

3D-Printed Hollow Microneedle Potentiometric Sensors: A Modular Approach

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Cite This: *ACS Sens.* 2026, 11, 6191–6202



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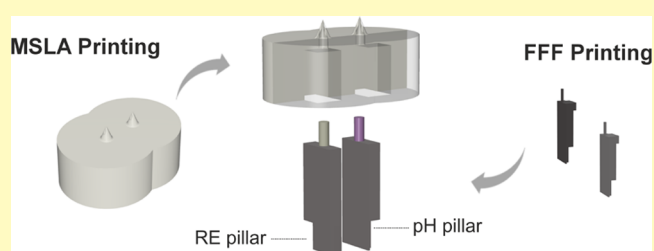
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ABSTRACT: Microneedle sensors represent a genuine approach to continuous health monitoring with minimally invasive access to skin interstitial fluid. However, their clinical deployment is hindered by complex fabrication and functionalization processes that compromise reproducibility and scalability. Truly, recent advancements in additive manufacturing have diminished certain obstacles; yet, single-modality techniques continue to encounter a significant trade-off between attaining high resolution and including electrochemical functionality. Accordingly, we introduce herein a novel modular hollow microneedle (HMN) architecture that separates insertion mechanics from ion sensing functionality. This new strategy synergistically integrates two complementary 3D printing modalities: high-resolution masked stereolithography (MSLA) to produce a robust, HMN shell, and fused filament fabrication (FFF) to fabricate a conductive pillar electrode to be modified with the ion-sensing role. The modularity of the sensor allows the pillar electrode to be functionalized prior to seamless assembly, protecting the sensing layer and ensuring robust and consistent potentiometric performance while addressing former drawbacks of the involved fabrication method: MSLA offers high-resolution hollow structures but is deficient in conductivity, whereas FFF facilitates conductive printing but suffers from restricted resolution. As a proof of concept, we have developed a potentiometric pH-HMN sensor that demonstrates excellent analytical performance, including a near-Nernstian response of -55.35 ± 0.54 mV/pH, high repeatability (RSD = 0.61%), reproducibility (RSD = 1.16%), and stability (0.37 mV/h) during *in vitro* testing. A complete sensing architecture comprising a single 3D-printed patch with two HMN to house both the pH sensing pillar electrode and a reference pillar electrode has demonstrated high accuracy in *ex vivo* tests using rat skin samples, showing a mean absolute difference of less than 0.05 pH units compared to a commercial pH electrode. The developed modular platform streamlines manufacturing, enabling the rapid, low-cost, and scalable production of reliable microneedle sensors, paving the way for their widespread use to other ions and analytes as well as future testing in live subjects.

KEYWORDS: wearable sensors, additive manufacturing, solid contact, electrochemical sensor, sensor customization



INTRODUCTION

The advancement of wearable sensors that detect biomarkers in interstitial fluid (ISF) is revolutionizing personalized healthcare. Thus, microneedle (MN) sensors have evolved as a prominent technology due to their capacity to access ISF in a minimally invasive way, with ISF serving as a reservoir of biomarkers that reflect the composition of blood plasma.¹ Engineered to be 150 to 1500 μm in length, these devices painlessly penetrate the skin's outer layers to provide a blood-free method for continuous analysis,² maximizing patient comfort and compliance in clinical and wearable health applications.³ Importantly, the utility of this approach extends beyond healthcare, finding applications in areas such as sports monitoring and smart agriculture, where MN sensors are being adapted as “plant wearables”.^{4,5} Nonetheless, the fabrication of MNs that simultaneously possess (i) the high resolution required for reliable skin penetration

and (ii) the integrated sensing properties needed for accurate monitoring, remains a significant manufacturing challenge.

To date, MN fabrication has mainly relied on techniques adapted from microelectronics and medical device manufacturing.⁶ While precise, these methods present significant limitations. On one hand, for solid MNs, polymer-based methods like micro-injection molding and hot embossing are cost-effective for mass production but suffer from low design flexibility. Any design modification requires fabricating an expensive,

Received: March 26, 2026

Revised: June 2, 2026

Accepted: June 3, 2026

Published: June 30, 2026



new master mold, which fundamentally obstructs rapid prototyping. Similarly, silicon-based approaches involve complex cleanroom processes and brittle materials,^{6,7} while metal fabrication is often slow and wasteful.^{8,9} On the other hand, the fabrication of hollow MNs faces similar hurdles, where traditional methods, such as computer numerical control micromachining and drawing lithography, are limited by slow processing speeds and inability to create complex internal geometries.^{10–14} The described drawbacks illustrate the importance of more versatile and efficient fabrication technologies and strategies. As a result, additive manufacturing (3D printing) has emerged as a transformative solution,¹⁵ offering unparalleled geometric freedom and rapid prototyping without the high costs of mold-based manufacturing.

Although 3D printing excels at producing MN architectures, fabricating that physical structure constitutes only half the challenge towards a MN-based sensor. Thus, converting the printed inert structure into a functional electrochemical sensor introduces a critical bottleneck where most current designs, including monolithic 3D-printed approaches, still fail. This bottleneck is particularly evident in potentiometry, where 3D-printed microneedle sensors remain scarce due to the fundamental challenge of establishing a reliable, compatible conductive transducer on inert printed polymers. To overcome this inertness, whether for specific potentiometric designs or more broadly across electrochemical applications, the most common fabrication strategy involves modifying the external surface of solid MNs by sputtering a conductive layer followed by coating the active sensing layer (e.g., electrodeposited polyaniline).^{16,17} However, this multi-step approach compromises the reproducibility and leaves the delicate sensing layer vulnerable to mechanical delamination during skin insertion. To protect the sensing element, alternative strategies have employed hollow MNs (HMNs) for ISF extraction connected to an external flat sensor.¹⁸ Despite this physically shields the sensor, it fails to achieve true real-time monitoring of dynamic physiological fluctuations. Other proposals includes the direct functionalization of the inner lumen of a HMN with conductive paste and other sensing materials, offering hence a solution for continuous and dynamic monitoring at the cost of fabrication complexity and the risk of sensing layer detaching.^{19,20} While some recent approaches have attempted to integrate separate, pre-modified metal micro-electrodes into the HMN lumen, these approaches require additional fixation and sealing steps.²¹ Such manual assembly processes are ill-suited for automation and present a major barrier to large-scale, reproducible manufacturing.

We herein propose a novel modular design comprising a 3D printing strategy that decouples the sensing element from the HMN structure. Thus, the approach synergistically combines two distinct 3D printing modalities. First, a HMN shell serving as the mechanical support and skin interface is fabricated using MSLA printing with high-resolution (lateral resolution of ca. 50 μm), aiming at providing the required sharpness for the microneedle. Second, the active ion-sensing component is incorporated into a conductive pillar electrode that is printed via FFF, with a conductive carbon black-poly(lactic acid) (CB-PLA) composite as the substrate. This modularity allows the ion-selective electrode to be easily prepared and assembled into the protective HMN shell, eliminating complex manual functionalization steps. Using pH as a model analyte, we further integrate both the working and reference electrodes needed for potentiometric measurements in a single 3D printed patch comprising two HMNs structures. The fabrication of the reference

electrode also follows the modular approach. The resulting sensor patch demonstrates robust analytical performance and furthermore *ex vivo* validation revealed high accuracy and reliability in conditioned rat skin samples. Overall, the developed manufacturing pathway enables the rapid, low-cost, and scalable production of reliable and reproducible microneedle ion sensors, a critical step toward advancing diagnostics and personalized health management.

■ EXPERIMENTAL SECTION

Fabrication of the pH Hollow Microneedle (pH HMN) Patch

The patch to detect pH consisted of a 3D-printed structure with two HMN housings to accommodate two pillar electrodes: a pH indicator electrode (or working electrode, WE) and reference electrode (RE). Figure 1 summarizes the entire fabrication process. The HMN housings (Figure 1a) and corresponding pillars (Figure 1b) were designed in Autodesk Fusion 360. The HMN housings and the patch holder were printed by vat photopolymerization on a Prusa SL1S using Clear Micro-fluidics Resin V7.0a, with a 25 μm layer height. Base layers were exposed for 25 s, and subsequent layers for 3.5 s, followed by isopropanol washing in a Prusa CW1S and post-curing in a Professional CureZone for 3 min at default power. These printing and post-processing conditions were adapted from our previous work.²² Conductive pillars were printed by fused filament fabrication (FFF) on an Original Prusa XL, with a 0.25 mm nozzle and using conductive PLA filament, with 0.10 mm layer height, 210 $^{\circ}\text{C}$ nozzle temperature, and 60 $^{\circ}\text{C}$ bed temperature.

To fabricate the pH-sensing pillar, 5 layers (2 μL for each layer) of H^{+} selective membrane (HSM) cocktail was coated on the surface of the tip part of the pillar and let the solvent dry completely before applying the next layer. The prepared pH pillar electrodes were conditioned in 1 mM HCl solution overnight before use. The RE pillar was prepared by firstly coating a thin layer of commercially available Ag/AgCl paste and drying in the oven at 60 $^{\circ}\text{C}$ for 1 hour. Afterward, 5 layers (2 μL for each layer) of reference membrane (RM) was coated on the surface of the pillar Ag/AgCl electrode. The obtained RE pillar was conditioned in 3 M KCl for over two days before use. The modification processes are illustrated in Figure 1c. The detailed compositions for the HSM and RM are provided in the Supporting Information.

■ RESULTS AND DISCUSSION

This work implements a wearable skin patch for potentiometric pH detection based on a modular HMN approach following this workflow: (i) separate optimization and printing of the HMN shell by high-resolution MSLA and the conductive CB-PLA pillar by FFF; (ii) modular assembly of the patch accompanied by *in vitro* potentiometric benchmarking to demonstrate stable, reproducible, and reversible responses; and (iii) *ex vivo* validation on conditioned rat skin to confirm calibration transfer and transdermal operation, supporting the strategy's scalability and applicability to other electrochemical sensors.

Optimization of the Design for HMNs and Pillar Electrodes

The final dimensions of the HMN (Figure 1a) and the pillar electrode (Figure 1b) resulted from a balance between the technical constraints imposed by the 3D printing resolution and the functional requirements of a microneedle device for intradermal measurements. The designed HMN has a tip length of 1.2 mm, tip angle of 45.3 $^{\circ}$ and base diameter of 1 mm, with fillet radius of 0.2 mm. These dimensions were selected to provide sufficient space for the subsequent internal pillar electrode assembly

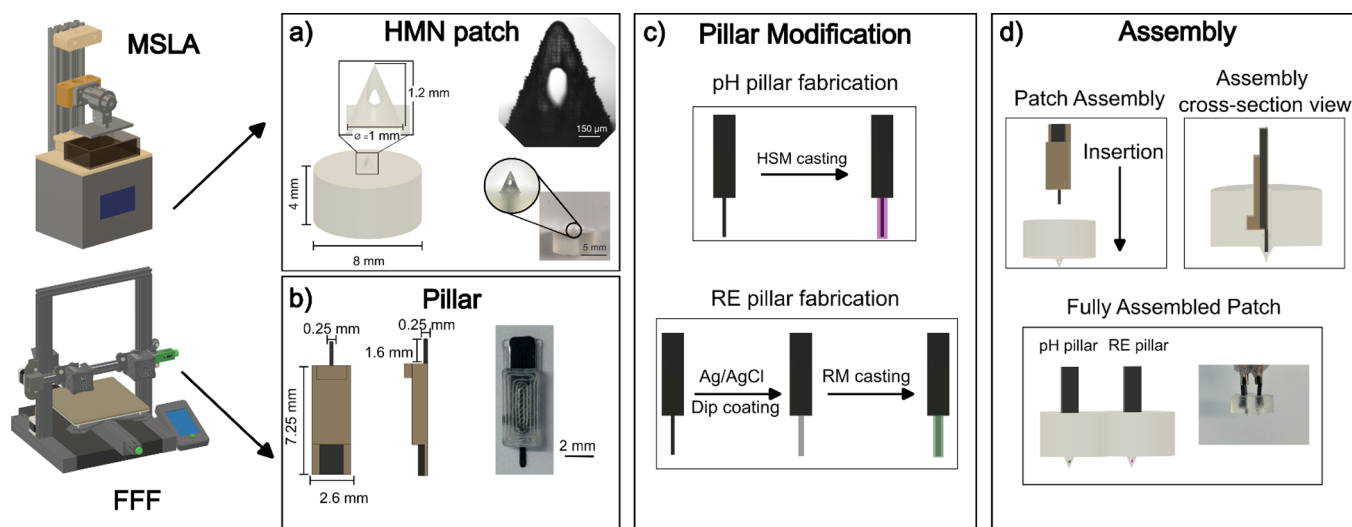


Figure 1. Fabrication workflow and design specifications of the pH HMN patch. The manufacturing process combines Masked Stereolithography (MSLA) 3D printing for the resin patch structure and fused filament fabrication (FFF) for the conductive carbon-black PLA (CB-PLA) pillars. (a) MSLA printed HMN patch. (b) FFF printed pillars. (c) Functionalization of the electrodes: the pillar is modified with the H^+ selective membrane (HSM) or it undergoes Ag/AgCl dip-coating followed by reference membrane (RM) casting for the indicator (WE) and reference electrode (RE), respectively. (d) Cross-sectional internal structure and fully assembling of single (only pH MN) and dual-pillar (pH and RE MNs) sensor patch.

(Figure 1d), while ensuring reliable insertion into the skin (reaching the ISF, $>500\ \mu\text{m}$ in depth), sufficient mechanical robustness, and minimizing insertion pain. As confirmed by microscopic and macroscopic imaging (Figure 1a,d and Figure S1), the printed HMN has a tip diameter $<30\ \mu\text{m}$, tip angle of ca. 46° , tip curvature radius of $46\ \mu\text{m}$, length of $997\ \mu\text{m}$ and base diameter of $1100\ \mu\text{m}$, dimensions within the requirements to ensure a smooth skin penetration and patient comfort.²³

The mechanical properties of the printed HMN were evaluated by compression testing using an Instron mechanical tester. As shown in Figure S2, the force-displacement curve demonstrated the HMN's response under axial load. The measured fracture force was $1.26 \pm 0.07\ \text{N}$, which is higher than the force generally required to penetrate the stratum corneum ($0.08\text{--}0.88\ \text{N}$).²³ This indicates that the HMNs possess sufficient mechanical strength for skin insertion without risk of fracture. The stiffness of the HMN, calculated from the force-displacement curve, was $17.95 \pm 0.33\ \text{kN/m}$, confirming the robust mechanical performance necessary for reliable and effective skin penetration.

As the sensing element is embedded inside the microneedle, two lateral holes ($200\ \mu\text{m}$ in diameter) and an internal chamber were introduced in the HMN design to allow solution access and increase the effective exposure area of the pillar electrode, thereby facilitating diffusion toward its surface (Figure 1a and Figure S3). Moreover, to optimize pillar electrode insertion, three different chamber designs were evaluated. Designs and dimensions are shown in Figure S3 and Table S1. Thus, three chamber geometries were compared for smooth pillar insertion without damaging either the electrodes or the HMN as well as for efficient solution diffusion to the pillar, which was assessed by cyclic voltammetry (CV) experiments in ferrocene methanol solution (Figure S4). The third design (see Figure S3) satisfied both criteria and was therefore selected for subsequent experiments.

The pillar electrode comprises a conductive CB-PLA core and insulating PLA sleeve (Figure 1b). The tip is a rectangular cuboid ($0.40\text{--}0.25\text{-mm}$ width and length, $1.6\ \text{mm}$ height).

Owing to FFF layer-thickness limits, the $0.25\ \text{mm}$ variant was printed entirely in conductive CB-PLA. After fixing the HMN housing in the third chamber design, we optimized the pillar (see Table S2 for the design and printing parameters) to fit the internal chamber efficiently. Pillar design #1, printed with the standard resolution, seated mechanically but showed poor electrolyte access in the assembled HMN, as indicated by the CV in $1\ \text{mM}$ ferrocene methanol with $0.1\ \text{M}$ KCl (Figure S4c). Reducing the size of the printed pillar tip (design #2) enabled smooth insertion and produced well-defined redox peaks (Figure S4d), with no visible damage to either part. Accordingly, this design was selected for subsequent experiments. Specifically, the pillar electrode has a width of $318 \pm 26\ \mu\text{m}$ (Figure S1c), that is 27% larger than the designed dimension ($250\ \mu\text{m}$), due to the extrusion and expanding of filament on the printing bed during the FFF process. Advantageously, this deviation is common and was considered in the overall design of the HMN, with the inner cylindrical chamber providing enough space to accommodate it. Figure S1d–f shows real and microscopic images of HMNs assembled with modified pillar electrodes, namely, pillar pH electrode and the pillar RE.

Evaluation of Structural Features and Analytical Performance of the pH Pillar

The composition of the unmodified pillars was characterized by X-ray diffraction (XRD), while scanning electron microscopy (SEM) was used to examine the surface morphology of both the unmodified pillars and the pH pillars. These studies are important because the FFF printing process and subsequent handling can affect the microstructure and surface properties of the conductive CB-PLA composite, which may in turn influence electrode performance.²⁴

The phase composition of the pillar electrodes was investigated by XRD, with the resulting pattern presented in Figure S5. The diffractogram displayed a broad amorphous halo centered at approximately $2\theta = 16.4^\circ$, which is characteristic of

the amorphous nature of the PLA matrix. A subtle shoulder is also visible at $2\theta \approx 21^\circ$, which is a known feature of PLA's amorphous structure. The presence of carbon black (CB) was confirmed by a distinct, albeit low-intensity, diffraction peak at $2\theta \approx 43^\circ$. This peak corresponds to the (100) crystallographic plane of the graphitic structure within the CB. The most intense diffraction peak for CB, i.e., the (002) plane typically expected to appear between $2\theta = 24\text{--}26^\circ$,²⁵ was not clearly resolved. This could be because this peak is obscured by the broad, overlapping amorphous halo from the PLA matrix.²⁶ This overlap indicates that the CB is well-dispersed within the polymer matrix even after the printing process, which can benefit the electron transfer in the CB-PLA composite transducer and thus contribute to the good electrochemical performance of the fabricated sensors. Furthermore, the good dispersion of CB in PLA was confirmed by SEM images, as discussed in the following section.

The morphology of the pillar electrode was investigated using SEM and the results are shown in Figure S6. The images revealed a rough surface composed of CB granules embedded within the PLA matrix. This roughness provides a high effective surface area, which should increase the interfacial double-layer capacitance and thus promotes a stable, low-noise potential response.²⁷ Furthermore, it is known that the THF solvent used in the membrane cocktail partially dissolves the PLA matrix.²⁸ This effect, combined with the inherent roughness, is expected to enhance the physical adhesion between the transducer and the ion-selective membrane. Notably, an improved contact is desired to minimize the formation of an aqueous layer at the transducer-membrane interface, ultimately helping achieve adequate long-term operational stability of the electrode.

The surface of the modified pH pillar exhibited elliptical porous structures (Figure S7), characterized by a width of

$1.07 \pm 0.11 \mu\text{m}$ and a length of $1.94 \pm 0.33 \mu\text{m}$ for the pore. This morphology is a direct result of the porous polyurethane (PU) utilized in the H^+ selective membrane. While these pores increase the surface area and provide abundant accessible sites for the ion-exchange equilibrium, the primary advantage of selecting a PU matrix over classical PVC for this wearable sensor lies in its superior structural and mechanical adaptability. Furthermore, PU exhibits excellent adhesion to the substrate, alongside established bio- and hemocompatibility, which are critical parameters for epidermal and in vivo applications.²⁹

The thickness of the ion-selective membrane was systematically optimized to balance kinetic response and sensor reproducibility. Bare pillar electrodes were coated with 1, 3, 5, and 7 layers of the H^+ selective membrane cocktail. As shown in Figure S8, while thinner membranes (1 and 3 layers) yielded poor inter-electrode reproducibility, increasing the thickness to 7 layers resulted in a sluggish average response time ($22.3 \pm 6.4 \text{ s}$) and physical dimensional constraints during final assembly. The 5-layer configuration was identified as the optimal balance, demonstrating excellent inter-electrode reproducibility with tightly clustered potentiometric traces and a rapid response time ($15.1 \pm 2.3 \text{ s}$). By comparing the dimensions of the unmodified and 5-layer coated pillar electrodes from the obtained SEM images, the final thickness of this optimal H^+ selective membrane was estimated to be $121.66 \pm 5.48 \mu\text{m}$.

Because PU possesses protonatable urethane groups that can theoretically induce pH cross-sensitivity, a control experiment was performed to isolate the background influence of the polymer matrix. An ionophore-free membrane (formulated with identical mass ratios of the PU matrix, plasticizer, and cation exchanger) was evaluated alongside the H^+ selective membrane. As depicted in Figure 2a, the ionophore-free PU matrix displayed a negligible potentiometric response across the relevant

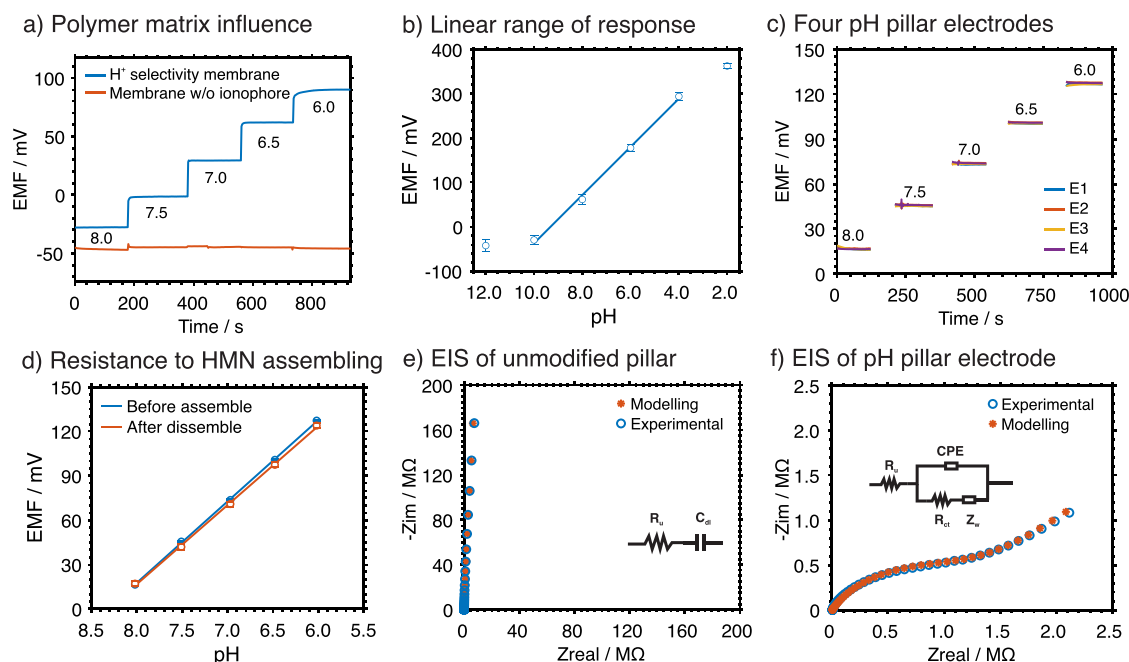


Figure 2. (a) Evaluation of polymer matrix influence. Potentiometric dynamic response of the H^+ selective membrane compared to an ionophore-free control. (b) Potentiometric calibration curve of the pH pillar electrodes from pH 12 to 2. (c) Dynamic response of four pH pillars (E1–E4) towards different pHs. (d) Calibrations obtained with the four pH pillars before assembling and after disassembling into/from 3D printed hollow microneedles. (e) Nyquist plot from EIS for the unmodified pillar electrode. (f) Nyquist plot from EIS for the pH pillar electrode. EIS spectra were recorded in 0.1 M NaCl at the respective open-circuit potential (OCP), over a frequency range of 10 kHz to 0.1 Hz and using a 10-mV sinusoidal amplitude.

physiological pH range (8.0 to 6.0), in contrast to the ideal Nernstian stepping of the H^+ selective membrane. This confirms that the intrinsic basicity of the PU matrix does not introduce cross-sensitivity or interfere with the primary pH response of the sensor.

To evaluate the operational limits of the pH pillar electrode, potentiometric calibrations were extended across a wide range from pH 2 to 12 (Figure 2b). The pH pillars demonstrated a highly linear ($R^2 = 0.9971$), near-Nernstian response of -54.36 ± 0.44 mV/pH between pH 4 and 10. Outside of this optimal window, potentiometric response deviations were observed. At highly acidic levels (pH < 4), the sub-Nernstian response is attributed to co-ion interference compromising membrane permselectivity. Conversely, at highly alkaline limits (pH > 10), the deviation occurs because the primary ion concentration approaches the detection limit, leaving the phase-boundary potential susceptible to interference from background cations. Because the intended application targets physiological monitoring, the practical testing range was set to pH 6 to 8 for all subsequent experiments.

Within the targeted physiological window, the analytical performance of the pH pillar was evaluated by calibrating four individual pillars. As shown in Figure 2c, the four electrodes exhibited a near-Nernstian response with a slope of -55.05 ± 0.13 mV/pH. High reproducibility was demonstrated, with relative standard deviations (RSDs) of 0.25% for the slope and 0.30% for the calibration intercept considering the average calibration graph of the four electrodes. To assess the robustness of the design, the pillars were calibrated before being assembled into the HMN and after disassembly from the HMNs. Advantageously, the calibration parameters showed a relative deviation of less than 3% (Figure 2d), confirming that the assembly process does not compromise electrode performance at all.

Also, the correct functioning of the conductive CB-PLA composite as the solid-contact transducer was investigated. Electrochemical impedance spectroscopic (EIS) experiments were performed on unmodified and modified pillar electrodes to study the capacitance, charge transfer kinetics, and ion diffusion, which govern the stability and response of the electrode. EIS of unmodified pillar electrodes revealed highly capacitive behavior (Figure 2e). The Nyquist plot showed a characteristic near-90° capacitive line extending to low frequencies, which signifies efficient charge transfer at the CB-PLA/solution interface. Furthermore, the impedance data was modeled using the equivalent circuit shown in the inset of Figure 2e. From this fit, the solution resistance (R_u) was determined to be 1.54 ± 0.07 k Ω , and the double-layer capacitance (C_{dl}) was 9.60 ± 0.18 nF. The area-specific capacitance was calculated to be 185 nF/cm² (see Table S3 with all the fitting parameters). As shown in our previous work, the low capacitance values seemed sufficient for a good-enough ion-to-electron transduction and acceptable potential drift for the target application.³⁰

The impedance response of the pillar electrode modified with the H^+ selective membrane is shown in Figure 2f. The Nyquist plot features a depressed semicircle at high frequencies (10 kHz to 50 Hz) followed by a distinct 45° Warburg tail at lower frequencies (50 Hz to 0.1 Hz). This shape is characteristic of a porous electrode where reaction kinetics is limited by diffusion.³¹ The EIS spectrum was fitted to the equivalent circuit model shown as an inset in Figure 2f. It consisted of a solution resistance (R_u) in series with a parallel combination of two

branches: a constant phase element (CPE) and a branch containing the charge transfer resistance (R_{ct}) in series with a Warburg element (Z_w). The CPE represents the non-ideal capacitance due to the surface roughness of CB-PLA previously confirmed by SEM (Figure S6), while Z_w accounts for diffusion through the membrane. The fitting results (Table S4) yielded values of $R_u = 3.70 \pm 0.27$ k Ω and $R_{ct} = 1.20 \pm 0.15$ M Ω .

The interfacial capacitance calculated from the CPE was 1.48 ± 1.0 nF, with the high relative standard deviation (~68%). This variance is attributed to the physical inhomogeneity of the electrode surface, which does not act as an ideal capacitor but rather presents a distribution of local time constants.³² This non-ideal behavior is quantified by the CPE exponent value (n), which ranged from 0.60 to 0.72. As an n value of 1 represents an ideal capacitor, these low values confirm a significant deviation and a wide distribution of time constants arising from the surface roughness of the electrode, consistent with SEM observations. The prominent Warburg tail observed at low frequencies indicates that a diffusion-controlled process significantly affects the electrode response³² and, given the porous PU membrane structure, this is most plausibly associated with ion diffusion within the membrane.

Investigation of the Analytical Performance of the pH HMN

The pH HMN sensor's performance was assessed based on several key metrics: repeatability, reproducibility, reversibility, stability, accuracy, and operational lifetime. The corresponding experiments were conducted in a two-electrode configuration, utilizing the pH HMN as the indicator electrode and a commercially available double-junction Ag/AgCl electrode as the reference electrode. All the calibrations were performed in 0.1 M phosphate buffer solutions of varying pH values.

As illustrated in Figure 3a for a representative dynamic trace, the pH HMNs exhibited a rapid and stable potentiometric response to step changes in pH, achieving an average response time (t_{95}) of 4.7 s. The average sensitivity of three pH HMNs was -55.35 ± 0.54 mV/pH, a value close to the theoretical Nernstian slope for monovalent ions. The pH HMN showed a highly linear response (R^2 of 0.9992) within the pH range from 6.0 to 8.0, which covers both physiological and pathological relevant conditions.² Then, the repeatability of the pH HMNs was assessed through three consecutive calibration cycles performed on a single pH HMN. The resulting slope and intercept (Figure 3b) were -55.96 ± 0.34 mV/pH and 448.42 ± 3.54 mV, respectively. The low RSDs for both parameters (0.61% and 0.79%, respectively) confirm the high precision of the developed pH HMN in repeated measurements.

Reproducibility of the pH HMN was assessed by calibrating six equally fabricated pH HMNs (Figure 3c). Notably, intra-batch performance was evaluated using three pillar pH electrodes fabricated within the same batch, while inter-batch reproducibility was assessed using three electrodes prepared in two separate batches, referring to the printing beds for pillars. To ensure consistency, all pillar electrodes were assembled with HMNs from a single production batch. The average slope and intercept for all six pH HMNs were -55.57 ± 0.64 mV/pH and 446.76 ± 5.48 mV, corresponding to RSDs of 1.16% and 1.28%. The intra-batch RSDs for the slope and intercept were 0.98% and 1.08%, while the inter-batch values were similarly low (1.20% and 1.23%). These results demonstrate that the fabrication method yields highly reproducible sensors, ensuring consistent performance both within and across batches.

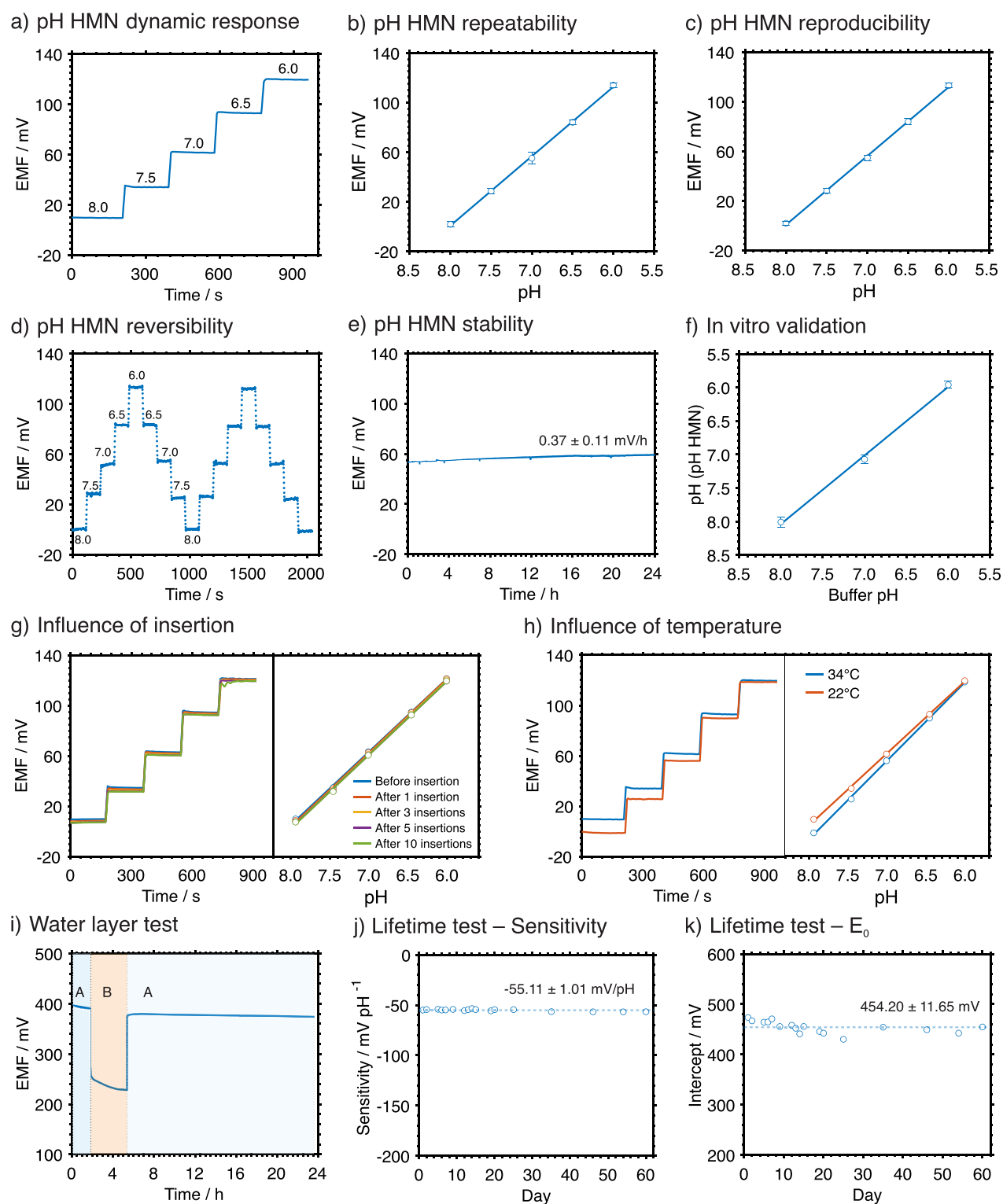


Figure 3. Evaluation of the analytical performance of the pH HMN. (a) Dynamic response of the pH HMN towards pH changes. (b) Average calibration graph from the repeatability study ($n = 3$). (c) Reproducibility study of pH HMNs ($n = 6$). (d) Dynamic response from the reversibility test by increasing the solution pH following the sequence of 8.0, 7.5, 7.0, 6.5, 6.0. and backwards for four times. (e) Long term stability test at pH 7.5 for 24 hours. (f) In vitro validation of the accuracy of the pH HMN using commercial pH standard buffers. (g) Potentiometric dynamic response and corresponding calibration curves of the pH HMN evaluated before and after repeated insertions into *ex vivo* rat skin sample. (h) Effect of physiological temperature on the potentiometric response of the pH HMN, comparing calibration curves obtained at 22 °C and 34 °C. (i) Water layer test for pH HMN by separate solution approach, A: 1 mM HCl, B: 0.1 M NaCl. (j) Lifetime test for the pH HMN ($n = 3$) in terms of sensitivity. (k) Lifetime test for the pH HMN ($n = 3$) in terms of intercept.

The reversibility was evaluated by sequentially immersing the pH HMN in buffer solutions following the order of pH 8.0 $\rightarrow$ 7.5 $\rightarrow$ 7.0 $\rightarrow$ 6.5 $\rightarrow$ 6.0, and then the reverse direction. This process was repeated for two cycles. As shown in Figure 3d, the potentiometric response exhibited minimal hysteresis between the forward and backward pH sweeps. The stability of the reading at each pH point was excellent regardless of the response cycle, with the standard deviation of the potential being typically within 1 mV and never exceeding 1.7 mV. To further quantify this, calibration curves were generated for the forward and backward cycles, yielding highly consistent slopes and intercepts with RSDs of 1.85% and 1.63%, respectively. This high degree of reversibility confirms the reliability of the developed pH HMN for accurately monitoring dynamic environments with fluctuating pH.

The operational stability of the pH HMN was evaluated to assess its suitability for continuous, long-term monitoring. First, the potentiometric response was monitored under physiological conditions, pH 7.5, for 24 hours. The profile is provided in Figure 3e. The pH HMN demonstrated excellent stability, with a minimal potential drift of only 0.37 ± 0.11 mV/h ($n = 3$). Such a drift will translate into a pH variance of ca. 0.006 pH units/h, which is rather adequate for clinical usage minimizing inherent errors of the developed technology. Importantly, the highly stable potential response during long-term measurements can likely be attributed to adequate interfacial capacitance, and good interfacial adhesion between the CB-PLA and the H^+ selective membrane, as above discussed. To further confirm appropriate robustness across its working range, the stability was tested at both low (pH 6.0) and high (pH 8.0) pH conditions for ca. 2.5-hour periods (see Figure S9). In both scenarios, the pH HMN maintained a highly stable response, with potential drift remaining below 0.9 mV/h.

Given the complex ionic composition of the target biological matrix, the selectivity of the pH HMN against common physiological interfering ions was systematically evaluated. The selectivity coefficients were determined using the separate solution method.³³ As detailed in Table S5, the pH HMNs exhibited high selectivity for H^+ , yielding average logarithmic selectivity coefficients ($n = 3$) of -5.87 ± 0.08 , -5.49 ± 0.09 , -5.67 ± 0.14 , and -10.71 ± 0.44 for K^+ , Na^+ , Ca^{2+} , and Mg^{2+} , respectively.

The accuracy of the fabricated pH HMN was *in vitro* validated using commercial pH standard buffer solutions (pH 6.00, 7.00, and 8.00, with an uncertainty of ± 0.01 pH unit) that were analyzed with three pH HMNs. Following a primary calibration, each pH HMN was immersed in the respective standard buffer, and the EMF was recorded over several minutes (as illustrated in Figure S10). The corresponding pH values were then determined using the previously established calibration curve. The results, summarized in Table S6, demonstrated the high reproducibility of the pH HMNs, with the standard deviation for all measurements remaining lower than 0.08 pH units. Furthermore, the accuracy of the sensors was revealed as excellent, as observed in an average absolute difference of less than 0.06 pH units when compared the MN-based measurements to the certified values of the standard buffers. A correlation plot of the measured pH vs the standard buffer pH is presented in Figure 3f, generating a Pearson's correlation coefficient of 0.9968.

To further evaluate the operational stability of the pH HMN following direct and repeated exposure to the complex tissue matrix, calibrations were performed before and after sequential

ex vivo skin insertions. As depicted in Figure 3g, the pH HMN exhibited negligible deviation in its analytical performance after 1, 3, 5, and up to 10 consecutive tissue penetrations. The sensor maintained a highly consistent near-Nernstian slope of -56.78 ± 0.39 mV/pH alongside a stable standard potential (470 ± 1.72 mV) across all testing cycles. This robust retention of calibration parameters confirms that the protective HMN shell and the internal pillar electrode successfully preserve their functional integrity upon exposure to the biological matrix and are not mechanically compromised by repeated tissue penetrations.

Given that the intended application scenario for the proposed HMN is epidermal monitoring, the effect of physiological skin temperature on the potentiometric response was evaluated. Calibrations of pH HMN were performed at both a controlled room temperature (22 °C) and an average skin temperature (34 °C). As illustrated in Figure 3h, elevating the temperature to 34 °C induced the change in the analytical performance of pH HMN, increasing the sensitivity from -57.43 mV/pH to -62.54 mV/pH, alongside a shift in the standard potential. To ensure high analytical accuracy during continuous *in vivo* or on-body measurements, the application of temperature-matched calibration profiles or dynamic thermal compensation is recommended.

Furthermore, to verify the stability of the solid-contact interface, a water layer test was conducted (Figure 3i). Initially, the electrode potential stabilized rapidly in a 1 mM HCl solution. Upon transfer to an unbuffered 0.1 M NaCl background solution, the potential exhibited a sharp negative shift due to the drastic decrease in primary H^+ activity. A minor, gradual downward potential drift observed within this NaCl phase is attributed to the transient equilibration of the outer phase boundary, as trace H^+ slowly diffuses from the previously saturated membrane surface into the H^+ deficient bulk solution. Crucially, when the electrode was reintroduced into the primary 1 mM HCl solution, the potential exhibited a rapid, precise recovery to its original baseline without the slow, continuous upward drift characteristic of a trapped aqueous layer. This swift and stable return confirms the absence of a detrimental water layer at the inner CB-PLA/membrane interface, validating the composite as a reliable solid-state transducer.

To assess the operational lifetime of the pH HMN, periodic calibrations were conducted over a 60-day period after its fabrication. The calibrations were performed frequently during the initial month (every 2–3 days) and approximately every five days thereafter. Throughout this extended testing duration, the pH HMN demonstrated remarkable stability. The sensitivity remained highly consistent at -55.11 ± 1.01 mV/pH (Figure 3j). Similarly, the standard potential (E^0), or intercept, was stable at 454.20 ± 11.65 mV (Figure 3k). The corresponding RSDs for the sensitivity and intercept were calculated to be 1.84% and 2.57%. These low values signify minimal signal drift over two months. This exceptional lifetime is likely attributed to the strong adhesion of the sensing membrane onto the CB-PLA pillar³⁰ but also, the innovative design of the sensing HMN, protecting the membrane core without any analytical limitation. Besides, it suggests the negligible leaching of membrane components and absence of deterioration of the solid-contact transducer under the specified testing and storage conditions.^{34,35} The long lifetime, coupled with the previously demonstrated 24-h stability, will enable long-term, uninterrupted monitoring, reducing the need for frequent sensor replacements in real context measurements.

To contextualize these results, the analytical performance and integration strategy of the proposed modular pH HMN were compared against recent state-of-the-art microneedle pH sensors (Table S7). While exhibiting highly competitive analytical metrics, the primary advantage of the modular microneedle sensor architecture lies in overcoming the fabrication bottlenecks, such as manual paste-filling and fragile surface coatings, common in existing approaches.

Evaluation of the Performance of the RE Pillar and Corresponding RE HMN

Following the modification of the pillar electrodes, the morphology and elemental composition of both the Ag/AgCl-modified pillar and the subsequent RM-coated Ag/AgCl pillar were investigated using SEM and EDX. As depicted in Figure S11, the characterization of the Ag/AgCl coated pillar electrode reveals a composite structure where AgCl particles are homogeneously embedded within the silver sheets matrix. This intimate distribution is crucial for the electrochemical stability of the electrode. The thickness of the Ag/AgCl layer was estimated to be approximately $87.84 \pm 4.93 \mu\text{m}$. Figure S12 presents the morphological and elemental analysis of the final pillar RE, where the Ag/AgCl layer is coated with the PVB membrane. The SEM images clearly showed that the PVB membrane possesses a smoother and more compact surface morphology compared to the porous PU surface of the pH pillar (Figure S7). The thickness of the PVB layer was estimated to be

approximately $45.15 \pm 2.88 \mu\text{m}$. With a width of $583.63 \pm 5.75 \mu\text{m}$, the pillar RE is narrower than the inner diameter of the HMN, which facilitates its insertion without causing any damage. EDX analysis confirmed the presence of crystalline NaCl particles embedded within the PVB matrix. These NaCl particles were introduced during the preparation of the RM cocktail, which functions as a Cl^- reservoir to maintain a saturated concentration and thus generating a stable Ag/AgCl redox potential over extended operational periods.³⁶

The analytical performance of the RE HMN was systematically evaluated, focusing on its operational stability and response to common potential interferents. Thus, key aspects, including the influence of Cl^- , light, pH, and solution redox potential, were assessed. The long-term stability was assessed by the continuously monitoring of the EMF in a pH 7.5 buffer for over 24 hours, using a double junction Ag/AgCl electrode as the reference electrode in the experiment. As observed in Figure 4a, the electrode demonstrated adequate stability, exhibiting a negligible potential drift of only $0.22 \pm 0.07 \text{ mV/h}$ ($n = 3$). For context in pH sensing, this corresponds to a measurement variation of just 0.0027 pH units/hour.

Beyond temporal baseline stability, the reliability of the RE HMN in varying sample matrices was evaluated by testing its response to fluctuating external Cl^- concentrations. While a large external concentration gradient could theoretically promote internal NaCl leaching, the PVB polymer matrix acts as a kinetic diffusion barrier. To demonstrate this, the RE HMN

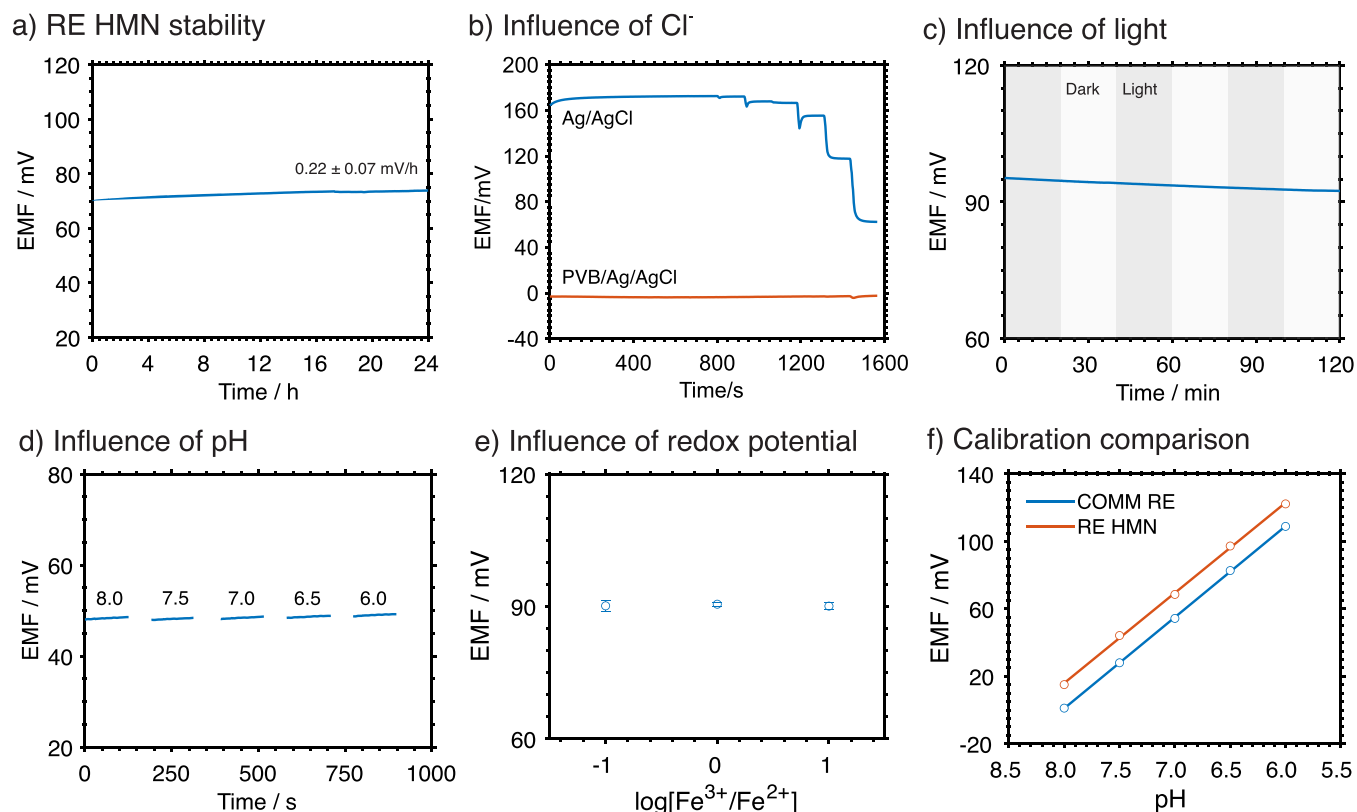


Figure 4. Evaluation of the performance of the RE HMN. (a) Long-term stability at pH 7.5 over 24 hours. (b) Dynamic potentiometric responses of the PVB/Ag/AgCl RE HMN and the Ag/AgCl HMN towards increasing concentrations (10^{-7} , 10^{-6} , 10^{-5} , 10^{-4} , 10^{-3} , 10^{-2} , and 10^{-1} M) of KCl. (c) Sensitivity to light over 2-hour test. (d) Influence of solution pH change on the dynamic response. (e) Influence of solution redox potential on the response. (f) Comparison of the calibrations of the pH HMN against a commercial Ag/AgCl reference electrode (COMM RE) and RE HMN as the reference electrode.

was exposed to step-wise changes in external Cl^- concentration ranging from 10^{-7} M to 10^{-1} M. As shown in Figure 4b, while a bare Ag/AgCl control exhibited severe potential shifts in response to the changing chloride levels, the PVB/Ag/AgCl RE HMN maintained a highly stable response with a maximum deviation of only 1.91 mV. This confirms the ability of the RE HMN to provide a robust, sample-independent potential.

Furthermore, the RE HMN performance under illumination and dark conditions was investigated. The electrode was subjected to repeated 40-minute light/dark cycles using a 5W LED lamp over a 22-hour period. The entire response is shown in Figure S13, with an expanded view of the first 2 hours being provided in Figure 4c. As observed, no significant potential fluctuations correlated with the light/dark cycles were observed. Although a baseline drift of 0.57 mV/h was noted during this extended measurement, the lack of correlation with illumination suggests this is attributable to the intrinsic long-term drift of the electrode rather than a direct photoelectric effect.

The influence of pH on the electrode's potential was studied by immersing the RE HMN in a series of buffer solutions with varying pH values. As presented in Figure 4d, the EMF remained remarkably constant across the tested pH range (6.0–8.0). The standard deviation of the potential across all buffers was 0.33 mV, corresponding to an RSD of 0.67%. This demonstrates that the RE HMN potential is independent of the sample solution pH. Also, the resilience to changes in solution redox potential was evaluated. The RE HMN was immersed in solutions containing different concentration ratios of the $\text{Fe}^{3+}/\text{Fe}^{2+}$ redox couple. The results in Figure 4e revealed nearly identical potential responses regardless of the solution, with a standard deviation of 0.23 mV (RSD = 0.26%), pointed out that the RE HMN is not susceptible to interference from redox-active species in the sample.³⁶

Finally, the comparison of calibrations of the pH HMN using either a commercial double-junction Ag/AgCl reference electrode or the RE HMN was conducted (Figure 4f). The two calibration curves exhibited nearly identical sensitivity, with a relative deviation of only 1.04%. However, the calibration intercept obtained with the RE HMN shifted upward by approximately 14 mV, variation that is commonly observed in custom-made reference electrode.^{37,38} In essence, the shift can be attributed to the distinct composition and structure of the RE HMN compared to the commercial option, introducing additional phase boundary potentials at the various interfaces:³⁶ the PVB membrane and the sample solution interface, the PVB membrane and the CB-PLA transducer layer interface, and the contact potential between the CB-PLA pillar and the Ag/AgCl ink. Importantly, this intercept shift does not compromise the practical application of the pH HMN and RE HMN system. In real-world use, the pH HMN is calibrated and used in conjunction with the RE HMN, ensuring that any offset is accounted for in the calibration. If the RE HMN demonstrates sufficient stability, the analytical performance of the pH HMN can be reliably maintained.

Evaluation of the Analytical Performance of the pH HMN Patch Containing the RE HMN

A key technological outcome in this work is the fabrication of an integrated microneedle patch using MSLA 3D printing to house the WE and RE pillars, as illustrated in Figure 5a,b. An inter-needle distance of 3 mm was selected to ensure the effective establishment of the potentiometric cell while minimizing

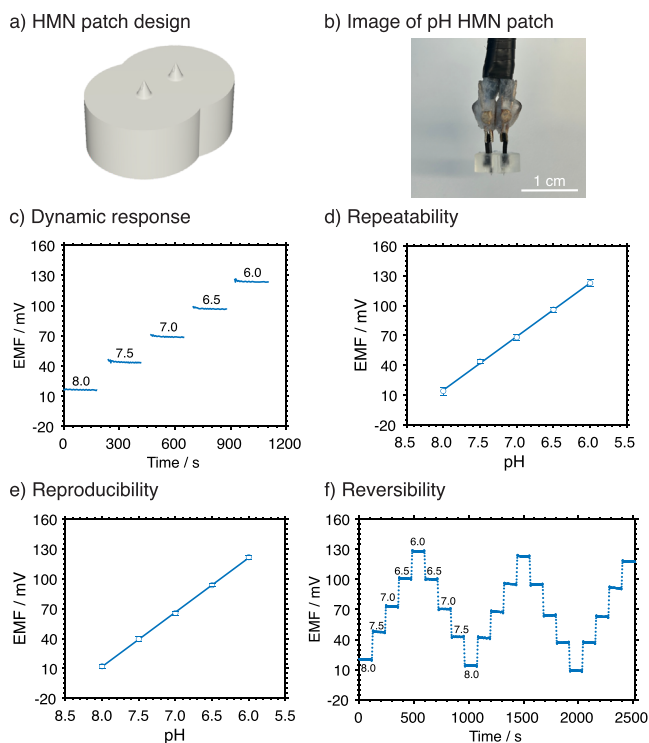


Figure 5. The entire pH HMN patch: illustration and evaluation of the analytical performance. (a) Design of the HMN patch. (b) Real picture of the pH HMN patch connected to the reader circuit. (c) Potentiometric dynamic response of the pH HMN patch towards pH changes in the sample solution. (d) Repeatability study ($n = 3$). (e) Reproducibility study ($n = 4$). (f) Reversibility test.

size and providing enough space for the electrical connections. Moreover, this compact arrangement creates a smaller sensing loop that improves noise rejection, thereby resulting in a highly stable potential difference and a more reliable sensor reading.³⁹ Furthermore, this facilitates skin penetration with minimal epidermal deformation.⁴⁰ Advantageously, the architecture of the patch is inherently adaptable due to the flexibility provided by the 3D printing, allowing for straightforward expansion into multi-electrode arrays for the simultaneous detection of a panel of key physiological analytes. Although multi-analyte detection was not investigated in this work, it represents a clear future direction for the herein developed modular approach.

As realized in the representative calibration plot depicted in Figure 5c, the pH HMN patch exhibited a linear and stable potentiometric response across the tested pH range. The slope of the calibration curve was -53.32 mV/pH, a near-Nernstian sensitivity. The repeatability of a single pH HMN patch was assessed through three consecutive calibrations. The patch showed appropriate response, yielding a highly consistent sensitivity of -53.86 ± 0.39 mV/pH and an intercept of 445.94 ± 4.11 mV (Figure 5d). The corresponding RSDs for the slope (0.72%) and intercept (0.92%) were rather low, confirming minimal signal change during repeated use. To evaluate reproducibility, four independently (but equally) fabricated patches were calibrated. The results (Figure 5e) revealed remarkable inter-patch consistency: The average sensitivity was -54.65 ± 0.58 mV/pH (RSD = 1.06%), and the average intercept was 449.08 ± 3.78 mV (RSD = 0.84%). Significantly low RSDs

across different devices underscore the reliability of the fabrication process. Finally, the reversibility was tested by subjecting a patch to dynamic, alternating changes between different pH buffer solutions. The sensor responded promptly and returned to a stable potential at each pH level (Figure 5f), with the calibration data (Figure S14) showing acceptable RSDs for the slope (3.06%) and intercept (2.66%). Overall, the results pointed out that the pH HMN patch can reliably track both increasing and decreasing pH changes.

To validate the analytical accuracy of the pH HMN patch in a physiologically relevant matrix, *ex vivo* pH measurements were performed on conditioned rat skin samples. Skin pieces were individually conditioned for 48 hours in buffer solutions of varying pH values (6.50, 7.00, 7.50, and 8.00) to ensure thorough proton diffusion and establish a stable pH within the tissue. Prior to testing with the pH HMN patch, the pH inside each conditioned skin sample was determined using a commercial Biotrode miniaturized pH electrode, providing a benchmark for accuracy determination. In parallel, each pH HMN patch was individually calibrated to establish the calibration parameters (i.e., sensitivity and intercept). Each calibrated patch was inserted into a skin sample (real picture in Figure S15a) for detection of intradermal pH. Importantly, a visual inspection (Figure S15b) was performed to confirm the proper insertion of the pH HMN patch into the rat skin sample. To ensure precise and objective measurements, the potentiometric signal was recorded continuously for 5 minutes to allow the phase boundary to fully equilibrate within the complex biological matrix. The final stable response was quantitatively defined as the average EMF recorded over the final 10 seconds of this measurement window. This averaged signal was then utilized to calculate the skin's pH via the corresponding calibration, as illustrated in Figure 6a. To validate mechanical robustness and measurement consistency, this measurement cycle was repeated in triplicate (three consecutive insertions) for each patch, utilizing three distinct patches per skin sample.

The *ex vivo* skin sample measurement results are summarized in Table 1, demonstrating excellent agreement between the HMN patches and the commercial reference electrode (0.01 pH unit resolution). As noted, the standard deviation across consecutive insertion cycles using the same patch remained consistently below 0.09 pH units, highlighting the high precision and mechanical reliability of the modular design. Crucially, the mean absolute difference between the HMN

Table 1. Results from Different Rat Skin Samples Analyzed with the Commercial pH Electrode (Labeled as Skin pH in the Table) and Various pH HMN Patches^a

Skin pH	Patch #1	Patch #2	Patch #3	Avg $\pm$ SD	Diff. %
7.52 $\pm$ 0.01	7.50 $\pm$ 0.04	7.49 $\pm$ 0.03	7.43 $\pm$ 0.07	7.47 $\pm$ 0.03	0.05
7.01 $\pm$ 0.01	7.05 $\pm$ 0.02	6.96 $\pm$ 0.09	7.01 $\pm$ 0.02	7.00 $\pm$ 0.05	0.01
6.52 $\pm$ 0.01	6.58 $\pm$ 0.03	6.60 $\pm$ 0.07	6.56 $\pm$ 0.04	6.58 $\pm$ 0.02	0.06
6.09 $\pm$ 0.01	6.13 $\pm$ 0.06	6.13 $\pm$ 0.07	6.14 $\pm$ 0.06	6.13 $\pm$ 0.00	0.04

^aAvg $\pm$ SD corresponds to the average for each skin pH considering replicates ($n = 3$ consecutive insertion cycles) performed with each patch. Diff. % refers to the difference between the skin pH and the average pH measured for each skin sample.

arrays and the commercial sensor was less than 0.05 pH units, yielding a maximum relative error of only 0.8%. This strong agreement was statistically confirmed in the correlation plot (Figure 6b), obtaining a Pearson's coefficient of 0.9980 and a coefficient of determination (R^2) of 0.9961. Furthermore, the regression slope of 0.9283 and intercept of 0.4996 are close to the ideal values of 1 and 0, respectively, confirming the high degree of accuracy. Overall, these results show that the pH HMN patch is highly accurate for reliable *ex vivo* pH measurements.

CONCLUSIONS

We have developed a modular hollow microneedle (HMN)-based platform that effectively decouples the electrochemical sensing functionality from the mechanical skin penetration requirement of microneedle sensors dedicated to transdermal measurements. By combining high-resolution MSLA printing for the structural HMN shell with FFF printing for the conductive CB-PLA pillar electrode, we overcome the trade-offs inherent in single-modality 3D printing. As a proof-of-concept, the resulting pH HMN demonstrated exceptional analytical performance, including a near-Nernstian sensitivity, high reproducibility, and long-term stability. The automation inherent in this process minimizes manual sensor modifications, thereby enhancing reproducibility and ensuring high consistency across sensor batches. Furthermore, *ex vivo* validation using rat skin samples confirmed the sensor's clinical potential, achieving high accuracy compared to commercial electrodes. This modular

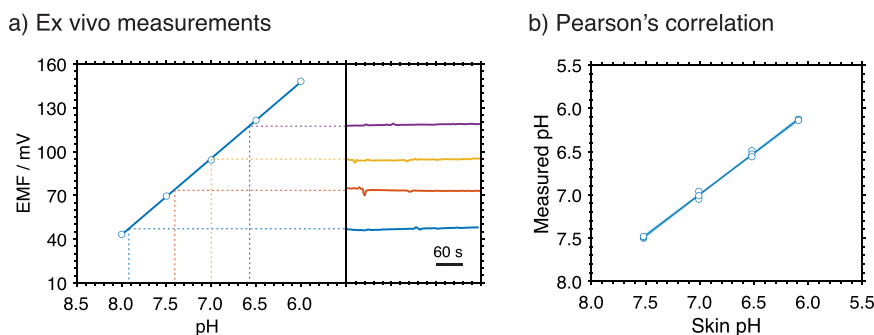


Figure 6. *Ex vivo* validation of the pH HMN patch using conditioned rat skin samples. (a) Calibration of the pH HMN patch and the responses observed in four samples. (b) Pearson's correlation plot of the skin pH measured with the commercial pH electrode and the herein developed pH HMN patch.

strategy not only streamlines the fabrication of reliable potentiometric sensors but also provides a scalable and customizable framework for the multiplexed detection of various ions and analytes in personalized health monitoring. Accordingly, we will demonstrate the utility for on body measurements in a near future, considering statistically significant number of tests and validated observations.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssensors.6c01291>.

Experimental details; EIS fitting results; Hollow micro-needle designs; Mechanical test; Microscopic images; X-ray diffraction spectrum; SEM images and EDX element mapping (PDF)

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<https://pubs.acs.org/doi/10.1021/acssensors.6c01291>

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the financial support from the Grant PID2022-140418NA-I00 funded by MICIU/AEI/ 10.13039/501100011033 and by ERDF/EU. M.C. acknowledges the

support of the Swedish Research Council (Project Grant VR-2023-04808).

■ REFERENCES

- (1) Friedel, M.; Thompson, I. A. P.; Kasting, G.; Polsky, R.; Cunningham, D.; Soh, H. T.; Heikenfeld, J. Opportunities and Challenges in the Diagnostic Utility of Dermal Interstitial Fluid. *Nat. Biomed. Eng.* **2023**, 7 (12), 1541–1555.
- (2) García-Guzmán, J. J.; Pérez-Ráfols, C.; Cuartero, M.; Crespo, G. A. Microneedle Based Electrochemical (Bio)Sensing: Towards Decentralized and Continuous Health Status Monitoring. *TrAC, Trends Anal. Chem.* **2021**, 135, No. 116148.
- (3) Kim, G.; Ahn, H.; Chaj Ulloa, J.; Gao, W. Microneedle Sensors for Dermal Interstitial Fluid Analysis. *Med-X* **2024**, 2 (1), No. 15.
- (4) Wang, Q.; Molinero-Fernández, Á.; Acosta-Motos, J.-R.; Crespo, G. A.; Cuartero, M. Unveiling Potassium and Sodium Ion Dynamics in Living Plants with an In-Planta Potentiometric Microneedle Sensor. *ACS Sens.* **2024**, 9 (10), 5214–5223.
- (5) Wang, Q.; Molinero-Fernández, Á.; Acosta Motos, J. R.; Crespo, G. A.; Cuartero, M. Microneedle Sensors for Ion Monitoring in Plants. One Step Closer to Smart Agriculture. *ACS Sens.* **2025**, 10 (7), 4771–4784.
- (6) Rad, Z. F.; Prewett, P. D.; Davies, G. J. An Overview of Microneedle Applications, Materials, and Fabrication Methods. *Beilstein J. Nanotechnol.* **2021**, 12 (1), 1034–1046.
- (7) Deng, Y.; Chen, J.; Zhao, Y.; Yan, X.; Zhang, L.; Choy, K.; Hu, J.; Sant, H. J.; Gale, B. K.; Tang, T. Transdermal Delivery of siRNA through Microneedle Array. *Sci. Rep.* **2016**, 6 (1), No. 21422.
- (8) Yan, X.-X.; Tang, G.; Hu, R.; Yang, B.; Zhang, L.-L.; Xu, B. Analysis of Process Parameters and Performance Test for Fabricating Stainless-Steel Metal Microneedles. *Sens. Mater.* **2018**, 30 (6), 1333–1340.
- (9) Liu, F.; Lin, Z.; Jin, Q.; Wu, Q.; Yang, C.; Chen, H.-J.; Cao, Z.; Lin, D.; Zhou, L.; Hang, T.; He, G.; Xu, Y.; Xia, W.; Tao, J.; Xie, X. Protection of Nanostructures-Integrated Microneedle Biosensor Using Dissolvable Polymer Coating. *ACS Appl. Mater. Interfaces* **2019**, 11 (5), 4809–4819.
- (10) Sun, H.; Zheng, Y.; Shi, G.; Haick, H.; Zhang, M. Wearable Clinic: From Microneedle-Based Sensors to Next-Generation Healthcare Platforms. *Small* **2023**, 19 (51), No. 2207539.
- (11) Martanto, W.; Moore, J. S.; Kashlan, O.; Kamath, R.; Wang, P. M.; O'Neal, J. M.; Prausnitz, M. R. Microinfusion Using Hollow Microneedles. *Pharm. Res.* **2006**, 23 (1), 104–113.
- (12) Lee, D.-S.; Li, C. G.; Ihm, C.; Jung, H. A Three-Dimensional and Bevel-Angled Ultrahigh Aspect Ratio Microneedle for Minimally Invasive and Painless Blood Sampling. *Sens. Actuators, B* **2018**, 255, 384–390.
- (13) Vinayakumar, K. B.; Kulkarni, P. G.; Nayak, M. M.; Dinesh, N. S.; Hegde, G. M.; Ramachandra, S. G.; Rajanna, K. A Hollow Stainless Steel Microneedle Array to Deliver Insulin to a Diabetic Rat. *J. Micromech. Microeng.* **2016**, 26 (6), No. 065013.
- (14) Thanh, H. L.; Ta, B. Q.; The, H. L.; Nguyen, V.; Wang, K.; Karlsen, F. Low-Cost Fabrication of Hollow Microneedle Arrays Using CNC Machining and UV Lithography. *J. Microelectromech. Syst.* **2015**, 24 (5), 1583–1593.
- (15) Economidou, S. N.; Douroumis, D. 3D Printing as a Transformative Tool for Microneedle Systems: Recent Advances, Manufacturing Considerations and Market Potential. *Adv. Drug Deliv. Rev.* **2021**, 173, 60–69.
- (16) Hu, Y.; Chatzilakou, E.; Pan, Z.; Traverso, G.; Yetisen, A. K. Microneedle Sensors for Point-of-Care Diagnostics. *Adv. Sci.* **2024**, 11 (12), No. 2306560.
- (17) Parrilla, M.; Steijlen, A.; Kerremans, R.; Jacobs, J.; den Haan, L.; De Vreeze, J.; Van Noten Géron, Y.; Clerx, P.; Watts, R.; De Wael, K. Wearable Platform Based on 3D-Printed Solid Microneedle Potentiometric pH Sensor for Plant Monitoring. *Chem. Eng. J.* **2024**, 500, No. 157254.

- (18) Parrilla, M.; Detamornrat, U.; Domínguez-Robles, J.; Donnelly, R. F.; De Wael, K. Wearable Hollow Microneedle Sensing Patches for the Transdermal Electrochemical Monitoring of Glucose. *Talanta* **2022**, 249, No. 123695.
- (19) Teymourian, H.; Moonla, C.; Tehrani, F.; Vargas, E.; Aghavali, R.; Barfidokht, A.; Tangkuaram, T.; Mercier, P. P.; Dassau, E.; Wang, J. Microneedle-Based Detection of Ketone Bodies along with Glucose and Lactate: Toward Real-Time Continuous Interstitial Fluid Monitoring of Diabetic Ketosis and Ketoacidosis. *Anal. Chem.* **2020**, 92 (2), 2291–2300.
- (20) Parrilla, M.; Vanhooydonck, A.; Johns, M.; Watts, R.; De Wael, K. 3D-Printed Microneedle-Based Potentiometric Sensor for pH Monitoring in Skin Interstitial Fluid. *Sens. Actuators, B* **2023**, 378, No. 133159.
- (21) Chen, H.; Zhou, S.; Chen, J.; Zhou, J.; Fan, K.; Pan, Y.; Ping, J. An Integrated Plant Glucose Monitoring System Based on Microneedle-Enabled Electrochemical Sensor. *Biosens. Bioelectron.* **2024**, 248, No. 115964.
- (22) Wei, Q.; Rojas, D.; Wang, Q.; Zapata-Pérez, R.; Xuan, X.; Molinero-Fernández, Á.; Crespo, G. A.; Cuartero, M. Wearable 3D-Printed Microneedle Sensor for Intradermal Temperature Monitoring. *ACS Sens.* **2025**, 10 (6), 4027–4037.
- (23) Ebrahiminejad, V.; Prewett, P. D.; Davies, G. J.; Faraji Rad, Z. Microneedle Arrays for Drug Delivery and Diagnostics: Toward an Optimized Design, Reliable Insertion, and Penetration. *Adv. Mater. Interfaces* **2022**, 9 (6), No. 2101856.
- (24) Rocha, R. G.; Ramos, D. L. O.; de Faria, L. V.; Gernscheidt, R. L.; dos Santos, D. P.; Bonacin, J. A.; Munoz, R. A. A.; Richter, E. M. Printing Parameters Affect the Electrochemical Performance of 3D-Printed Carbon Electrodes Obtained by Fused Deposition Modeling. *J. Electroanal. Chem.* **2022**, 925, No. 116910.
- (25) Ungár, T.; Gubicza, J.; Ribárik, G.; Pantea, C.; Zerda, T. W. Microstructure of Carbon Blacks Determined by X-Ray Diffraction Profile Analysis. *Carbon* **2002**, 40 (6), 929–937.
- (26) Grigora, M.-E.; Terzopoulou, Z.; Tsongas, K.; Bikiaris, D. N.; Tzetzis, D. Physicochemical Characterization and Finite Element Analysis-Assisted Mechanical Behavior of Polylactic Acid-Montmorillonite 3D Printed Nanocomposites. *Nanomaterials* **2022**, 12 (15), No. 2641.
- (27) Howlader, M. M. R.; Doyle, T. E.; Mohtashami, S.; Kish, J. R. Charge Transfer and Stability of Implantable Electrodes on Flexible Substrate. *Sens. Actuators, B* **2013**, 178, 132–139.
- (28) Kalisz, J.; We, grzyn, K.; Maksymiuk, K.; Michalska, A. 3D-Drawn Supports for Ion-Selective Electrodes. *Anal. Chem.* **2022**, 94 (8), 3436–3440.
- (29) Cuartero, M.; Crespo, G. A.; Bakker, E. Polyurethane Ionophore-Based Thin Layer Membranes for Voltammetric Ion Activity Sensing. *Anal. Chem.* **2016**, 88 (11), 5649–5654.
- (30) Rojas, D.; Torricelli, D.; Cuartero, M.; Crespo, G. A. 3D-Printed Transducers for Solid Contact Potentiometric Ion Sensors: Improving Reproducibility by Fabrication Automation. *Anal. Chem.* **2024**, 96 (39), 15572–15580.
- (31) Huang, J.; Gao, Y.; Luo, J.; Wang, S.; Li, C.; Chen, S.; Zhang, J. Editors' Choice—Review—Impedance Response of Porous Electrodes: Theoretical Framework, Physical Models and Applications. *J. Electrochem. Soc.* **2020**, 167 (16), No. 166503.
- (32) Lazanas, A. C.; Prodromidis, M. I. Electrochemical Impedance Spectroscopy—A Tutorial. *ACS Meas. Sci. Au* **2023**, 3 (3), 162–193.
- (33) Bakker, E.; Pretsch, E.; Bühlmann, P. Selectivity of Potentiometric Ion Sensors. *Anal. Chem.* **2000**, 72 (6), 1127–1133.
- (34) Wardak, C.; Pietrzak, K.; Morawska, K.; Grabarczyk, M. Ion-Selective Electrodes with Solid Contact Based on Composite Materials: A Review. *Sensors* **2023**, 23 (13), No. 5839.
- (35) Bühlmann, P.; Umezawa, Y.; Rondinini, S.; Vertova, A.; Pigliucci, A.; Bertessago, L. Lifetime of Ion-Selective Electrodes Based on Charged Ionophores. *Anal. Chem.* **2000**, 72 (8), 1843–1852.
- (36) Guinovart, T.; Crespo, G. A.; Rius, F. X.; Andrade, F. J. A Reference Electrode Based on Polyvinyl Butyral (PVB) Polymer for Decentralized Chemical Measurements. *Anal. Chim. Acta* **2014**, 821, 72–80.
- (37) Molinero-Fernández, Á.; Casanova, A.; Wang, Q.; Cuartero, M.; Crespo, G. A. In Vivo Transdermal Multi-Ion Monitoring with a Potentiometric Microneedle-Based Sensor Patch. *ACS Sens.* **2023**, 8 (1), 158–166.
- (38) García-Guzmán, J. J.; Pérez-Ráfols, C.; Cuartero, M.; Crespo, G. A. Toward In Vivo Transdermal pH Sensing with a Validated Microneedle Membrane Electrode. *ACS Sens.* **2021**, 6 (3), 1129–1137.
- (39) Colburn, A. W.; Levey, K. J.; O'Hare, D.; Macpherson, J. V. Lifting the Lid on the Potentiostat: A Beginner's Guide to Understanding Electrochemical Circuitry and Practical Operation. *Phys. Chem. Chem. Phys.* **2021**, 23 (14), 8100–8117.
- (40) Potts, M. R.; Evans, S. L.; Pullin, R.; Coulman, S. A.; Birchall, J. C.; Wyatt, H. An Analysis of the Relationship between Microneedle Spacing, Needle Force and Skin Strain during the Indentation Phase Prior to Skin Penetration. *Comput. Methods Biomech. Biomed. Engin.* **2023**, 26 (14), 1719–1731.