (5–10 mM glucose) with a maximum value of 7 μW cm⁻² for the 25 mM glucose solution. The stability of the microneedle based BFC sensor during a continuous 60 h period monitoring was further evaluated in artificial ISF containing 10 mM glucose and 20.6 mg dL⁻¹ BSA. Selectivity of the microneedle based BFC glucose sensor was then assessed by recording the glucose power signal in the presence of common electrochemical interferences (i.e., ACT, AA, UA, and lactic acid), under physiological conditions. No significant effects on the glucose power-density signal were observed for any of the tested interferences.

Jina et al. described clinical studies using a prototype microneedle-based continuous glucose monitor that accurately detected glucose in human skin for up to 72 hours.³⁶ The device consisted of 200 hollow silicon microneedles, each with a length of 300 μm and a lumen diameter of 50 μm, over a total area of 6 mm × 6 mm. A screen-printed enzymatic working electrode in connection with the respective reference and counter electrodes was placed directly behind the microneedle array. This structure was separated by a proprietary buffer solution that simultaneously catalyzed the mutarotation of glucose and citrate ion to control the analyte flux for enhanced long-term stability and performance. The sensor worked on the basis of direct detection of hydrogen peroxide, a side product of the GOx enzyme catalysis at an applied potential of 0.46 V versus an Ag/AgCl reference electrode. The sensor pod was applied to the skin using a spring-loaded applicator. This applicator accelerates the microneedle array into the skin so that the needles penetrate reproducibly. The sensor pod was fixed to the skin, using skin adhesive, on the zone outside the microneedle array and protruding around the perimeter. In this prototype device, the buffer was introduced into the diffusion chamber by syringe after application of the sensor pod to the skin. A study involving 10 diabetic subjects showed that the microneedle-based sensor was able to measure accurately the glucose with a mean absolute relative difference (MARD) of 15% over a 72 h period. 98.4% of the paired points were located in the A and B region of the Clarke error grid.

Chua et al. reported the use of hollow silicon microneedle arrays for in vivo minimally invasive CGM.³⁸ Straight silicon microneedle arrays (SSMAs) and tapered silicon microneedle arrays (TSMAs) were fabricated using standard silicon micromachining techniques. TSMAs and SSMAs shared similar DRIE steps, though TSMAs were sharpened via HNA (hydrofluoric acid/nitric acid/acetic acid) etching, whereas SSMAs were sharpened via a mask depletion process using DRIE. Microneedle heights were about 325 μm and 350 μm and pitches were 400 μm and 450 μm for SSMAs and TSMAs, respectively. Microneedle lumen was about 50 μm × 50 μm in size. A CGM system prototype was achieved by assembling an electrochemical glucose sensor and a hollow microneedle array on opposite sides of a glucose chamber using a PC housing. The glucose sensor consisted of screen-printed electrodes (Pt working electrode, Ag/AgCl reference and counter electrodes) with the working electrode (about 6 mm × 6 mm) coated with GOx chemistry formulation. In vivo experiments were carried out on human subjects who were asked to fast for 2 h before taking a meal to increase the glucose concentration in blood. The biosensor current was continuously measured over time for 6.5 h, at a sampling frequency of 1 Hz. A commercial glucose meter was used to monitor glucose concentration in blood as control. The sensor currents of both the CGM system prototypes appeared to trace the reference blood glucose values (between 90 and 220 mg dL⁻¹) reasonably well.

Wang et al. have reported for the first time, solid glass microneedles for in vivo extraction of ISF to detect glucose.³⁹ The use of glass for microneedles was driven by the peculiarities of this material, which is physiologically inert, sterile, and transparent. Moreover, conventional glass needles have largely been used in intracellular recording as well as microinjection and patch clamping applications, due to the low cost and easy fabrication. Glass needles were fabricated by means of a programmable thermal micropipette pulling using borosilicate glass capillary tubing (outer diameter of 1.5 mm, inner diameter from 0.86 to 1.10 mm). Demonstration of multi-needle array fabrication was given through the mechanical assembling of seven single-needles. The fabricated microneedles have a tip radius of 15–40 μm with a cone angle of 20°–30°. The needles had a hollow bore and the needle tips were sealed by glass melting in order to increase their mechanical strength. Glass microneedles were successfully used to penetrate the skin up to a depth of 700–1500 μm and extract dermal ISF from hairless rats and adult human volunteers. In particular, a 1-cm² large area of the skin was pierced to make 7 to 10 holes, using either repeated insertions of a single microneedle or a single insertion of a multi-needle array. A cone-shaped geometry of microneedle-created holes with radii of 80–250 μm and depths of 700–1500 μm that is with the dimensions similar to those of the needles themselves was confirmed by different analyses. ISF was extracted by applying a negative pressure of 200–500 mm Hg (using a vacuum rotary pump) to the punctured skin for either 2–10 min in animal tests or 5–20 min in human tests. Ultimately, ISF drops were collected from the treated skin using glucose test strips, which were immediately analyzed to assess the glucose concentration. ISF volumes extracted were typically 1–10 μL, which were sufficient to measure glucose concentration with the help of commercially available devices. As controls for ISF glucose levels, blood was also collected from both rats and human subjects by lateral tail vein laceration and fingertip puncturing, respectively, and similarly analyzed. By comparing measured ISF and blood glucose levels, a tight correlation with a linear dependence was observed for both animals and humans, with 95% of measurements in rats and 100% of measurements in humans falling within the region of A and B of the Clarke Error Grid analysis. A kinetic study was carried out to monitor glucose levels both in ISF and in blood at time intervals of 20 min, after intraperitoneal injection of 1U of insulin. Measurements showed a rapid decrease in blood glucose level after insulin injection, closely followed by microneedle-extracted ISF glucose level assessment, with no significant time lag given the 20 min time resolution; these results showed that glass microneedles can be used for painless glucose monitoring of dermal ISF extracted in a minimally invasive manner.

Hwa et al. developed a low cost, enzymatic and amperometric microneedle sensor for minimally invasive CGM.³⁹ Electrochemical studies were carried out in a conventional three-electrode cell using 0.51 mm, coated Au microneedle (CHI) as working electrode, Ag coated microneedle as reference electrode and uncoated Au microneedle as counter electrode. The enzyme GOx immobilization on microneedles involves the immersion of Au microneedle electrode arrays in 1 mM euthanolic solution of 3-MPA for 1 h and subsequent treatment with EDC (2 mM)/NHS (5 mM) to activate carboxyl group for the enzyme (5mg mL⁻¹) immobilization. The sensor detected glucose based on 1st generation glucose biosensing principles, by catalyzing the oxidation of glucose to gluconic acid. For in vivo studies, the GOx immobilized microneedle sensors were pinned into 1% agarose gels with different concentrations of glucose, and current responses were measured at 0.7 V. A linear response to glucose was observed with increasing glucose concentration from 50 mg dL⁻¹ to 400 mg dL⁻¹. The microneedles showed a good storage stability, with 80% activity retained after 7 days.
Sharma et al. fabricated a minimally invasive glucose biosensor based on a microneedle array electrode from an epoxy-based negative photoresist (SU8 50) material and designed for continuous measurement in the dermal compartment with minimal pain. The sensor device consisted of a three-dimensional out of plane microneedle array, with 64 microneedles perpendicular to the basal plate and arranged as four 4 × 4 arrays (Figures 2A and 2B). Fabrication procedure of microneedle array electrode involves (a) making of aluminum masters using an electrical discharge machining (EDM) technique to create moulds of polydimethoxy siloxane (PDMS); (b) the PDMS moulds were subsequently used to cast SU8 50 using vacuuming and spinning; (c) crosslinking of SU8 50 by exposure to UV light at $\lambda_{365\text{nm}}$ for 30 min; (d) peeling off the final epoxy sensor devices from the PDMS layer and subsequent metallization of the sensor devices by conformal sputtering in a clean room to produce the working and reference electrodes. The microneedles metalized with platinum and Ag/AgCl were used as working and counter/reference electrodes, respectively, in a two-electrode configuration. The sensor was finally functionalized with an enzyme GOx (10 mg mL$^{-1}$) using phenol (50 mM) using an electro-polymerization technique. In-vitro studies, showed a sensor performance down to 0.5 mM, with a response time of 15 s and dynamic range of 0–30 mM at +0.7 V against the integrated counter/reference electrode. For in-vivo studies, the needles were subjected to sterilization by 25 kGy of gamma radiation with assay of the bio burden levels on the microneedle arrays. These studies involved the insertion of sterilized needles into the forearm of a healthy volunteer and measurement of glucose concentration for every 15 minutes. The results showed a correlation and time lag between the capillary blood and the dermal ISF (Figures 2C and 2D), but the major operational challenge faced was to keep the sensor fixed in the sub dermal space.

Li et al. demonstrated the fabrication of one touch-activated blood multi-diagnostic system involving the synergistic integration of a hollow microneedle and paper-based sensor. The biocompatible minimally invasive hollow microneedle for blood collection was fabricated by draw lithography technique with a length of 1800 μm, an inner diameter of 60 μm, an outer diameter of 130 μm, and a bevel angle of 15° (Figure 3A). The fabrication of one touch microneedle sensor involves the (a) assembling of microneedle onto the bottom of the sensor chamber, which was made of mechanically processed acrylic (b) casting and curing the PDMS touch-switch on the aluminum master mold, which was fabricated using standard soft lithography replica molding techniques (c) placing the paper-sensor inside the sensor chamber and adhering it to the upper PDMS touch-switch.
Figure 3. Schematic representation of the fabrication of one-touch-activated blood multi-diagnostic system (OBMS) (A); image of the biocompatible minimally invasive hollow microneedle (60 μm inner diameter, 120 μm outer diameter, 15° bevel angle) contained within the OBMS (B); calibration curves for glucose in the OBMS with different concentrations of standard blood samples. k/s: k, absorption coefficient; s, scattering coefficient of the membrane (C); in-vivo application of the OBMS in a rabbit ear artery, initiated by a one-touch finger press. The blood sample was collected into the sensor-chamber and then reached the sample pad. Subsequently, the serum was separated from the collected blood sample by using the asymmetrical polysulfone membrane (dashed-line 25 rectangle) and transferred into the reaction zones. After 5 min the final image showing the color change was obtained (D). Reproduced with permission from Ref. 41.

by double-sided polyvinylchloride tape prepared by punching 1 mm diameter circular holes using a flat-tip needle in a concentric shaft (Figure 3B). The in-vitro studies of this fabricated microneedle sensor showed a linear range of 0–270 mg dL$^{-1}$ for glucose level (Figure 3C). In-vivo studies showed, one touch finger activation and sampling of blood from a rabbit model via a nickel microneedle with 10 s lag time. The integrated paper-based sensor was successfully able to detect blood glucose levels using this automated approach within 3 min (Figure 3D).

Sato et al. fabricated an array of solid microneedles made from polycarbonate (PC), which contained 305 needles with length of 300 μm over an area of 50 mm$^2$. The research group has developed a new technology that extracts and accumulates ISF for monitoring postprandial hyperglycemia without blood sampling. This minimally invasive ISF extraction technology comprised two steps: (a) stamping of the microneedle array on the forearm skin as a pretreatment to form micropores for enhancing ISF extraction; (b) placing of a reservoir on the pretreated area of the skin, consisting of a hydrogel patch containing polyvinyl alcohol (PVA) with 2% KCl solvent to accumulate ISF for a specific time. The glucose area under the curve (AUC) was calculated as accumulated ISF glucose (IG), with concurrent calibration with sodium ions (Na$^+$) as an internal standard. A handheld spring-activated applicator was used to apply the microneedle array to the forearm skin at an application speed of 6 ms$^{-1}$, which resulted in a penetration depth of approximately 100 μm. No additional force was needed to extract ISF from the skin, except passive diffusion and osmotic pressure. The glucose AUC during the collection time-period (from 1 to 3 h with step of 1 h) was measured by analyzing glucose levels in the ISF accumulated in the reservoir. Na$^+$ ions were chosen as an internal standard for calibration, their concentrations in both ISF and blood being stable over time (i.e., not dependent on time) and comparable among different individuals. Hydrogels were immersed overnight in 5 mL of pure water to extract glucose and Na$^+$ ions. Glucose levels were obtained by mixing 0.1 mL of the sample solution with 0.1 mL of glucose analysis reagent (2.6 U of GOx, 0.023 U of mutarotase, 0.25 U of peroxidase, 0.49 U of ascorbic acid oxidase, 0.016 ml of amplex red dye), and measuring the fluorescence intensity of the Amplex Red dye after incubation for 60 min. Na$^+$ ion levels were analyzed using an ion chromatography system. Glucose concentration was confirmed by blood measurements obtained every...
15 min for 3 h with a commercial glucose meter used as control. A correlation between glucose and Na$^{+}$ ion levels was evaluated in 16 subjects (healthy volunteers), with stable blood glucose (BG) levels during fasting. A high correlation was found between glucose and Na$^{+}$ ion levels when BG levels were stable ($R = 0.87$), indicating that Na$^{+}$ ions were a good internal standard for calibration. Furthermore, BG and IG time courses were evaluated in three subjects to investigate whether IG variation was coupled with BG variation, before and after a meal. Finally, the accuracy of glucose AUC measurements in ISF extracted via microneedles was evaluated several hours after a meal in 30 healthy subjects. A Bland–Altman plot showed a mean bias of 0.8 mg h dL$^{-1}$ ($SD = 35.4$), with no correlation between the difference and BG-AUC. The mean coefficient of variation between simultaneous measurements was 4.6% and a strong correlation ($R = 0.92$) between IG-AUC and BG-AUC after a meal was observed, thus indicating that IG-AUC was a good substitute for BG-AUC and a potentially useful index for postprandial glycemic excursions.

Sakaguchi et al. described the usefulness of ISF extraction via microneedles for monitoring IG-AUC through the method described by Sato et al.,$^{43}$ by comparing data obtained from subjects with (37) and without (10) diabetes, using the oral glucose tolerance tests (OGTTs) being performed as a part of medical therapy.$^{44}$ Plasma glucose (PG) levels were measured every 30 min for 2 h by means of a commercial glucose meter and used to calculate PG-AUC as reference. IG-AUC strongly correlated with PG-AUC ($R = 0.93$) over a wide range (227–675 mg. h dL$^{-1}$), with correlation being independent of glucose tolerance classification. Further, the level of correlation between PG peak and predicted IG-AUC was also good ($R = 0.86$) and independent of the PG peak level. Interestingly, results from a patient questionnaire on pain caused by using either microneedles or commercial self-monitoring blood glucose systems, confirmed that the former were painless in 97% of subjects (against 45% for the latter). The described glucose AUC monitoring system using IG provided good estimates of reference for PG-AUC and maximum PG levels during OGTTs in subjects with and without diabetes. This system provides easy-to-use monitoring of glucose AUC, which is a good indicator of postprandial glucose.

Sharma et al. has reported a minimally invasive, continuous glucose sensor based on glucose dehydrogenase-direct electron transfer enzymatic system.$^{45}$ The microneedle arrays were fabricated by following the methods reported by Trzebiński et al.$^{46}$ The authors reported a closed loop system comprising a CGM sensor and an insulin pump interfaced via suitable control software for management of type 1 diabetes mellitus. The functionalization of working electrodes with glucose dehydrogenase was carried out by following the methods reported by Hanishi et al. and Yamashita et al.$^{47,48}$ The Direct electron transfer (DET) allows the operation of the electrochemical sensor at lower potentials to minimize the effect of interference from acetaminophen, ascorbic acid and uric acid. The design of the microprobe array electrodes is such that the arrays are partitioned into working, reference and background compensation electrodes to enable parallel measurements of glucose and the background currents, respectively.

**In-vitro Enzymatic Microneedle Glucose Sensors**

Due to the large number of individuals in the developed and developing countries who suffer from diabetes mellitus, home glucose sensors are among the most well studied point-of-care diagnostic sensors. As described above, this situation accounts for the fact that the majority of microneedle-based sensor studies are dedicated to glucose sensing. It is noteworthy that (a) commercial point-of-care systems for detection of glucose, using microneedle devices are not as well developed as needed and (b) there is little information in the scientific literatures about the in-vitro enzymatic microneedle glucose sensors. This section describes recent efforts to integrate transducers for detection of glucose with microneedle-based platforms.

One of the first works for in-vitro monitoring of glucose in blood using microneedles was conducted by Windmiller et al.,$^{49}$ who reported the fabrication and in-vitro testing of an integrated electrochemical biosensor for glucose monitoring making use of both solid and hollow (i.e., bicomponent architecture) microneedles (Figure 4). The biosensor was based on an array of Pt-coated solid microneedles, which acted as the working electrode. This was arranged into an array of hollow microneedles, which was used as a cover and yielded an array of multiple micro-cavities. Solid and hollow microneedles were fabricated according to a standard UV rapid prototyping technique.

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**Figure 4.** A bicomponent microneedle array glucose biosensor. SEM images of solid (A) and hollow (B) polymer microneedle arrays. In-vitro sensitivity of the microneedle-based glucose biosensor for increasing glucose concentrations (0–14 mM) (C). In vitro selectivity of the microneedle-based glucose biosensor in the presence of electroactive physiological interferents (AA, UA, CYS, and ACT) (D). Reproduced with permission from Ref. 49.
using E-shell 200 acrylate-based polymer as the constituent material. The solid needles were cone-shaped (base diameter of 390 ± 14 μm and height of 818 ± 35 μm), whereas the hollow needles were pyramid-shaped with a triangular base (edge length of 1174 ± 13 μm, height of 1366 ± 15 μm and bore diameter of 342 ± 5 μm) (Figures 4A and 4B). Both solid and hollow needles were prepared in 3 × 3 square arrays with spatial period of 2 mm. After fabrication, the surface of the solid microneedles was coated with a thin film (~12 nm) of Pt using pulsed laser deposition (PLD), in order to provide the device with a working electrode. The solid needles were eventually arranged within the borehole of the hollow needles under an optical microscope, thus obtaining a bicomponent microneedle array with solid needles protruding from hollow ones, surrounded by recess micro-cavities. These were later used for the effective entrapment of GOx enzyme into a poly (α-phenylenediamine) (PPD), a thin film deposited by subsequent electrochemical polymerization. The PPD-based enzyme entrapment ensured high selectivity and stability by minimizing the interference caused by common electroactive interference compounds generally present within body fluids. The chronoamperometric study of enzyme entrapment in the microneedle array showed a dynamic range of 0–14 mM, (R² = 0.996) in PBS, with a high sensitivity (0.353 μA mM⁻¹) and a low standard deviation (RSD = 6.44%, n = 3) (Figure 4C). The sensor showed a limit-of-detection (LOD) of 0.1 mM (signal-to-noise ratio, S/N = 3), over the entire range of tested concentrations. High selectivity was observed in the presence of common electroactive interferents, such as ascorbic acid (AA), uric acid (UA), cysteine (CYS), and acetaminophen (ACT) at physiological levels, which resulted in negligible deviations (in the range of 0.88%–2.21%) from the current response at 10 mM glucose (Figure 4D). Finally, stability studies of the GOx-functionalized microneedle array biosensor were carried out in a PBS solution containing 10 mM glucose over an 8h time-period and results showed a stable current response retaining 97% of the original response over the whole time-period.

Miller et al. reported packing carbon pastes into open wells on an insulated wire strip for the simultaneous multiplexed detection of glucose, lactate, and pH over a range of physiologically relevant concentrations. The microneedle arrays were fabricated using dynamic light micro-stereolithography system and the microarray design was made using commercially available computer-aided design software. Openings in the top insulation layer of the flexible flat cable were created by a CO2 laser ablation exposing the underlying conductors. A layer of single-sided polyester tape was laser ablated with well patterns that corresponded to the flexible flat cable openings. This structure was aligned and adhered to the flexible flat cable. Each hole was packed with carbon paste formulations that were tailored specifically for glucose detection in 0.1 M phosphate buffer. The chronoamperometric detection of glucose at −0.05 V vs. Ag/AgCl showed a dynamic range of 2 mM to 12 mM. The sensor relied on the catalytic reduction of enzymatically produced peroxide while minimizing the responses of common interfering electroactive interferents such as AA, UA and AP. The electrode showed a good selectivity toward glucose (4 mM) in presence of lactate (4 mM), supporting that the electrodes in the array are capable of performing analyte specific detection in a complex environment.

Trzebinski et al. demonstrated a microfluidic based platform to study the performance of 3D out-of-plane micro-spike array-based
enzyme overnight at 4°C. The sensor showed a dye-oxidative catalysis of glucose and subsequent electron transfer using an outlet as shown in Figure 5B. The sensor works on enzymatic interfering agents present in biological fluids. The 4-microspike array was fabricated and tested, namely type#1 chips with period \( p = 16 \) \( \mu \)m, external and internal diameter \( d_e = 9 \) \( \mu \)m and \( d_i = 7 \) \( \mu \)m, respectively, and type#2 chips with \( p = 10 \) \( \mu \)m, \( d_e = 6 \) \( \mu \)m, \( d_i = 4 \) \( \mu \)m. Both type#1 and type#2 chips were used to quantify the capability of such microneedles to draw fluids [i.e., deionized water (DIW), standard physiological solution (PSS), and synthetic ISF solution] and collect them into the integrated reservoir by only capillary action that is without the use of external pumps. In order to release microneedle-based biosensors, both type#1 and type#2 chips were coupled with an enzymatic glucose biosensor, which was placed into the reservoir integrated on the back-side of the needle chips. The biosensor electrodes were fabricated by mixing gold nanoparticles into the photoresist material from array platform was dissolved using acetone to expose the patterned with plain silver electrodes. A part of the photoresist material from array platform was dissolved using acetone to expose the metal layer, which was then connected to the silver electrode contact pads using silver epoxy resin (Figures 5A and 5C). A silver pattern was modified separately with 0.1 M FeCl\(_3\) as reported by Shim et al.,\(^{54}\) to act as both reference and counter electrodes. The micro-spikes were cleaned with 0.5 M H\(_2\)SO\(_4\) and metalized with gold using full bright cyanide free gold plating solution (10 g/L, pH 9.0) with a standard three electrode cell. The micro-spikes were functionalized with 0.4 M thiomalic acid (TMA) for 1 h at room temperature and subsequently activated the carboxyl group of TMA by incubating with EDC and NHS for 2 h. The enzyme GOx was immobilized on micro-spikes by immersing in 0.1 M PBS, 0.001% poly-l-lysine and 10 mg L\(^{-1}\) of GOx (from Aspergillus niger - lyophilized powder, \( \sim 200\) units/mg) enzyme overnight at 4°C. Finally, an epoxy-polyurethane (PU) with an electron transfer mediator tetra thiofulvalene (TTF) was coated on the micro-spikes to increase the linear range and resistance to interfering agents present in biological fluids. The 4 \( \times \) 4-microspike array was integrated with PDMS microfluidic chip, consisting of 2 inlets with meanders leading to hexagonal chamber that finally terminates into an outlet as shown in Figure 5B. The sensor works on enzymatic oxidative catalysis of glucose and subsequent electron transfer using TTF as a mediator to the gold electrode. The sensor showed a dynamic range of 2–25 mM (R\(^2\) = 0.976) (Figure 5D), response time of 15 ± 9 s and remained stable for a period over 48 h when stored at room temperature.

Strambini et al. reported a self-powered microneedle-based transdermal biosensor for pain free high-accuracy real time measurement of glycaemia in ISF.\(^{55}\) The research group described the self-powered extraction of ISF using tiny SiO\(_2\) hollow microneedles as well as their in-vitro use for glucose detection in ISF by combining the microneedle chip with an enzymatic glucose sensor. The microneedle chip consisted of a silicon dye integrating a two-dimensional array of hollow SiO\(_2\) (thickness of 1 \( \mu \)m) needles protruding from the front-side of the chip for about 100 \( \mu \)m. The needles were, in turn connected with a reservoir groove on the back side of the chip through a 200-\( \mu \)m-long internal channel. Two different types of microneedles arrays with different diameters and spatial periods were fabricated and tested, namely type#1 chips with period \( p = 16 \) \( \mu \)m, external and internal diameter \( d_e = 9 \) \( \mu \)m and \( d_i = 7 \) \( \mu \)m, respectively, and type#2 chips with \( p = 10 \) \( \mu \)m, \( d_e = 6 \) \( \mu \)m, \( d_i = 4 \) \( \mu \)m. Both type#1 and type#2 chips were used to quantify the capability of such microneedles to draw fluids [i.e., deionized water (DIW), standard physiological solution (PSS), and synthetic ISF solution] and collect them into the integrated reservoir by only capillary action that is without the use of external pumps. In order to release microneedle-based biosensors, both type#1 and type#2 chips were coupled with an enzymatic glucose biosensor, which was placed into the reservoir integrated on the back-side of the needle chips. The biosensor electrodes were fabricated by

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**Figure 6.** A three-electrode microneedle/CNT non-enzymatic glucose sensor. Deep reactive ion etching of silicon to form rectangular pillar array (A-i). Wet etching of the rectangular pillar Si array to make sharp Si needle array (A-ii). Iron deposition through a shadow mask and MWCNT growth followed by Pt nano-particles electroplating (A-iii) and Ag deposition through a shadow mask and formation of Ag/AgCl reference electrode (A-iv). SEM images of the 15 \( \times \) 15 Si pillar array after DRIE (B-i) and Si microneedle array after wet etch process (B-ii). A TEM image of the MWCNT grown on the microneedle array (C-i). A SEM image showing well dispersed 50–100 nm Pt nano-particles in the MWCNT forest grown near the tip of the non-planar Si microneedle array (C-ii). A SEM image showing well dispersed 50–100 nm Pt nano-particles in the MWCNT forest by electrode position (C-iii) and a SEM image of the well dispersed 260 ± 20 nm AgCl nanoparticles on the RE (C-iv). Chronoamperometry electrochemical response of the non-enzymatic microneedle glucose sensor as a function of glucose concentration in 0.01 M PBS solution at a +0.4 V potential vs. Ag/AgCl reference electrode (D-i) and the linear fitting of the response curve (D-ii). Reproduced with permission from Ref. 2.
a screen-printed process using a carbon-based polymeric ink to act as the working and counter electrodes as well as contact leads on the polyester foil. In addition, an insulating ink was used to cover the electrode surfaces and to define the electrode working area as well as to cover the unnecessary part of the contact leads. After fabrication, the electrodes were modified with a layer made of carboxymethylcellulose (CMC), the glucose-specific enzyme GOx and potassium ferricyanide (K$_3$[Fe(CN)$_6$]). Microneedle-based glucose biosensors (both type#1 and type#2) were characterized in vitro by chronoamperometry (+0.5 V vs. Pseudo-reference electrode), using synthetic ISF solution with glucose concentrations in the range 0–35 mM (0–630 mg dL$^{-1}$), which were collected by capillary-action through the needles. The sensor worked on second-generation (mediator based) glucose biosensor principles where, current recorded at the needles. The sensor worked on second-generation (mediator based) glucose biosensor principles where, current recorded at

**Figure 7.** A three-electrode and two-electrode microneedle based non-enzymatic Pt black/Nf glucose sensor. Photograph of the fabricated microneedle Au electrode with 4 mm scale bar and schematic representation of the fabricated microneedle electrode with Pt black catalytic layer for non-enzymatic glucose sensing (A). SEM images of Pt black-deposited Au microneedle (B-i & B-ii), and Nafion-coated Au/Pt black microneedle (B-iii & B-iv). Chronoamperometric response of the Au/Pt black/Nf microneedle electrode measured at +0.12 V (vs. Ag/AgCl electrode) during successive additions of glucose from 1–40 mM in three-electrode configuration (C-i) and 1–20 mM in two-electrode configuration (C-ii). Inset shows the linear fitting of the response curve with respect to the glucose concentration from 1–40 mM (C-i) and 1–20 mM (C-ii) in 0.1 M PBS (R$^2$ = 0.9945 and 0.9846) for three- and two-electrode systems, respectively. Chronoamperometric response of the Au/Pt black/Nf microneedle electrode in the three- (D-i) and two-electrode (D-ii) configurations in the presence of common interfering substances (AA: ascorbic acid, LA: lactic acid, UA: uric acid, DP: dopamine, and AP: acetaminophen) at +0.12 V in PBS (0.1 M, pH 7.4).

**Non-Enzymatic Microneedle Glucose Sensing**

Since enzyme-based electrochemical glucose sensors had the problem of instability (in terms of temperature, pH and humidity) due to the intrinsic nature of enzyme. Unlike the enzymatic glucose sensors, non-enzymatic sensors have several advantageous aspects such as stability, simple fabrication, reproducibility, low cost, and free from oxygen limitation. Many research groups have attempted to detect glucose on the basis of direct electrochemical oxidation of nanomaterials (e.g., Nano-porous Pt-nanoparticles, carbon nanotube, and Pt nanotube arrays). Several research efforts have been performed to develop implantable non-enzymatic glucose sensors for continuous glucose monitoring. One of the major problems at the implantable glucose sensors is the host response when the sensor is exposed to blood. Thus, CGM techniques are still at experimental stage because of their poor performance characteristics for biofluidic solutions. In most cases, the electrode surface of the non-enzymatic sensor can easily be fouled by protein adsorption followed by platelet activation, adhesion, and formation of thrombus, resulting in partial or complete malfunction of the sensor. Thus, much research has been performed to minimize surface fouling. In the enzymatic glucose sensors, packaging technology, which was used to coat the sensors with biologically inert materials, is being widely used to prevent fouling and increase their biocompatibility. For example, cellulose acetate, polyethylene glycol, polyvinyl chloride, polyurethane, and Nafion are being widely employed as biocompatible packaging materials.
Table I. The main analytical characteristics of enzymatic microneedle-based CGM for in-vivo/in-vitro biosensing applications.

| Microneedle Configuration | In-vivo/In-vitro | Dynamic range | Stability | Reference |
|---------------------------|------------------|---------------|-----------|-----------|
| Needle type: Hollow       | Enzymatic/In-vivo| 0–600 mg dL\(^{-1}\) | N.R       | 16        |
| Height: 200 \(\mu\)m     |                  |               |           |           |
| Needles type: Hollow–Silicon Array: 20 \(\times\) 20 | 80–120 mg dL\(^{-1}\) | N.R       | 34        |
| Height: 250–350 \(\mu\)m |                  |               |           |           |
| Spacing: 300 \(\mu\)m    |                  |               |           |           |
| Needle type: Solid-Stainless steel | 36–432 mg dL\(^{-1}\) | Stable up to 7 days | 35        |
| Length: 680 \(\mu\)m     |                  |               |           |           |
| Width: 250 \(\mu\)m      |                  |               |           |           |
| Needles type: Hollow      |                  | 25% response lost after 60 h of operation | 36        |
| Array: 3 \(\times\) 3    |                  |               |           |           |
| Edge length: 1250 \(\mu\)m |                  |               |           |           |
| Height: 1500 \(\mu\)m    | Enzymatic/In-vivo| 0–450 mg dL\(^{-1}\) | N.R       | 37        |
| Cylindrical bore: 425 \(\mu\)m |                  |               |           |           |
| Spacing: 2 \(\mu\)m      |                  |               |           |           |
| Needles type: Hollow      |                  |               |           |           |
| Array: 6 \(\times\) 6    | Enzymatic/In-vivo| 50–400 mg dL\(^{-1}\) | 20% lost after 7 days | 39        |
| Length: 300 \(\mu\)m     |                  |               |           |           |
| Lumen: 50 \(\mu\)m       |                  |               |           |           |
| Needles type: Hollow–Silicon Height: 325 \(\mu\)m & 350 \(\mu\)m | Enzymatic/In-vivo | 90–220 mg dL\(^{-1}\) | N.R       | 40        |
| Needles type: Solid-Glass |                  |               |           |           |
| Tip radius: 15–40 \(\mu\)m |                  |               |           |           |
| Cone angle: 20°–30°       |                  |               |           |           |
| Needles type: Solid       |                  |               |           |           |
| Length: 510 \(\mu\)m     | Enzymatic/In-vivo| 50–400 mg dL\(^{-1}\) | Stable for 6.5 h | 41        |
| Needles type: Solid–PDMS Array: 4 \(\times\) 4 | Enzymatic/In-vivo | 0–540 mg dL\(^{-1}\) | N.R       |           |
| Needles type: Hollow      |                  | 3% response lost after 8 h of operation | 49        |
| Height: 1800 \(\mu\)m    | Enzymatic/In-vivo| 0–270 mg dL\(^{-1}\) | N.R       |           |
| Inner diameter: 60 \(\mu\)m |                  |               |           |           |
| Outer diameter: 130 \(\mu\)m |                  |               |           |           |
| Bevel angle: 15°          |                  |               |           |           |
| Needles type: Solid needles Height: 818 \(\pm\) 35 \(\mu\)m | Enzymatic/In-vitro | 0–270 mg dL\(^{-1}\) | Stable for 48 h | 46        |
| Needles type: Hollow      |                  | 3% response lost after 8 h of operation | 49        |
| Height: 1174 \(\pm\) 13 \(\mu\)m |                  |               |           |           |
| Edge length: 1366 \(\pm\) 15 \(\mu\)m |                  |               |           |           |
| Bore diameter: 142 \(\pm\) 5 \(\mu\)m |                  |               |           |           |
| Array: 3 \(\times\) 3    | 36–216 mg dL\(^{-1}\) | N.R       | 51        |
| Spacing: 2 \(\mu\)m      |                  |               |           |           |
| Needle type: Hollow      |                  |               |           |           |
| Bore diameter: 750 \(\mu\)m | Enzymatic/In-vitro | 36–648 mg dL\(^{-1}\) | Stable for 48 h | 46        |
| Needles type: Hollow      |                  |               |           |           |
| Height: 400 \(\mu\)m     | 36–432 mg dL\(^{-1}\) | Stable for 48 h | N.R       |           |
| Array: 10 \(\times\) 10 |                  |               |           |           |

N.R: Not Reported.

### In-vivo Non-Enzymatic Microneedle Glucose Sensors

Lee et al. developed a new patch-shaped enzyme free amperometric biosensors using a micro-needle array with Pt black sensing electrode layer for painless CGM applications. The microneedles were patterned from 316-L grade stainless-steel by using jet of ferric chloride wet chemical etchant under the pressure of 2 kg f cm\(^{-2}\) for 60 s. The needles were then punched-out to bend them to 90° by using a jig, and a thin gold layer was electroplated on stainless-steel micro-needle substrate as a seed layer. The fabricated micro-needle was 650 \(\mu\)m high and 150 \(\mu\)m wide. The parylene was used to passivate gold layer and the microneedle tip area was dry etched to deposit Pt black layer. The Pt black layer was electroplated from solution comprising lead acetate, hydrochloric acid, and platinic acid and dip coated with nafion and ethanol mixture. The final manufactured microneedle array consisted of a Pt black working electrode and an Ag/AgCl reference/counter electrode, which were formed by an electroplating technique. The electrochemical measurements were carried out in a 0.1 M PBS (20 mL volume) solution under continuous stirring, at a potential of 400 mV vs Ag/AgCl. The sensor showed a sensitivity of 1.62 \(\mu\)A mM\(^{-1}\), with high linearity of 0.9939, and a response time of 13 s, in glucose concentrations ranging up to 36 mM. The biosensor also exhibited a low detection limit of 50 \(\mu\)M. The selectivity test was done by consecutive addition of glucose solution, AA, and AP, and the sensor exhibited a minor response to the interferents. The
sensor showed a good storage stability for 6 days in PBS buffer. For in-vivo test, the sensor was coated with nafion membrane to prevent protein fouling and the Pt black sensing electrode was formed on the 150 µm long microneedle tip. The sensor was partially inserted into a guinea pig, rat and rabbit, and the glucose solutions were orally administered, and then monitored for the interstitial glucose levels in subcutaneous tissues electrochemically for every 5 minutes. The correlation between glucose levels in ISF and blood were monitored in subcutaneous tissues electrochemically for every 5 minutes. The correlation between glucose levels in ISF and blood were monitored in subcutaneous tissues electrochemically for every 5 minutes. The correlation between glucose levels in ISF and blood were monitored in subcutaneous tissues electrochemically for every 5 minutes. The correlation between glucose levels in ISF and blood were monitored in subcutaneous tissues electrochemically for every 5 minutes.

In-vitro Non-Enzymatic Microneedle Glucose Sensors

Yoon et al. fabricated a microneedle-based three-electrode integrated non-enzymatic sensor and its in-vitro characterization for glucose detection (Figure 6). A 15 × 15 array of sharp silicon microneedles (height of 380 µm and tip dimension smaller than 1 µm) was produced through anisotropic dry etching of patterned silicon chips, which was used to fabricate an array of silicon pillars (Figure 6A). This was followed by isotropic face-up/face-down wet etching of the silicon micropillars, which was used to obtain an array of sharp silicon microneedles (Figure 6B). A 500-µm-thick silicon dioxide (SiO2) layer was then conformally deposited on the needle surface via plasma enhanced chemical vapor deposition (PECVD). On the surface of SiO2; in a selected area of the array, a 5-µm-thick iron catalyst was deposited via electron beam evaporation (through a shadow mask) to create the working electrode (WE) and counter electrode (CE). A vertically aligned forest of 135-µm-tall multiwalled carbon nanotubes (MWCNTs) was directly grown on the iron-coated silicon microneedle array, so as to increase the electroactive surface area of the electrodes (Figure 6C). The vertically aligned MWCNT forest was collapsed by immersing the sample in ethanol for minimizing any potential loss of the MWCNT bundles from the sharp Si microneedle-based electrode surface. Finally, Pt nanoparticles (diameters in the range of 50–100 nm) were electrodeposited on the electrode surface using Hexachloroplatinic acid bath, so as to enhance non-enzymatic electrochemical glucose sensing. To create a RE, a 100-nm-thick Ti layer and a subsequent 300-nm-thick silver layer were sequentially coated on the tip of Au-deposited microneedles and used as the sensing electrode, Pt coil counter electrode, and Ag/AgCl reference electrode in three-electrode configuration. The Pt black-deposited microneedle and Ag/AgCl ink-coated microneedle were used as working and counter/reference electrodes, respectively in the case of the two-electrode configuration. SEM images of the fabricated microneedle electrode deposited with and without Pt black are recorded (Figure 7B). From the micrographs, it was observed that the features of the microneedles closely corresponded with those specified by the design, and that the microneedle-to-microneedle uniformity was excellent. The attractive performance of the Au/Pt black/NF microneedle electrode was illustrated for the low-potential (+0.12 V) detection of glucose. The sensor showed a linearly increase in response with increase in glucose concentration and reached saturation at 40 mM (720.7 mg dL−1) of glucose for the three-electrode configuration and 20 mM (360 mg dL−1) for the two-electrode configuration. The electrode showed a measurement sensitivity of 175 ± 0.84 µA mM−1 or 205.57 ± 48.65 µA mM−1 (average and standard deviation: SD, n = 3) in the wide dynamic ranges of 1–40 mM and 4–20 mM for the three- and two-electrode configurations, respectively. The response time of the sensor was 2 s and limits of detection (DL) for glucose were 0.023 ± 0.002 mM and 0.006 ± 0.001 mM for the three- and two-electrode configurations, respectively (Figure 7C). The microneedle sensor exhibited a good selectivity in the presence of various common interferents (Conc. Of the interferents was 10-fold higher than the physiologically relevant levels) in blood and showed a negligible effect on the glucose response (Figure 7D).

Conclusions

From the past two decades, an increased research effort has been focused toward the use of microneedles for sensing of a number of analytes of clinical interest, majorly engaged in glucose (bio)sensing. This new trend has germinated naturally from former efforts of the use of microneedles for drug administration, perfectly compli-
the same. The challenge is the development of pain-free and easy-to-use miniaturized sensors for point-of-care analysis, either in vivo (peripheral blood and interstitial fluid) or in vitro. The main goal is to develop microneedle-based glucose sensing that will be commercialized and ready for markets in a few years. Non-enzymatic microneedle-based glucose sensing technology is currently undergoing in-vivo validation on animals, and it is likely that in vivo experiments on human subjects will be carried out in the next years. There is great potential for scientists in the next few years to develop microneedle-based sensors for other analytes and their in-vivo/on-vitro validation.

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