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Electrochemical sensors: From the bench to the skin

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A B S T R A C T

Sixty years have passed since Clark proposed the concept of glucose enzyme electrodes. Herein, we review major advances in such analyses based on electrochemical sensor systems over the past three decades that have paved the way to the leading role of wearable electrochemical sensing systems for non-invasive real-time chemical monitoring. These past developments of chemically modified electrodes, solid-contact potentiometric sensors, printable disposable electrodes, paper-based sensing devices, soft microfluidic detection systems, and miniaturized instrumentation along with the digital revolution and related advances in flexible electronics and material science have facilitated the evolution of wearable electrochemical sensors which have led to exciting possibilities for on-body analyses. Particularly, the introduction of non-invasive epidermal sensing platforms for monitoring health and wellness has been found fascinating and promising. Such skin-interfaced electrochemical sensors have shown to be extremely useful for continuous non-invasive biochemical monitoring of sweat and the interstitial fluid (ISF). A major driving force for these advances has been the large diabetes management market that has led to the introduction of self-testing glucose strips in the 1980s and continuous wearable glucose sensors in the 2000s. The current status of epidermal electrochemical sensors is discussed along with future prospects towards the broader scope and further integration and miniaturization towards the realization of complete lab-on-the-skin capable of multiplexed sensing of key biomarkers. Such use of wearable electrochemical sensors is expected to bring new opportunities in medical diagnostics, wellness, and nutrition, which will support the rapid changes from traditional, blood-centered diagnostics to decentralized personalized remote diagnostics.

1. Introduction

The digital revolution has resulted in the exponential availability of smartphones/watches, rings, or bracelets, which have found tremendous attention for the development of various handy portable accessory devices. Among these, wearable sensors have received considerable attention owing to their usability, portability, and tremendous promise for recording an optimal health and fitness status [1,2]. The early efforts have resulted in a plethora of wearable physical sensors for tracking mobility and assessing the vital signs of individuals, such as heart rate, skin temperature, blood oxygen concentration, etc. However, until recently, the progress in the wearable sensors field has been hindered by the lack of real-time molecular information of clinically important chemical constituents found in biofluids, such as sweat, tears, and subcutaneous ISF.

Over the past 5 years, we have witnessed tremendous progress towards the realization of electrochemical sensors for non-invasive continuous monitoring of chemical markers [1–3]. Particular attention has been given to skin-worn electrochemical sensing platforms that represent a radical departure from traditional laboratory-based electroanalytical systems. Transitioning conventional bulky electrochemical instruments and large electroanalytical cells to the arms or wrists of individuals requires special attention to a variety of major design and operational challenges. Despite these challenges, electrochemical sensors currently play a leading role in the wearable chemical sensors field. Such success is not surprising as electroanalysis has long been recognized to offer tremendous promise for decentralized testing and scaling down analytical systems, owing to its inherent features of easy miniaturization, low-power requirements, low costs, and excellent compatibility with high-throughput microfabrication technologies [4,5]. The new generation of wearable electrochemical sensors offers continuous molecular information on dynamically changing chemical constituents of different biofluids in a non-invasive manner toward diverse biomedical, wellness, or security applications [1,2,6]. By offering

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real-time biomarker monitoring such skin-worn wearable chemical sensors can dramatically change the way our health and wellness are monitored. Such skin-conforming wearable electrochemical biosensors could provide patients a more comfortable and convenient chemical sensing experience, as well as improved diagnostic outcomes and quality of life.

This article reviews early advances in electroanalysis that paved the way for modern wearable electrochemical sensor systems and discusses the current status and future prospects of such skin-worn platforms for non-invasive monitoring of sweat and ISF metabolites and electrolytes.

2. Historical path to the current success of wearable electrochemical systems

During the 1960s and 1970s, electroanalytical techniques relied on bulky benchtop instruments and large electrodes, such as the hanging mercury drop or rotating platinum disk, immersed in large-volume (50 mL sample) cells (Fig. 1A). During the 1980s, we witnessed tremendous interest in electrochemical biosensors, reflecting the growing emphasis on biotechnology. Intense efforts during this decade has been focused on the introduction of chemically modified electrodes for enhancing the analytical performance of the electrochemical sensors [7] which eventually led the development of mediator-based glucose biosensors [8] along with the commercialization of self-testing blood glucose strips [9]. In the 1990s, we witnessed the intense activities towards the miniaturization of electrochemical systems which led to the evolution of compact instrumentation and introduced various types of screen-printed and microscale electrodes, and compact portable analyzers [4,10]. Parallel efforts towards decentralized testing of trace metals, particularly blood lead testing in children, have led to the replacement of mercury drop electrodes with bismuth and gold-based sensor strips [11,12]. These developments allowed one to move electrochemical measurements from centralized laboratories to the field, office, or home, and to perform them more rapidly and inexpensively. In the early 2000s, we saw major advances towards solid-contact potentiometric sensors [13], flexible electrode materials [14], compact hand-held electrochemical instruments [5,15], and microfluidic systems with electrochemical detection [16], along with the exponentially growing usage of nanomaterials, such as carbon nanotubes (CNT), graphene, metallic nanoparticles, etc. for the electrochemical sensing applications [17,18]. Nanomaterials such as CNT or graphene have also been widely useful for fabricating flexible and stretchable skin-conformal electrochemical devices. The parallel commercialization efforts towards the management of diabetes have led to the introduction of commercial Continuous Glucose Monitoring (CGM) systems for subcutaneous (7–10 days) monitoring of interstitial glucose levels as well as to the first non-invasive commercial GlucoWatch electrochemical biosensor platform [19,20]. CGM devices have successfully transitioned into routine clinical diagnostic practices and have inspired tremendous efforts to develop similar devices with sensing capabilities towards the management of other diseases.

All of the advances in electroanalytical chemistry and biosensor technology during the 1980s and 1990s, along with the digital revolution and related technological developments in diverse fields (such as flexible materials, wireless communications or printed electronics), have drastically shaped electrochemical sensors; initially for point-of-care biomedical applications and more recently for on-body wearable applications. While the digital revolution and the widespread use of smart mobile phone devices have initially accelerated the introduction of wearable sensors for tracking mobility and vital signs, these advances were followed in the 2010s by the rapid development of wearable electrochemical sensors for monitoring key metabolites and electrolytes.

3. Portable electrochemical analyzers

Although relatively large bench-top electrochemical analyzers

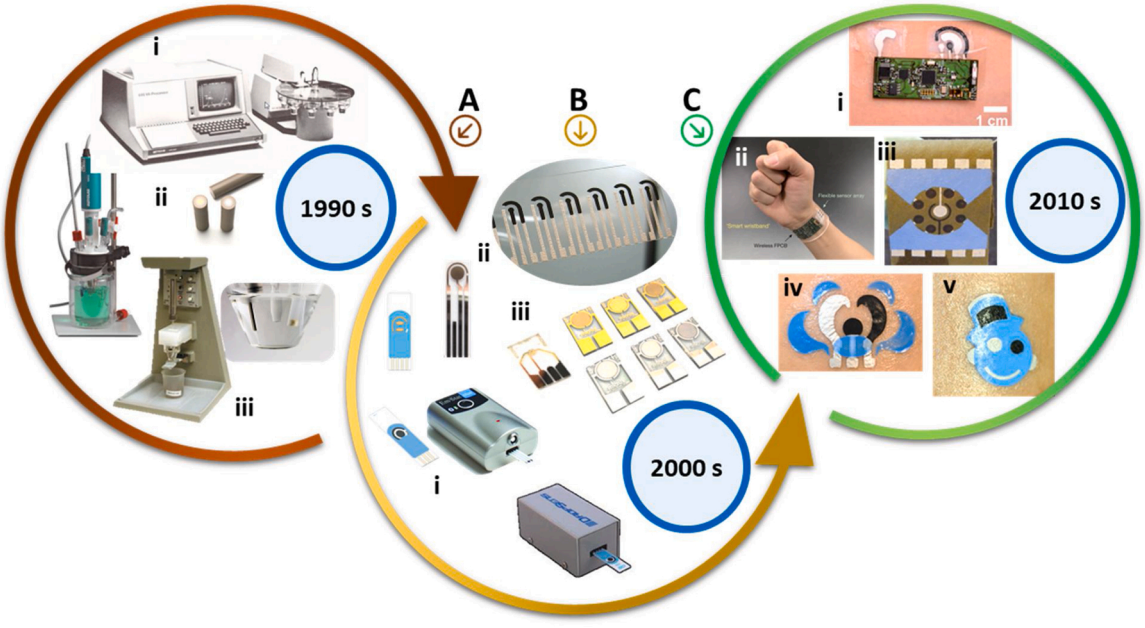

Fig. 1. Evolution of electrochemical analyses: (A) Classical benchtop instrument based analytical devices in 1990s: (i) Benchtop electrochemical analyzer with the conventional electrochemical cell setup [21], (ii) electroanalytical cell setup with rotating disc electrodes for analyses (Web-source: https://www.metrohm-autolab.com/), (iii) dropping mercury based electroanalytical cell system (Web-source :http://www.princetonappliedresearch.com); (B) Handheld systems for onsite electroanalyses in 2000s: (i) the portable hand-held palm-sized analyzers (Web-source: https://www.palmsens.com), (ii) the commercial screen printed electrode systems for onsite analyses in small sample amounts (Web-source: http://www.dropsens.com), (ii) screen printed electrodes with the flexible substrate, (iii) photolithographic electrode system for ultra-trace analysis (Websource: https://www.micruxfluidic.com/); (C) Skin-worn tattoo / patch / textile based wearable biosensors in 2010s: (i) tattoo based wearable sensor for alcohol detection [22], (ii) wearable patch "Smart wristband" for multi-analyte detection [2], (iii) textiles based wearable system for detecting multiple analytes [51], (iv) printed temporary transfer tattoo epidermal electrochemical sensors [33], (v) the tattoo based "smiling" wearable for sweat pH sensing [32].

coupled to bulky cells have been seen common in centralized academic and industrial laboratories [21], major efforts during the 1990s were associated with the growing demands of environmental field analyses and point-of-care clinical testing that has led to a significant reduction in instrument size and weight. Such smaller, lighter, cheaper, and user-friendly instruments offered reliable performances comparable to that of their established bulky counterparts. The successful development of such portable electrochemical analyzers along with the widespread use of blood glucose meters has resulted in the introduction of commercial hand-held electrochemical analyzers (such as the PalmSense) in the early 2000s (Fig. 1B). Such compact electrochemical analyzers have also been interfaced with smartphones that offer the ability to store, process, and send sensor readings. These efforts towards miniaturized electrochemical analyzers have facilitated the realization of wearable electrochemical systems based on flexible printed circuit boards, integrating circuits for instrumentation, control, and telemetry in a variety of wearable form-factors. These include skin-worn epidermal flexible potentiostatic device [22] (Fig. 1Ci), smart glasses [23], smart rings [24], and smartwatches [21,25]. The latter contained photo charging batteries which offer in-situ data processing and display. Such compact wearable platforms incorporated the customized electronic interface along with the energy module and wireless real-time data transmission capabilities. Smartphone-enabled electrochemical sensing offers a powerful user-friendly software interface and hardware, holds considerable promise for decentralized and remote measurements toward personalized self-testing and wellness management [26,27]. Highly integrated conformal epidermal systems for simultaneous multiplexed amperometric and potentiometric detection have been reported [2] (Fig. 1Cii). The latter relied on silicon integrated circuits consolidated on a flexible printed wireless circuit board on a polyethylene terephthalate (PET) substrate, for complex signal conditioning and processing (amplification, filtering, calibration, and compensation).

4. Screen printed sensors: from planar glucose strips to flexible epidermal devices

Since the mid-1980s, screen-printing technology has offered mass production of highly reproducible low-cost electrode systems. The growing interest in decentralized field analysis during the 1990s, and the widespread use of disposable glucose strips, accelerated the replacement of conventional beaker-type electrochemical cells with planar screen-printed electrodes [4]. Besides the significant cost reduction, such replacement of large cells and bulky electrodes offered assays of significantly smaller sample volumes. Although traditional printing technologies are well established [10], early devices have been too fragile to resist the extreme mechanical strains experienced by the human body. Due to the trade-off of the mechanical and electrical properties of screen-printed electrodes, increasing the amount of conductive filler in the ink (for higher conductivity) also increases the stiffness of such devices and thus decreases their stretchability. The realization of epidermal sensing platforms requires printing of electrodes that are compatible with the soft/curvilinear human skin.

Increasing efforts have thus been devoted to developing stress-enduring inks that exhibit not only high conductivity but also shown high mechanical durability [28,29]. The resulting printable sensing devices survive severe mechanical strains without compromising their analytical performance. Such stress-enduring inks have been combined with judiciously designed serpentine and island-bridge structures to offer printed wearable sensors with two degrees of (materials and structural) stretchability to accommodate extreme strains of up to 500 % [30]. Potential cracks formed at higher strains have been addressed in connection to self-healing inks [31]. Such autonomous self-healing property has improved the lifespan of epidermal electrochemical sensing devices. Screen-printing technology has also been widely used for fabricating solid-contact potentiometric sensors [32] (Fig. 1Cv), which obviate the need for bulky traditional ion-selective electrodes (containing an inner solution) and pave the way to on-body monitoring of electrolytes.

Another variable in screen-printed sensing electrodes is the substrate itself. Traditional solid supports (e.g. alumina ceramic) are not suitable for use in on-body operations. Early work in 2009, we demonstrated that electrodes printed on flexible plastic substrates can be bent to extremely small radii of curvature and functions well electrochemically [14]. In 2012 we introduced temporary transfer tattoo-based electrochemical sensors, based on screen printed electrodes on transfer tattoo paper [33]. These flexible tattoo sensors rely on the elasticity, simplicity, low-cost of tattoo papers, and readily conform to the contours of the body. The screen-printing process also offers large-scale mass production of stretchable low-cost reproducible textile sensors. Such direct printing of electrochemical sensors onto clothing was demonstrated in our laboratory in 2010 [34].

5. Towards noninvasive epidermal monitoring of metabolites and electrolytes

With major interest in wearable technologies and electronic-skin (e-skin), tremendous attention has been given over the past decade to the development of skin-worn flexible electrochemical sensors for monitoring sweat and ISF based on a variety of different wearable form factors such as patches, wrist watches, transfer tattoos, stickers, or bandages. The rich composition of chemical biomarkers in sweat and its ease of non-invasive collection makes this biofluid an extremely attractive candidate for non-invasive point of care diagnostics [6]. While sweat is commonly generated over the entire epidermal space, its flow rate is very low for practical sensing applications. Accordingly, to address the limited accessibility of sweat, modern skin-worn electrochemical sensors sample the sweat in connection to iontophoretic extraction (that stimulates local sweat secretion at the selected sensor site) or via exercise activity for generating sufficient amounts of sweat. Alternately, it is possible to rely on the fast sweat flow rate at the fingertip to collect the natural perspiration. Enzyme-based flexible sweat sensors were introduced for the detection of sweat lactate [35], glucose [36], alcohol [22] or uric acid [37] in connection to immobilized lactate oxidase (LOx), glucose oxidase (GOx), alcohol oxidase (AOx) and uricase enzymes, respectively. Sweat electrolyte measurements commonly rely on flexible solid-contact ion-selective electrodes (ISEs), that replace the bulky and rigid ISE (containing an internal solution). For example, Bandodkar et al. developed an epidermal tattoo-based solid-contact ISE for pH monitoring by combining a screen printed solid-contact ISE with tattoo transfer paper (Fig. 1Cv) [32]. Such epidermal pH sensors rely on pH-responsive polyaniline-based solid-contact ISEs. Gao et al. have demonstrated a fully integrated wristband-based multiplexed wearable sweat sensing platform capable of monitoring simultaneously multiple electrolytes and metabolites (Fig. 1C) [2]. Nutrients and supplements, such as vitamin C or zinc, have also been monitored in sweat in connection to ascorbate-oxidase and Nafion/bismuth modified electrodes, respectively, along with corresponding amperometric and stripping-voltammetric measurements [38, 39]. These assays illustrated the potential of wearable electrochemical sensors for personalized nutrition.

Emaminejad et al. [40] described an autonomous integrated epidermal platform that enables continuous and noninvasive sweat monitoring. This system combined periodic sweat extraction and in situ electrolyte detection. The programmable sweat extraction was coupled to solid-contact sodium and chloride potentiometric sensors (Fig. 2Aiii). The ion-selective electrodes were patterned on a flexible PET substrate and were placed between the iontophoretic electrodes to enable assays of the induced sweat. The sweat stimulating electrodes were interfaced with the skin by a separating thin layer of agonist agent hydrogel. Such operation offered the reliable detection of elevated sweat electrolytes of cystic fibrosis patients compared with that of healthy control subjects.

Since analytes in the ISF originate from blood, this fluid has the

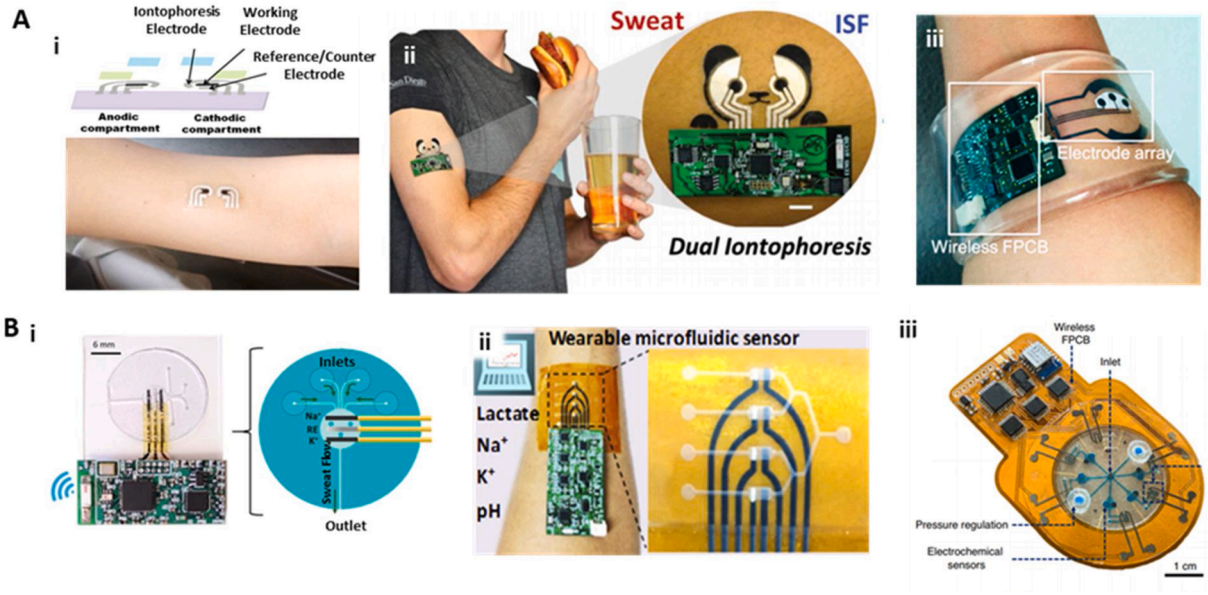

Fig. 2. Advanced wearable electrochemical sensors for determining sweat based analytes (A) Wearable tattoo/patch based electrochemical sensor: (i) Skin-worn epidermal tattoo platform for non-invasive sensing of ISF glucose [42], (ii) Simultaneous measurements of sweat alcohol and ISF glucose [43], (iii) multi-metabolite sensors [40]. (B) Microfluidics assisted electrochemical sensor patches for non-invasive sweat monitoring/sensing: (i) epidermal microfluidic system for potentiometric detection of sweat electrolyte (Na^{+} and $K^{+)}$ [44]; (ii) multi-channel multi-electrode multiplexed fluidic system for detecting sweat electrolytes and metabolites [46]; (iii) programmed epidermal microfluidic valving based wearable patch for glucose and lactate detection [47].

closest correlation of biomarker concentrations to blood (compared to other biofluids) [41]. Similarly, the temporal profiles of most analytes in ISF are commonly similar to their profiles in blood. Bandodkar et al. described a tattoo-based platform for noninvasive detection of ISF glucose [42]. The flexible system relied on screen-printed electrodes and combined the iontophoretic ISF extraction with selective low-potential amperometric glucose detection at a GOx-modified Prussian Blue transducer at -0.10 V (Fig. 2Ai). To realize such ISF extraction, additional Ag/AgCl reverse-iontophoresis electrodes (coated agarose hydrogel-film), have been incorporated for efficient delivery of ISF close to the working and counter/reference electrodes. The skin-worn tattoo-based glucose detection system used a lower current density for 10 min to extract the ISF followed by the amperometric detection. On-body evaluation of the tattoo-based iontophoretic-biosensing platform demonstrated the ability to detect non-invasively dynamic changes in the glucose level after a meal.

Kim et al. described a tattoo-based dual-fluids sampling epidermal detection combining reverse iontophoretic ISF extraction across the skin and iontophoretic delivery of a sweat-inducing drug (pilocarpine) [43] (Fig. 1Ci). Such a flexible iontophoretic system was integrated with electrochemical biosensors to enable simultaneous monitoring of glucose ISF and sweat alcohol (Fig. 2Aii). The new printed flexible device was optimized to ensure efficient simultaneous collection of the sweat and ISF at the corresponding enzyme electrodes without any cross mixing. The new 'Glucohol' tattoo approach was illustrated for non-invasive alcohol and glucose measurements following drink and meal consumptions which have shown good correlation to parallel commercial blood glucometer and breath-analyzer measurements.

6. Towards lab-on-the skin

Soft skin-mounted microfluidic detection platforms couple the advantages of epidermal sensing systems with those of soft epidermal microfluidic detection and of electrochemical microchip flow detectors. Such epidermal microfluidic devices can enhance the collection of sweat and its transport over electrochemical detectors and address challenges of early epidermal electrolyte sensors, including potential sweat mixing or skin contamination while ensuring efficient sweat transport over the detector surface. For example, Fig. 2Bi shows a skin-worn soft fluidic system that enables efficient sweat pumping to the potentiometric detection chamber containing potassium and sodium ion-selective electrodes [44]. Such operation holds considerable promise toward multiplexed electrochemical measurements, as was demonstrated in another study towards amperometric biosensing of sweat lactate and glucose [45]. These flexible microchip devices provide direct contact to the skin sweat pores to route the sweat toward the detection compartment while displaying resiliency against continuous mechanical strains. Such skin conformity and mechanical resiliency has been accomplished by integrating polymeric PDMS-based soft microchip material, with Young modulus similar to the skin.

Vinoth et al. described recently an advanced multi-channel multi-electrode multiplexed fluidic system [46]. The system, shown in Fig. 3Bii, relies on the placement of the individual sensing electrodes in different flowing channels and offers simultaneous amperometric lactate and potentiometric ion sensing (Na, K, and pH) using different microchannel patterns. The hydrophilicity of channel layers was tailored by silane functionalization to enhance the sweat sampling. The circuit board facilitated such wireless multiplexed detection, with no apparent cross talk. The sweat composition was analyzed in human trials at different (underarm and upper back) locations.

Emaminejad's team developed a fully integrated wearable bioanalytical platform based on an electronically programmable microfluidic valving system, capable of sampling and routing sweat and compartmentalization for subsequent electrochemical detection [47]. Fig. 2Biii shows such in situ active sweat management using a pressure-regulated six-compartment valving system, with a sweat collection inlet at the center and an electrochemical detection sensing in each of the compartments. Temperature controlled hydrogel shrinkage/expansion served for such programmable valving while amperometric lactate and glucose enzyme electrodes were used for the biomarker detection. The sample manipulation capabilities of epidermal microfluidics systems offer considerable promise for facilitating complex bioassays involving multiple steps, such as washing or tagging. The versatility of the skin-mounted microfluidic chemical sensing systems, demonstrated in the above examples, can be expanded to the non-invasive monitoring of other sweat electrolytes and biomarkers,

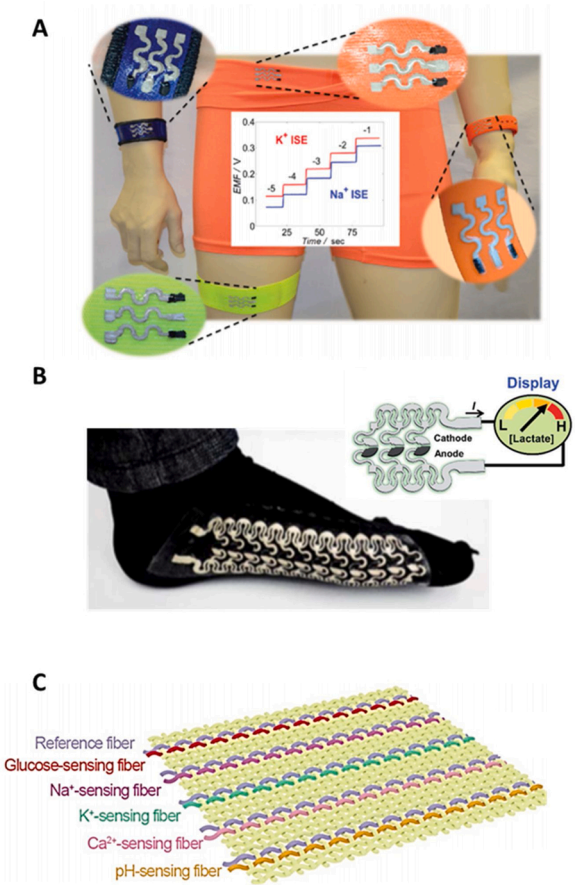

Fig. 3. Wearable textile-based electrochemical sensors: **(A)** the ion-selective potentiometric sensor for electrolyte (sodium and potassium) detection in sweat [48]. **(B)** Sock-based self-powered sensor for sweat lactate detection [49]. **(C)** Sensor array of 4 ion-selective electrodes (Ca, K. Na and pH), along with an amperometric glucose biosensor, based on CNT fiber woven within traditional fabric for multiplexed biomedical detection [50].

paving the way for a new generation of powerful soft epidermal microfluidic systems.

7. Textile-based electrochemical sweat detection

Textiles represent an attractive platform for wearable devices, since they are worn everywhere in a variety of form factors and offer attractive elastomeric properties towards achieving conformal sensor-skin contact. Textile-based sensors represent a rapidly emerging class of wearable devices. Integrating electrochemical sensors directly into garments offer distinct advantages for wearable health monitoring systems. With the rapidly growing digitalization, we have witnessed growing trends of developing smart E-textiles based on weaving electronics into fabrics. Yang et al. described the direct screen-printing of amperometric biosensors onto the textile substrates and illustrated that the attractive electrochemical performance of these sensors is maintained under stretching and bending stress, relevant to the deformation of clothing [34]. Printing on the elastic waist of the underwear offered direct contact with the skin. Parrilla et al. realized stress-enduring textile-based potentiometric sensors by combining polyurethane-based ion-selective membranes and inks with a serpentine sensor pattern [48]. Such stretchable dual-electrolyte (Na, K) textile-based wearable potentiometric sensor printed on different common textiles, is displayed in Fig. 3A, along with typical potential-time trace signals for the two ions that exhibit a Nernstian behavior under extreme conditions.

The ability to operate textile-based electrochemical sensors under extreme mechanical tensions, without compromising their analytical performance, was demonstrated by Jeerapan et al. using the soak-based self-powered sensing device shown in Fig. 3B [49]. This textile device was printed from stress-enduring inks, that along with its serpentine pattern, offered remarkable stretchability. The resulting stretchable biofuel cell acted as a self-powered sensor, with the electricity generated was proportional to the concentration of the lactate fuel.

Peng's group described smart textiles consisting of traditional fabric woven with conductive CNT fibers acting as electrochemical sensors [50]. For example, Fig. 3C displays a sensor array of 4 ion-selective electrodes (Ca, K, Na and pH), along with an amperometric glucose biosensor, constructed by coating active recognition materials onto the CNT fiber electrodes. Such integration of potentiometric and amperometric sensors within textiles has not compromised the basic properties of these fabrics. Another textile-based sensor array based on screen-printed voltammetric electrodes [51] is displayed in Fig. 1Ciii. Such tremendous recent progress has revealed the importance of textile-based sensing platforms. These textile-based sensors offer great promise for next-generation smart clothing for monitoring personal health and performance.

8. Conclusions and future prospects

Biomedical diagnosis is witnessing tremendous efforts of shifting from traditional, blood-centered invasive diagnostics - commonly implemented in hospital settings - to personalized, point-of-care and remote diagnostics. Wearable electrochemical sensors have been playing a major role in these rapid changes and are already bringing a major paradigm shift to the field of analytical chemistry. Such a rapidly emerging field of epidermal electrochemical sensors represents a major transition away from traditional centralized laboratory-based electroanalytical systems. The recent success of wearable electrochemical sensors reflects the tremendous progress over the past three decades in diverse fields, including chemically modified electrodes, miniaturized instrumentation, printed planar electrodes, flexible materials, and lab-on-chip detection microsystems. These major advances in electrochemical sensor systems, along with the digital revolution, have paved the way for the gradual shift of electrochemical assays from the bench to the home and onto the skin. Wearable electrochemical sensing systems currently hold a leading role among wearable sensor systems, reflecting the fact that miniaturizing such systems does not compromise their attractive analytical performance. Many of these recent advances have relied on the lessons scientists and engineers learned during the evolution of mobile and wearable glucose monitoring systems for the management of diabetes over the past 4 decades of miniaturizing such glucose analyzers (Fig. 4) that benefited from huge financial investments [9]. Such wearable electrochemical sensors continue to become more sophisticated, exploiting novel materials, designs, and creative sensing strategies to achieve high analytical performance.

Although skin-worn electrochemical sensors are at the early stages of critical evaluations, such epidermal sensing devices offer considerable promise for monitoring health and disease status, performance, nutrition, and wellness. While current epidermal systems target primarily key metabolites and electrolytes, future systems will provide non-invasive monitoring of important biomarkers, such as hormones and protein disease markers. Expanding the scope of epidermal sensors to these important biomarkers will require the adaptation of new receptors, such as aptamers, or of advanced skin-worn microfluidic devices, that can meet the challenges of receptor regeneration and needs for various washing steps. Non-invasive assays of drugs and nutrients will be developed to meet the demands of personal therapy and precision nutrition, respectively [52]. Future electrochemical monitoring devices will also be built directly on our clothing and will be integrated with the electronic circuitry and displays. Microneedle sensor arrays will also be developed towards multiplexed detection of multiple biomarkers under the skin [53]. Integrating multiplexed wearable chemical sensing

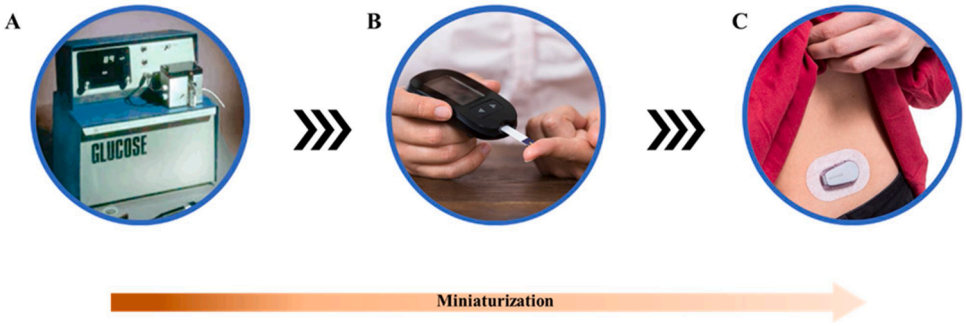

Fig. 4. Miniaturization of glucose analyzers: from the bench onto the skin. (A) Benchtop YSI glucose analyzer (https://www.ysi.com); (B) hand-held meeting for self-testing of blood glucose (https://www.diabetes.co.uk); (C) The G6 Dexcom CGM system (https://www.dexcom.com).

devices with advanced machine learning and AI approaches will facilitate real-time extraction of the rich continuous analytical information to allow patients and caregivers hospital consultant decision making timely decision and interventions.

These developments would allow one to move the measurement of biomarkers from the central laboratory to the body, and to perform them rapidly, reliably and inexpensively. Wearable electrochemical sensors are thus expected to play a major role in the monitoring of health and wellness and in the move towards remote telemedicine (that is being accelerated by the current COVID-19 pandemic). Hybrid skin-worn platforms, coupling such biomarker monitoring with the tracking of vital signs, such as blood pressure [54], are expected to offer a more comprehensive understanding of the health and wellness status of individuals. Meeting the energy demands of wearable electrochemical sensors requires the development of anatomically compliant power sources. Efforts in this direction have led to the introduction of epidermal electrochemical energy harvesting and storage systems [55, 56], including self-powered biosensors using lactate-sweat biofuel cells [49]. While the field of wearable electrochemical sensors is expected to continue to grow very rapidly over the next decade, such sensing devices face technological gaps towards realizing their full potential. With the exception of CGM, there are no commercial sensing products for on-body molecular monitoring, reflecting (besides marketing issues) potential problems due to limited sensor stability (related biofouling and receptor degradation) and the limited understanding of the correlation between sweat and blood analyte concentrations. Establishing such correlation and achieving widespread acceptance of such epidermal electrochemical sensors require large-scale clinical trials and broad validation efforts (against blood gold standard assays). Continued multidisciplinary efforts between chemists, electrical engineers, materials, data scientists, and medical practitioners, are expected to address these and other major gaps and key challenges. We envision that such collaborative efforts will eventually lead to the complete lab-on-the skin that will continuously and reliably access important molecular information.

CRediT authorship contribution statement

Kuldeep Mahato: Writing - review & editing, Visualization. **Joseph Wang:** Conceptualization, Writing - review & editing, Supervision, Resources.

Declaration of Competing Interest

The authors report no declarations of interest.

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