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Recent advances in electrochemical paper-based analytical devices for drug analyses

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ABSTRACT

Electrochemical paper-based analytical devices are sustainable and smart analytical tools that have gathered relevant attention from academic and industrial sectors thanks to their multifaceted properties and versatile applications in diverse fields.

This review delves into a critical overview of electrochemical paper-based analytical devices in drug measurements for sustainable quality control in pharmaceutical industries, for assessing the drug residues in wastewater and foodstuffs, and for delivering the next generation of devices for precision medicine, facing the requirements of the pharmaceutical industries, medical sector, and environmental safety.

The advantages and the challenges in the development and application of electrochemical paper-based analytical devices for drug analyses in 2019–2025 are highlighted, to give a picture of the ongoing scenario and the future direction in their growth in the pharmaceutical field.

1. Introduction

The global market of drug delivery is a continuously growing market, with a value of USD 1949.4 million in 2024 with a forecast of USD 2546.0 million by 2029 [1]. The upward trend is driven by heightened public health consciousness, evolving lifestyle habits, greater investment in pharmaceutical innovation, and an ageing demographic [2].

The next steps in the advancement of the pharmaceutical industry will rely on [3,4]:

1) Innovation in the engineering of multifunctional excipients capable of managing with a single drug different diseases, boosting the augmentation of solubility, optimisation of bioavailability, and precise modulation of drug release kinetics. Such innovative excipient systems are increasingly pivotal due to the escalating complexity of pharmaceutical formulations and the increase in precision medicine approaches.
2) Use of natural and plant-based excipients in response to increasing demand from consumers and regulatory agencies for sustainable and eco-compatible pharmaceutical components. This transition addresses ecological sustainability while potentially enhancing biocompatibility and minimising adverse reactions.
3) Engineering of nanoscale excipients aimed at augmenting solubilisation, optimising site-specific drug targeting, and enhancing the pharmacological performance of medicinal formulations. These innovative nano-based excipients possess the potential to revolutionise drug delivery modalities, particularly for therapeutics characterised by poor dissolution properties or suboptimal systemic availability.
4) Transition toward patient-centric packaging systems, reflecting a broader emphasis on usability and therapeutic efficacy, considering as drivers the demographic shifts resulting in a growing geriatric population with polypharmacy requirements, the heightened focus on enhancing pharmacological adherence to improve clinical outcomes, and the accelerated adoption of self-administration modalities and decentralised care models.

In all 4 points, we can find the main aspects of the future in the pharmaceutical industry, namely precision medicine, sustainability, improvement of drug delivery, and self-administration modalities at home. In this overall scenario, the point-of-care testing (POCT) will acquire a prominent position in 3 of 4 points by fostering *precision medicine, sustainability,* and *drug self-administration at home*.

The glucose electrochemical biosensor is the first POCT based on a printed miniaturised electrochemical biosensor that reached the market,

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thanks to the stability of the biocomponent, the concentration of glucose to detect in the linear range without sample preconcentration or dilution, and the need for a POCT for diabetes management [5]. This POCT has been able to improve i) the *precision medicine,* by the customization of the drug administration depending on the analysis output, ii) the *sustainability* of glucose management by reducing the cost and enhancing the quality of patients, iii) the *drug self-administration at home* thanks to the possibility to carry out the analysis of glucose in capillary blood by the patient. Notably, the development of diverse POCTs has increased after the 2020 COVID-19 pandemic event, having demonstrated the utility of this type of analytical tool. Indeed, if before 2020 the main marketed POCTs were the glucose biosensor and the lateral flow immunoassay for pregnancy test, after 2020, there has been a growing industrial interest in POCTs for several diseases, fostered further by the telemedicine approach.

Electrochemical paper-based analytical devices (e-PAD) have introduced a novel paradigm in the sensing area, by delivering affordable, cost-effective, ecodesigned, sensitive, and versatile analytical tools. The several features of the paper have paved the way for unprecedented POCTs by harnessing i) the porosity and the hydrophilicity of the paper for capillary-driven microfluidics and reagent loading, ii) the versatility of different paper substrates to be functionalised with conductive materials, iii) the foldability for the origami design establishing a new concept namely paper-based vertical microfluidics, and iv) the cuttability and burning by reducing the waste with a simple step of incineration (Appendix in Supporting Information). Additionally, e-PADs can be fabricated by using several manufacturing techniques, including wax printing, screen printing, inkjet printing, laser toner printing, flexographic printing, wax dipping, spraying deposition, which push the mass production of these cost-effective POCTs.

The versatility of the applications of e-PADs is well highlighted and reported in the literature by several reviews addressing the challenges and applications of these devices in several fields [6–11]. In the pharmaceutical field, in 2020, Henry group published a review entitled “Emerging Applications of Paper-Based Analytical Devices for Drug Analysis: A Review”, shedding light on the state-of-the-art technologies and applications of PADs for drug analysis [12]. In the same year, we published a review entitled “Paper-Based Electrochemical Devices for the Pharmaceutical Field: State of the Art and Perspectives" by reporting e-PAD for Antioxidants, Hormones, Anti-inflammatory Drugs, Anaesthetic Drugs, and Stimulants of the Central Nervous System detection [13], focussing on the e-PAD for the detection of different classes of drugs. Considering the fast growing of this field and the enlarged use of drugs, in this review we give an overview of the e-PADs designed and applied in the period 2019–2025 for drug analyses in different contexts, starting from e-PADs for the quality control of the formulation in pharmaceutical industries with well-established application and higher technology readiness level (TRL), moving towards the design of e-PADs to improve the monitoring of drug residues considering the ongoing European water legislation to align the legal framework with the scientific and technical progress and the recent Food Contaminants Regulation (EU) No 2023/915 [14], up to the development of e-PADs for their use in precision medicine by developing POCTs for drug monitoring in biological fluids (Fig. 1). Furthermore, the perspective development and applications of e-PADs in Organ-on-a-Chip (OoC) devices have been envisioned. Despite growing research interest and promising applications that have emerged, several limitations hinder the widespread translation of e-PADs into the pharmaceutical field. Considering the different contexts, while e-PADs have demonstrated significant potential in environmental monitoring [29,30,33–37], food safety [32,34–36], and POCT for precision medicine [40,41,43–54], leveraging the advantages of paper-based platforms, their application in pharmaceutical quality control remains highly limited due to lack of standardization and regulatory validation. Technically, ongoing research efforts aim to address key challenges such as improving sensitivity and lowering detection limits i.e. exploiting paper porosity or enabling high-throughput automated analyses thanks to paper-assisted microfluidic systems, to foster the transition of e-PADs in the pharmaceutical field.

The ongoing applications and the future perspective are reported, with our vision to foster the next generation of the combined concept of e-PAD with drugs at the pharmacy, for enlarging in a sustainable way the precision medicine.

2. e-PADs for quality control in the pharmaceutical industry

Quality control in the pharmaceutical industry plays a critical role in ensuring the safety, efficacy, and purity of drugs, having a direct impact on consumers’ health. Starting from the screening of raw materials, e.g. the active pharmaceutical ingredients (API) for drug discovery, quality control is an ongoing process that involves a range of activities throughout the manufacturing cycle and post-marketing surveillance, in terms of performance, stability, and safety of the drug product.

Analytical methods are applied to the study of the whole pharmaceutical chain, including formulation, dosage forms, intermediates and degradation products, as well as stability after going to the market, tests for counterfeit, and substandard drugs. Laboratory testing relies on Gold-standard methods with reliable accuracy to meet the needs of regulatory requirements in the pharmaceutical field, especially under ICH Q2(R1) guidelines. Consequently, before the implementation of the analytical method for routine analyses, it must first be validated to demonstrate that it is suitable for its intended purpose. Common techniques include titrimetry, spectrometry, chromatography, electrochemistry, capillary electrophoresis, flow/sequential injection analyses, and combined for reliable outputs [15]. These techniques require technologically advanced equipment and highly skilled personnel; thus, in recent years, there has emerged a necessity to develop easier and faster techniques for analysis, without losing the high-quality

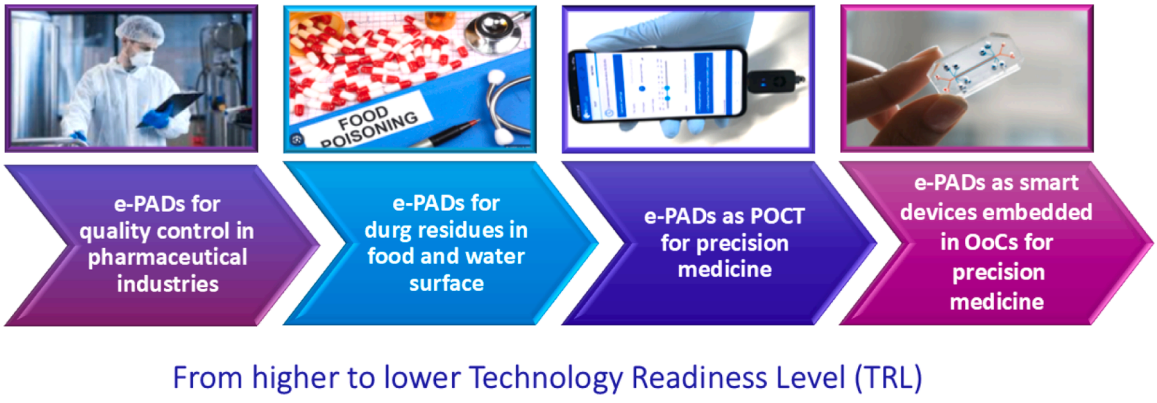

Fig. 1. e-PADs for drug analyses in diverse applications addressed in this review, highlighting the TRL of the different e-PADs.

requirements. Within this framework, electrochemical (bio)sensors have emerged as fast and reliable tools for rapid detection of drugs within a wide range of pharmaceutical and biological samples, as a promising alternative to traditional laboratory techniques [16]. Electrochemical sensors offer practical benefits such as cost-efficiency, short response time, ease of use, good limit of detection and sensitivity, and ease of miniaturisation, all while consistently delivering reliable analytical results [17]. Despite the technological advantages potentially offered by e-PADs, the lack of regulatory validation and standardised protocols still hinders their diffusion in quality control.

Entailing the needs of sustainable development, paper has been exploited as a biocompatible and biodegradable material for electrode production. Disposable (bio)sensors have been produced on different substrates depending on the intended purpose due to the wide range of applications [18]. Filter and chromatographic papers have been successfully employed as eco-friendly and flexible support for electrode production, leveraging paper porosity, permeability, and ability to store reagents, and enabling microfluidics to control sample flow. Facing the needs of multiple analyses for the determination of different pharmaceuticals, filter paper was combined with wax to create a multiplex screen-printed electrochemical cell for the detection of ascorbic acid and simultaneous detection of paracetamol and caffeine in pharmaceutical formulation samples (Fig. 2A) [19]. Wax printing onto paper enables the formation of hydrophobic barriers that confine the solution to the hydrophilic portion of the paper where the electrodes are printed, for obtaining the electrochemical cell after sample addition. Wax printing was optimised to overcome the limitation due to the current lack of wax printers, using a stamp strategy with chromatography paper. The e-PAD showed good analytical performances in the simultaneous detection of paracetamol and caffeine, requiring only 3 μL of sample thanks to the preloading of 5 μL of supporting electrolyte onto paper, and obtaining limits of detection of 0.04 mM for paracetamol and 0.22 mM for caffeine. However, an acidic treatment of the samples is required to disintegrate and dissolve the drug tablets tested. Sample preparation in quality control remains one of the main challenges, since data quality, assay throughput, and analysis costs are all strongly impacted by the

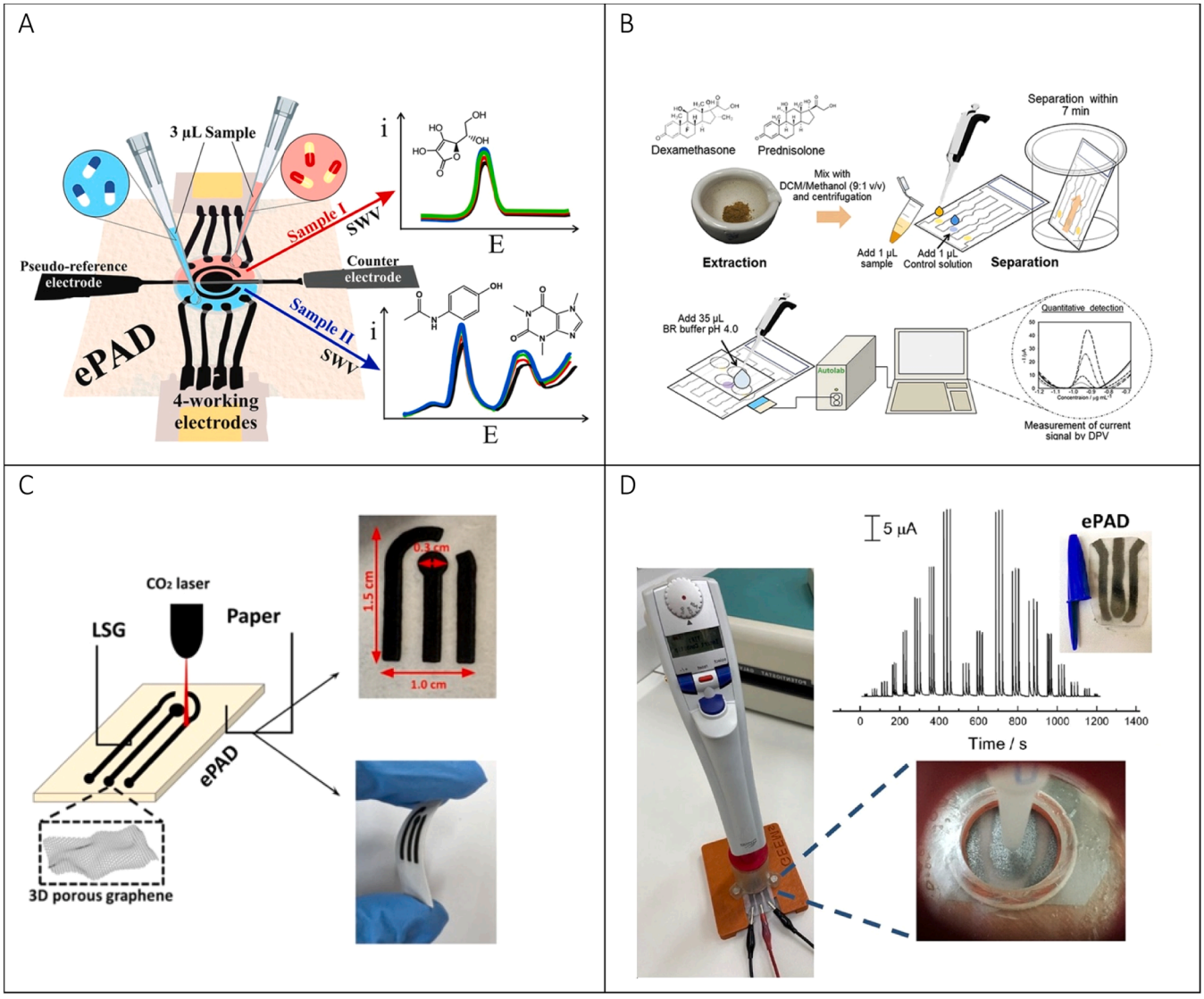

Fig. 2. A) Multiplexed electrochemical paper-based analytical device developed using a craft cutter printer to create a wax barrier and screen-printed electrodes for simultaneous detection of paracetamol, ascorbic acid, and caffeine. Reprinted with permission from ref [19] Copyright 2019 Elsevier. B) Electrochemical paper-based analytical device for extraction and determination of dexamethasone and prednisolone in adulterated traditional medicines. Reprinted with permission from ref [21] Copyright 2019 Elsevier. C) Laser-scribed graphene e-PAD modified with nanocomposites for lidocaine detection in pharmaceutical samples. Reprinted with permission from ref [24] Copyright 2024 Elsevier. D) e-PAD combined with the BIA system for measuring 5-hydroxytryptophan in foodstuff and pharmaceutical samples. Reprinted with permission from ref [26] Copyright 2022 Elsevier.

sample preparation process.

To overcome this limitation, efforts have been made to reduce sample preparation prior to analysis, and paper has been exploited as a versatile substrate. Pharmaceuticals are usually delivered in specific formats to patients, usually liquid or solid, depending on their intended use, the amount of API that needs to be delivered, the mode of administration by the patient, and the stability of the formulation. A sample preparation step is often required prior to analytical detection of specific ingredients in pharmaceutical formulation, thus thwarting analysis of multiple samples often required in the pharmaceutical industry, due to the large number of samples to test for quality control purposes [20]. To simplify the procedures, paper can act as a loading substrate for avoiding the use of chemicals and off-device sample pretreatment. Recalling separation and chromatography, e-PADs represent a step forward from thin layer chromatography, leveraging paper porosity and functionalization for affinity-based separation. Paper-based devices aim to recreate the standard method configurations, translating paper-based chromatography to fully integrated devices to accomplish and meet the needs of more complex analyses in only one device. Using cation-exchanger chromatographic paper SG81, Primpray et al. [21] successfully extracted prednisolone and dexamethasone from a powder formulation, using as extracting solution a mixture of dichloromethane:methanol (9:1 v/v), within 7 min of analysis (Fig. 2B). An integrated device was obtained by printing a 3D cassette housing for microfluidic separation paper and screen-printed electrodes, obtaining comparable results to those obtained with HPLC. The attempt is made to bring chromatography back to paper, scaling up small and simplifying the analyses, which, however, require high standards that slow down their transition into pharmaceutical applications.

Depending on the intended use, the hydrophilicity and hydrophobicity of the paper can be tailored. For the development of a sustainable device maintaining the requirement of non-permeability and enabling sample dropping on the surface, waterproof paper was employed as a substrate to construct disposable screen-printed electrodes for the voltammetric detection of paracetamol and melatonin in pharmaceutical samples [22]. Combination of paper and graphite sheets creates an irregular morphological surface presenting cavities that provide active sites able for the interaction or preconcentration of target analytes. The device was employed for paracetamol and melatonin detection via differential pulse voltammetry in pharmaceutical drops and tablets using the standard addition method, obtaining recovery values from 94.6 to 113 %.

The incorporation of nanomaterials, such as metal nanoparticles and carbon-based nanomaterials, has significantly improved the performance of electrochemical (bio)sensors. This enhancement is attributed to their high electrocatalytic activity and improved sensing capabilities, which result from their large surface area, abundant defect sites, excellent electrical conductivity, and strong mechanical properties [23].

Whatman chromatographic paper was engraved using a laser to produce an e-PAD for the detection of lidocaine in a commercial anaesthetic sample (Fig. 2C). Paper was treated before engraving with sodium tetraborate solution as a flame retardant, and graphene electrodes were obtained and modified with a nanocomposite based on the mixture of multi-walled carbon nanotubes (MWCNT) and poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS). Modification with nanocomposite successfully enhances electrochemical performances of the sensor in the detection of lidocaine in an injectable anaesthetic sample, obtaining a concentration equal to 20.1 ± 2.6 mg/mL, close to the value reported on the label by the manufacturer (20 mg/mL). The effective combination of a paper-based device with nanomaterials is confirmed by SEM analysis, showing, under optimised engraving conditions, that the paper-based laser-scribed graphene electrode presents high porosity with interconnected fibres, enabling high loading of nanomaterials, thus enhancing the electroanalytical performances of the e-PAD for redox probe quantification. The device was validated accordingly to AGREE standards of Green Analytical Chemistry, obtaining a score of 0.86, confirming also its sustainability [24]. Combining molecularly imprinted polymers (MIPs) with paper, Hassan et al. developed a potentiometric biosensor modified with reduced graphene oxide (rGO) for monitoring losartan drug in pharmaceuticals samples. The drug tablets containing losartan were crushed, grinded, dissolve in phosphate buffer solution pH 7.4, sonicated, and filtered before potentiometric measurements. The results showed an average recovery of 96.3 ± 0.5 % of the nominal values reported. Moreover, data obtained using a standard spectrophotometric method confirmed the suitability of the proposed method. Approaching the demands for the effective transition to real application in the pharmaceutical field, the method was also validated by measuring accuracy, trueness, bias, within-day repeatability, between-days reproducibility, standard deviations, precision, sensitivity, robustness, range, stability, durability, and limit of detection, designing a method validation protocol in accordance with ISO/IEC 17025, AOAC, USP, U.S.EPA and U.S. FDA standards, to test the quality, reliability, and consistency of the analytical data [25].

For boosting the automatic analysis, e-PAD was combined with a batch injection analysis system for the amperometric detection of 5-hydroxytryptophan. The e-PAD was fabricated using tracing paper and the electrodes were manually drawn using a 6B pencil, while the batch injection analysis system cell was manufactured with a 3D printing technique. The injection volume for analysis was 50 µL dispensed by electronic micropipette, obtaining a limit of detection (LOD) and quantification (LOQ) of 50 nM and 165 nM, respectively. 5-hydroxytryptophan was successfully detected in food and pharmaceutical supplement samples with high agreement with values declared on the labels [26].

Analysis of drugs in quality control can impressively be simplified by the introduction of POCTs leveraging the sustainability, easiness of use, fast, rapid and selective response when compared to traditional laboratories analyses. However, when facing the needs of pharmaceutical companies to obtain validated methods for drug quality control, especially for market entry, the transition to point of care device encounters difficulties related to the ease of changing well-established and accredited methods of analysis that must also be performed in large quantities, ensuring accuracy and reproducibility that are fundamental for the pharmacopoeia. Moreover, despite significant achievements in improving sensitivity and lowering detection limits [22], as well as efforts towards automating testing protocols [26] and including or even eliminating sample preparation step within the e-PADs [19,21], most of current analytical devices still face important technical limitations. For example, many systems report relative standard deviation (RSD) values around 10 % [13], which indicates limited reproducibility. Additional challenges include the lack of standardized and validated fabrication methods and testing protocols that slows down the diffusion of these devices compared to validated and well-established standard testing methods.

3. e-PADs for drug residue monitoring in water samples and foodstuffs

Environmental pollution is rapidly rising as global development accelerates, increasingly prioritising human needs, neglecting the effects of chemical waste production on the health of people and the environment. While efforts continue worldwide to address well-established pollutants, the ongoing emergence of new contaminants poses a significant threat; thus, the risk assessment and regulation of these emerging substances are pivotal issues to address [27]. Among emerging contaminants, pharmaceuticals and personal care products represent one of the largest groups, including a wide range of compounds with diverse physical-chemical properties, including medicines and their metabolites [28].

The presence of pharmaceuticals in the environment and the food industry results from incomplete removal during water treatment and

improper disposal of medications. Traditional analytical methods like tritimery, chemiluminescence, chromatography, and mass spectrometry are commonly employed, but are costly, long, and operated by skilled personnel. Thus, e-PADs offer the possibility to obtain fast and reliable device for simple, rapid and selective detection of contaminants using sustainable devices.

Capillarity, porosity, and adsorbent capacity of paper supports, including chromatography paper and glass fibre filter paper, are harnessed for direct collection and loading of the sample, reducing the amount of volume required, filtering the solution to limit possible interferences, and enabling reagent preloading for reagent-free systems [29,30]. An all-in-one platform was designed using Whatman No.1 chromatography paper for voltammetric detection of paracetamol in wastewater, harnessing paper porosity to preload KCl as electrolyte which is redissolved by sample addition (Fig. 3A). With the use of the standard addition method, the sensor displayed recoveries ranging from 82 % to 98 % and LOD equal to 0.7 µM in starndard solution and ca. 1.5 µM in real samples [29]. Leveraging paper porosity to decrease the amount of volume required for analysis, a reagent-free device was developed, combining pencil leads as electrochemical probes for the determination of the emerging contaminant namely antidepressant drug venlafaxine in wastewater (Fig. 3B). Paper was wrapped around the graphite leads electrodes, enabling i) filtering the particulate that can compromise the mechanical stability of pencil leads, ii) absorbing the sample requiring lower volume of µL compared to standard electrochemical cell requiring mL of sample, iii) storing of reagents, in this case the buffer solution for on-site pH adjustment. Using adsorptive stripping square wave voltammetry, the electrochemical cell exhibited a linear range from 0.8 µM to 10 µM, with a LOD equal to 0.4 µM and a precision with an RSD equal to 2.4 % [30].

Among biologically active emerging contaminants, antibiotics have become a significant concern due to their increasing consumption rate and the associated threat of antibiotic resistance [31]. Hence, having a rapid system that monitors the presence of antibiotic residues can improve the management of this risk. For antibiotic detection, immunosensors are valid candidates, offering high specificity, sensitivity, and rapid response times by leveraging the selective binding between antibodies and target antibiotic molecules. For the introduction of label-free e-PADs, paper porosity is harnessed for loading antibodies and electrochemical probes onto the pads to obtain a reagent-free system. An origami configuration, shown in Fig. 3C, was designed for simultaneous detection of quinolone antibiotics (norfloxacin and enrofloxacin). The paper was chemically oxidised to facilitate antibodies immobilisation, while the electrochemical redox probes were drop-cast onto an adjacent pad. The sample was added into the antibody-loaded pad and, after incubation and washing, the origami configuration, by folding the pads, enabled the detection with the simple addition of buffer. LODs equal to 2.02 and 1.70 ng/mL were obtained, respectively, for norfloxacin and enrofloxacin, values comparable to other reported devices and significantly lower than the concentrations established by international

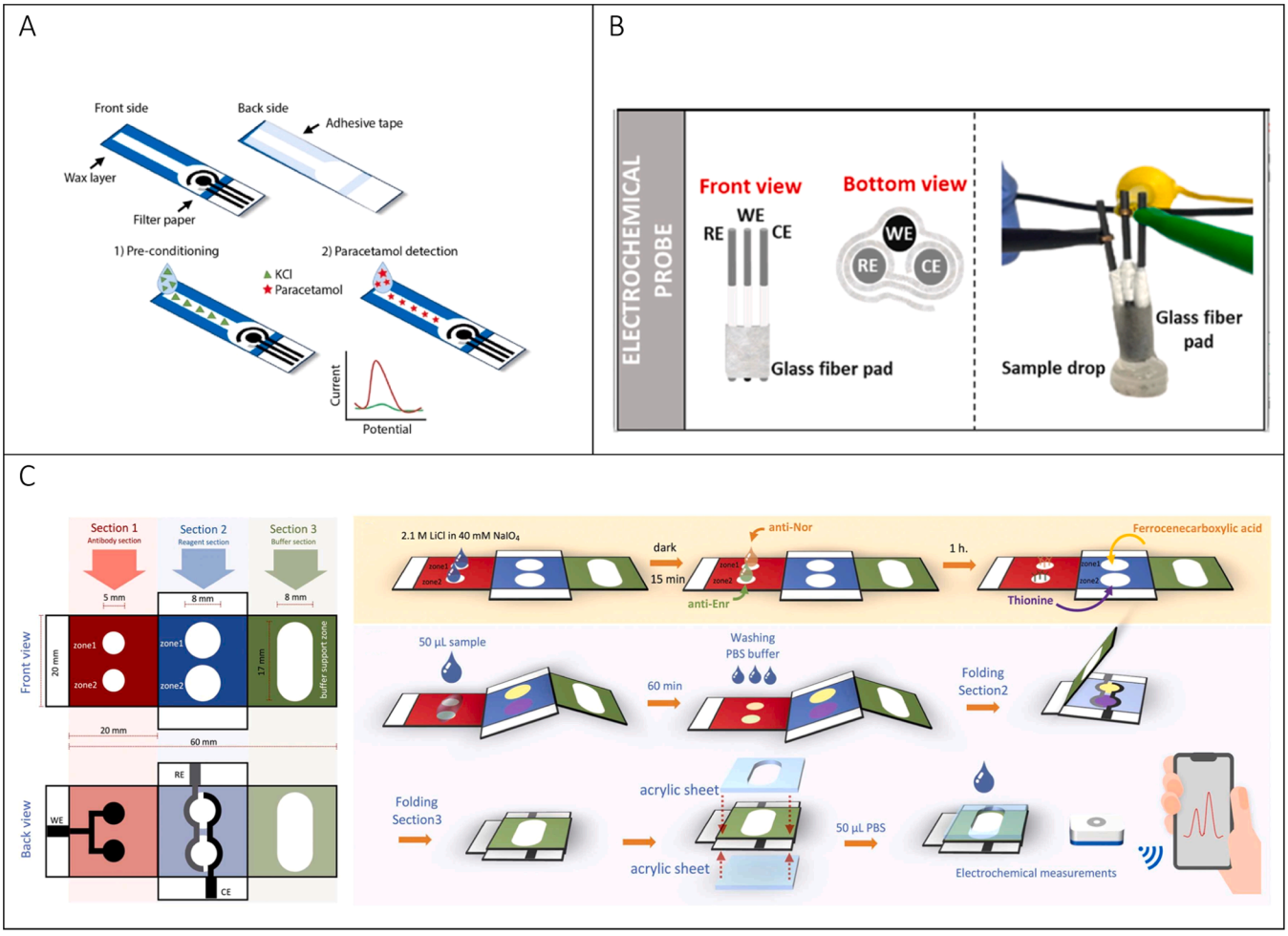

Fig. 3. A) Electrochemical paper-based electrode in 2D microfluidic configuration for the detection of paracetamol in wastewaters. Reprinted from ref [29] under the terms of the Creative Commons license CC BY. B) Field-deployable pencil lead-based electrochemical cell combined with paper for the determination of the emerging contaminants in wastewaters. Reprinted with permission from ref [30] Copyright 2025 Elsevier. C) Label-free electrochemical paper-based analytical device in origami configuration for simultaneous detection of quinolone antibiotic residues. Reprinted with permission from ref [32] Copyright 2024 Elsevier.

regulations and the detection cut-offs of the commercially available strip tests. Fish, milk, and honey samples spiked with 0.1, 0.5, 1, or 10 μg/mL of antibiotics were tested using the paper-based immunosensor, obtaining recovery values in a good agreement with those obtained by HPLC method and commercially available strip tests, with recovery in the range of 80.64 % – 106.8 % [32].

One of the main challenges in the analysis of emerging contaminants is the requirement for ultrasensitive methodologies since they are often present at trace levels in environmental waters. Therefore, by preconcentration, it is possible to obtain a lower LOD, enhancing applicability. In this regard, the porous structure of paper offers the possibility to entrap the target analyte in the paper structure, with its redissolution in a smaller volume, obtaining an easy and cost-effective preconcentration. Whatman chromatographic paper grade 1 was employed as: i) a platform for fabricating the carbon ink-based working electrode (by deposition of the ink), ii) a support for sample preconcentration (by solvent evaporation), and iii) a reservoir to place the electrodes as well as to cast the supporting electrolyte. The preconcentration helped in increasing the concentration present close to the working electrode, enhancing the signal. An increased sensitivity was obtained for diclofenac detection in two dynamic ranges, from 0.1 to 5.0 μM (with a slope of 0.85 μA/μM) and between 0.5 and 100 μM (with a slope of 0.48 μA/μM), with a LOD of 70 nM and accurate results (RSD ~ 5 %), and recoveries of 100 % and 94 % for real measurements in tap water samples spiked with 0.5 and 50 μM diclofenac [33].

Not only for sample and reagent, but the loading ability of paper can also be exploited for effective functionalisation to develop sensing conductive systems. Cardboard paper has been exploited for electrode printed using nail polish and graphite powder, providing a porous topography and surface irregularities with a large number of active sites. The sensor was used for sulphanilamide electrochemical monitoring in milk, environmental and pharmaceutical samples. The methodology showed good analytical performances with a LOD equal to 4.1 μM, wide linear range up to 100 μM, adequate precision (RSD <2.0 %), and recovery values ranging from 80 to 102 % for the spiked sample analyses. In addition, the construction of the sensor does not require laborious steps, as well as the sample preparation is minimal (simple dilution in the supporting electrolyte) [34].

Several types of paper can be exploited as electrode support, depending on the intended use. Different kinds of filter paper have demonstrated ability in sampling, loading, and treating the sample, also fostering functionalisation with active groups for immobilisation or separation. Not only for sample treatment or reagent loading, paper can be functionalised to obtain conductive sustainable substrates. Carbon paper, usually exploited in fuel cells, demonstrates high electrical conductivity, surface-to-volume ratio and porosity, facilitating the diffusion of reactants, making it an optimum candidate for sensing applications. The high porosity (80 %) and thin structure (0.19 mm) facilitate the permeability of analytes through the fibres with both sides of the paper acting as one, which significantly increases the surface area. It is worth noting that these dimensional characteristics boost the design of sensors with different shapes and sizes. In addition, it demonstrated superior electrochemical performances over glassy carbon electrodes and pencil drawn electrodes. For voltammetric analysis of ketoprofen in wastewater and fish, carbon paper demonstrated good accuracy with recoveries varying from 80.7 ± 12.1% to 88.6 ± 4.5 %, and high selectivity against other commonly present interferents and anti-inflammatory drugs, with a LOD of 0.11 μM [35].

Combining this performative paper with nanocomposites entails the detection of a lower amount of analyte, improving electroanalytical performances of the electrodes. Conductive carbon paper was used as electrode and easily functionalised using the drop-casting technique with reduced graphene oxide, covalent organic framework, and platinum nanoparticles as nanozymes to obtain selective detection of furazolidone in water coming from fish tank after raising with given amounts of medicine, to assess the part absorbed by the fish and evaluating food poisoning. The proposed sensor showed a LOD equal to 0.23 μM, higher compared to same analysis conducted using conventional electrodes (platinum wire as an auxiliary electrode, saturated calomel as a reference electrode, and glassy carbon as working electrodes), showing a LOD equal to 5 nM [36]. As paper is well exploited for its wettability, when dealing with electrochemical modification, this property limits its application since the electrode surface can be used only for one measurement and adsorption of species onto the surface passivating the working electrode. In this regard, other types of paper can be employed for guaranteeing the reusability of the device, for example, after chemical functionalisation. Much effort has been dedicated to functionalising paper's surface to enhance selectivity and sensitivity. Waterproof paper was exploited for MIPs electro polymerisation, requiring a functionalised waterproof environment for robustness and reusability of the modified electrode. Compared to biological receptors, MIPs offer superior chemical and physical stability and are produced by a simpler and more cost-effective process. The 3D porous structure of paper enables a higher loading of polymer, increasing the sensing surface area, and consequently its sensitivity, reducing rebinding time. Moreover, functionalisation of the paper with nanomaterials such as graphene and metal nanoparticles improves electron transfer and reduce limits of detection. A paper-based MIP biosensor was successfully employed for sensing hydrochlorothiazide in tap water and effluent from a wastewater treatment plant, with recovery studies ranging from 84.0 to 95.8 %. Differential pulse voltammetric measurements revealed that the paper-based electrochemical cell exhibited a 2.2-fold increase in current compared to the carbon-based screen-printed electrodes. The developed MIP-based biosensor displayed a LOD and LOQ of 1.8 and 5.7 μM, respectively. For reproducibility testing, three MIP biosensors were prepared and used on different days, yielding an RSD of 2.26 % for 50 μM hydrochlorothiazide, which confirms the reproducibility of the results of the developed biosensor. However, leading with minimal pharmaceutical contamination areas, the LOD of this device is not sufficiently low, but the sensitivity can be increased by a preconcentration step [37].

High sensitivity and low LODs remain significant challenges for the application of e-PADs in environmental monitoring and food analysis. Although progress has been made in lowering LODs, primarily by exploiting the inherent porosity of paper to enable analyte preconcentration and improved surface interactions [33,35], ultrasensitive detection capabilities are still required to meet the stringent demands of these fields. As a result, research in this area remains relatively immature and has yet to reach the level of robustness needed for widespread implementation. In addition, the typically single-use nature of paper-based devices limits their applicability for high-throughput analysis, especially when large sample volumes or repeated measurements are necessary. This limitation complicates routine testing workflows, despite the advantage that e-PADs offer for on-site and decentralised analyses, which can significantly enhance rapid screening capabilities in the field.

4. e-PADs as sustainable POCTs for precision medicine

Conventional therapeutic strategies typically adhere to a uniform model predicated on population averages, which may yield favourable outcomes in certain individuals while proving suboptimal in others. In contrast, precision medicine represents a progressive paradigm that customises preventive and therapeutic interventions by integrating interindividual variability in genomic architecture, environmental exposures, and behavioural patterns. The principal objective of precision medicine is to optimise clinical efficacy by aligning specific therapeutic modalities with the unique biological and contextual characteristics of each patient [38]. A critical domain within precision medicine involves the quantitative assessment of patient-specific pharmacokinetic profiles to facilitate real-time therapeutic modulation [39]. e-PADs are well-suited for this purpose because the paper network is able to treat

the sample, manage the fluids without any external device, and make the measurement, shifting the sample treatment and analyses from the bench to the hand-held device.

In the case of the measurement of drugs in formulation, the electrochemical transduction is preferred over the colorimetric one for the higher sensitivity. For precision medicine, the electrochemical detection is mandatory because of the complexity of the matrix, such as in the case of capillary blood.

Capillary blood as a matrix was managed by using lateral flow with a hybrid device constituted by a paper-based microfluidics and polyethylene terephthalate (PET)-based electrochemical sensor for evaluating the clearance and diffusion of lidocaine into the bloodstream [40] or by using vertical microfluidics with a whole paper-based electrochemical sensor for precision medicine in Alzheimer's disease [41]. In the lateral flow configuration, the system comprised a PET-based printed three-electrode sensor integrated with a paper-based microfluidic channel, assembled using a double-sided adhesive tape (Fig. 4A). The reference electrode was fabricated using a standalone stencil screen printer, while the working and counter electrodes were fabricated using inkjet printing and graphene ink. The paper microfluidic channel was laser-cut and aligned with a PET substrate containing the printed graphene sensor to manage the sample without any additional task for the end user. The lidocaine was electrochemically detected by square wave voltammetry after dilution of the blood sample 1:4 (v/v) with a peak at a potential close to +0.8 V, with a linear range comprised between 1 and 100 μM and under 15 s as analysis time [40].

In the case of a paper-based electrochemical sensor for precision medicine in Alzheimer's disease, we designed origami e-PADs for measuring the residual butyrylcholinesterase activity in the capillary blood, considering that some drugs (e.g. rivastigmine (EXELON®) and donepezil (ARICEPT®)) inhibit the key enzyme of nervous transmission namely acetylcholinesterase, and there is a correlation between inhibition of acetylcholinesterase in nervous transmission and butyrylcholinesterase in capillary blood [42]. The origami device was conceived in three layers: ii) the first upper layer was Vivid™ Plasma Separation membrane capable to threat 20 μL of whole blood sample diluted 1:2 v/v by harnessing the vertical microfluidics, supplying treated sample i.e. serum which contained butyrylcholinesterase ii) the second layer made of filter paper and preloaded with the enzymatic substrate to have the reaction between the enzyme present in the treated sample and its substrate obtaining thiocholine as enzymatic by-product, and iii) the third layer, which was made of an office paper-based electrode in which the working electrode surface was modified with Carbon Black/Prussian Blue nanoparticles to electrocatalyse the oxidation of thiocholine at +0.3 V applied potential. This smartphone-assisted origami e-PADs (Fig. 4B) demonstrated a linear range up to 25 μM and 30 μM, and detection limits of 0.4 μM and 0.3 μM for rivastigmine and donepezil, respectively [41].

In the case of simpler matrices, like serum and saliva, the diluted sample was added directly to the paper-based devices. In the case of serum, a three-electrochemical cell embedded in an acrylic-based device was developed for the detection of antipsychotic drug clozapine [43]. The device encompassed three grooves to host three pieces of Toray carbon paper. In the case of the reference electrode, the Toray carbon paper was successively modified with silver paste (Ag/AgCl), while for the working and counter electrodes, the Toray carbon paper did not require any additional modification (Fig. 4C). The clozapine was detected in standard solution in chronoamperometry at a fixed applied potential of + 0.320 V, obtaining a linear range of 0.5–5 μM. When tested with serum samples, the serum was diluted ten times to avoid interference from other higher concentration biomolecules. MIP-based biosensors have been recently developed to improve the sensitivity and selectivity. Haghgouei and Alizadeh developed two interesting electrochemical e-PADs for the quantification of naproxen in biological fluid samples [44,45]. The device encompasses two zones, the first section relies on the extraction zone for electrochemically controlled solid-phase microextraction and the second zone where the determination of naproxen with a potentiometric ion-selective electrode happens (Fig. 4D). Pyrrole was used as monomer and dodecylbenzene sulfonate as anion dopant to deliver a conductive paper. Successively, the conductive papers were utlised to be functionalised with naproxen imprinted polymers by using naproxen as template molecule and pyrrole as monomer. For the measurement, the injected biological sample solutions are passed through the sorbent in the chip under the control of a pump, in the extraction zone. After a positive potential was applied for the adsorption, the desorption step was performed by applying a negative potential. The solution successively flowed into the detection zone, where the potentiometric measurement was made using MIP-based paper as the working electrode and Ag/AgCl μelectrode as the reference electrode. The saliva samples were diluted 5 times and directly injected into e-PADs. This device was characterised by a linear range comprised between 4.0×10^{-7} to 1.0×10^{-2} M with a Nernstian slope equal −58.5 mV, with recovery value close to 100 % [44] demonstrating the reliability of the paper-based device.

If the application of e-PADs is largely reported in the literature for diagnosis of several diseases, the applications in precision medicine are restricted to a few examples. In this context, the most challenging is the detection of the drug in untreated capillary blood to deliver a POCT without any sample treatment, which is mandatory to reach the market.

Recently, precision medicine has been permeated by wearable devices, which have the advantage of detecting the target analyte in an untreated sweat sample. One electrochemical biosensor of note is the one developed by the Gao group, which consists of a wearable aptamer-based electrochemical biosensor for non-invasive, real-time monitoring of the female sex hormone oestradiol in sweat, for delivering personalised reproductive healthcare solutions [46]. The combination of diverse technologies including nanomaterials, i.e. gold nanoparticles and MXene, iii) electrochemistry i.e. applied external electric field to boost the transport of the released labelled biocomponent, and ii) electronics and microfluidics i.e. a smart sweat sampling and collection system allowed for a for non-invasive and personalised reproductive hormone monitoring able to identify cyclical fluctuation of oestradiol in sweat during menstrual cycles, with a relevant correlation with blood oestradiol [47]. In this overall scenario, e-PADs have the advantages of easy sweat management, but at the state of the art were mainly developed in the sports field by measuring pH, sodium ions, potassium ions, glucose, and lactate in sweat [48–52].

In the precision medicine context, the stress hormone cortisol has been recently detected using e-PAD-based wearable devices by creating a hybrid device in which the electrode is printed on a plastic support and the paper microfluidics has been harnessed to manage a low volume of the sample without the requirement of an external pump. Cheng et al. developed an origami structure which included colorimetric detection for glucose, lactate, uric acid, magnesium ions, and pH and electrochemical sensing for cortisol detection by MIP-based biosensor (Fig. 5A). The detection of cortisol with electrochemical biosensor was based on the selective affinity of cortisol for polypyrrole-based MIP, which inhibits electron transfer from the incorporated Prussian Blue redox mediator. A calibration curve was obtained over a concentration range of 1×10^{-9} M to 1×10^{-5} M, requiring only 5 μL as volume and 10-minute as incubation time [53].

We reported e-PAD-based wearable devices for cortisol detection in sweat by using i) filter paper to regulate fluid flow and reagent loading, ii) magnetic beads for competitive immunoassay, and iii) the polyester-based printed electrode modified with Carbon Black/Prussian Blue for thiocholine enzymatic byproduct detection (Fig. 5B) [54]. The assay relied on a competitive binding mechanism between free cortisol and acetylcholinesterase-labelled cortisol and started when a few μL of sweat sample wetting the paper-based microfluidic system. The end user needed to only close a substrate paper-based pad and add a drop of distilled water to carry out the measurement. The paper-based immunosensor was further integrated with a Near-Field Communication

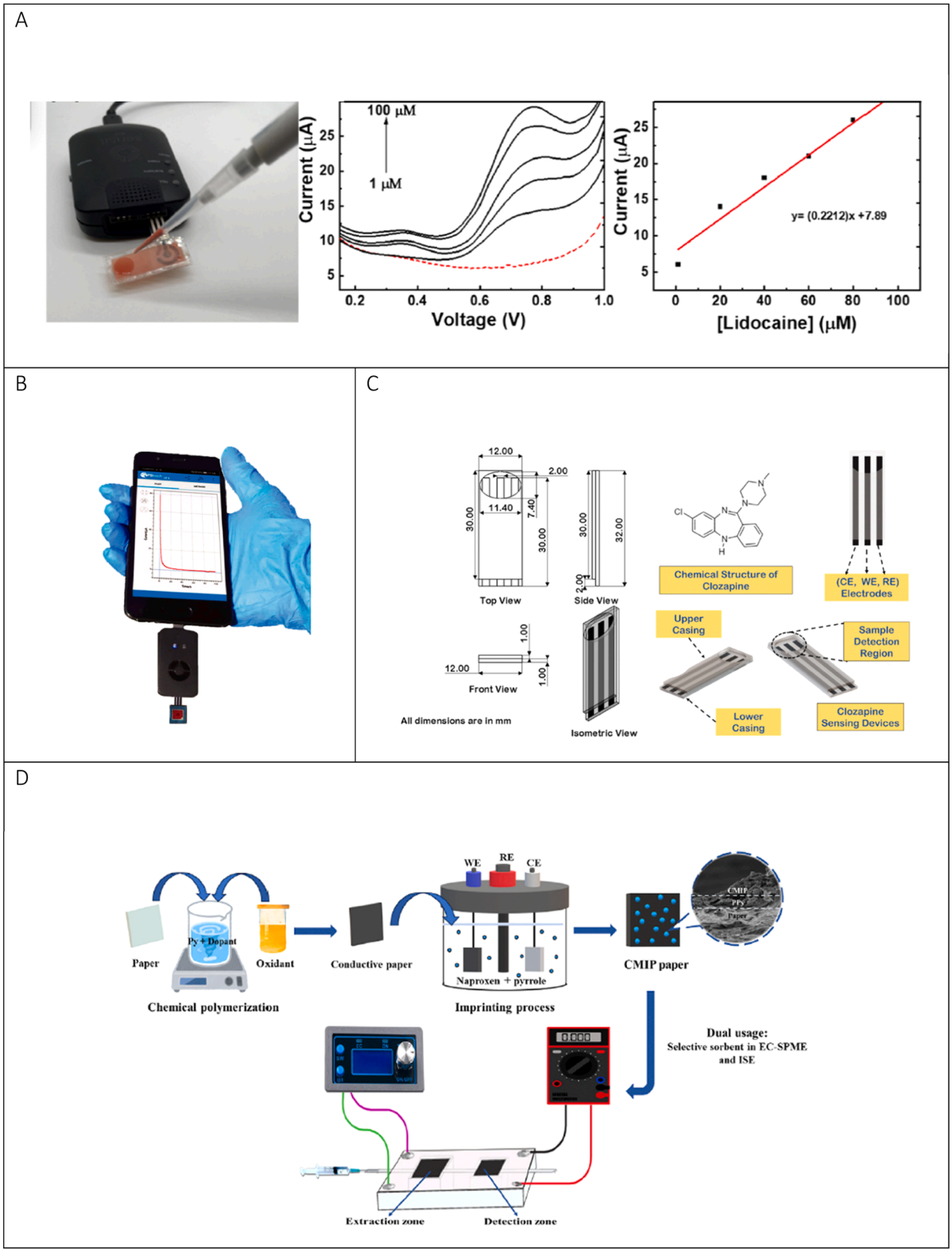

Fig. 4. A) Paper-based lateral flow microfluidics combined with a PET-based graphene printed electrochemical sensor for lidocaine in blood. Reprinted with permission from ref [40] Copyright 2022 Elsevier. B) Origami paper-based device for precision medicine in Alzheimer's disease patients by measuring residual butyrylcholinesterase activity in capillary blood. Reprinted with permission from ref [41] Copyright 2020 Elsevier. C) Paper-based device based on Toray carbon paper for the detection of Clozapine in serum. Reprinted with permission from ref [43] Copyright 2023 Elsevier. D) MIP-based electrochemical paper-based device for extraction and potentiometric detection of naproxen in saliva. Reprinted with permission from ref [43] Copyright 2024 Elsevier.

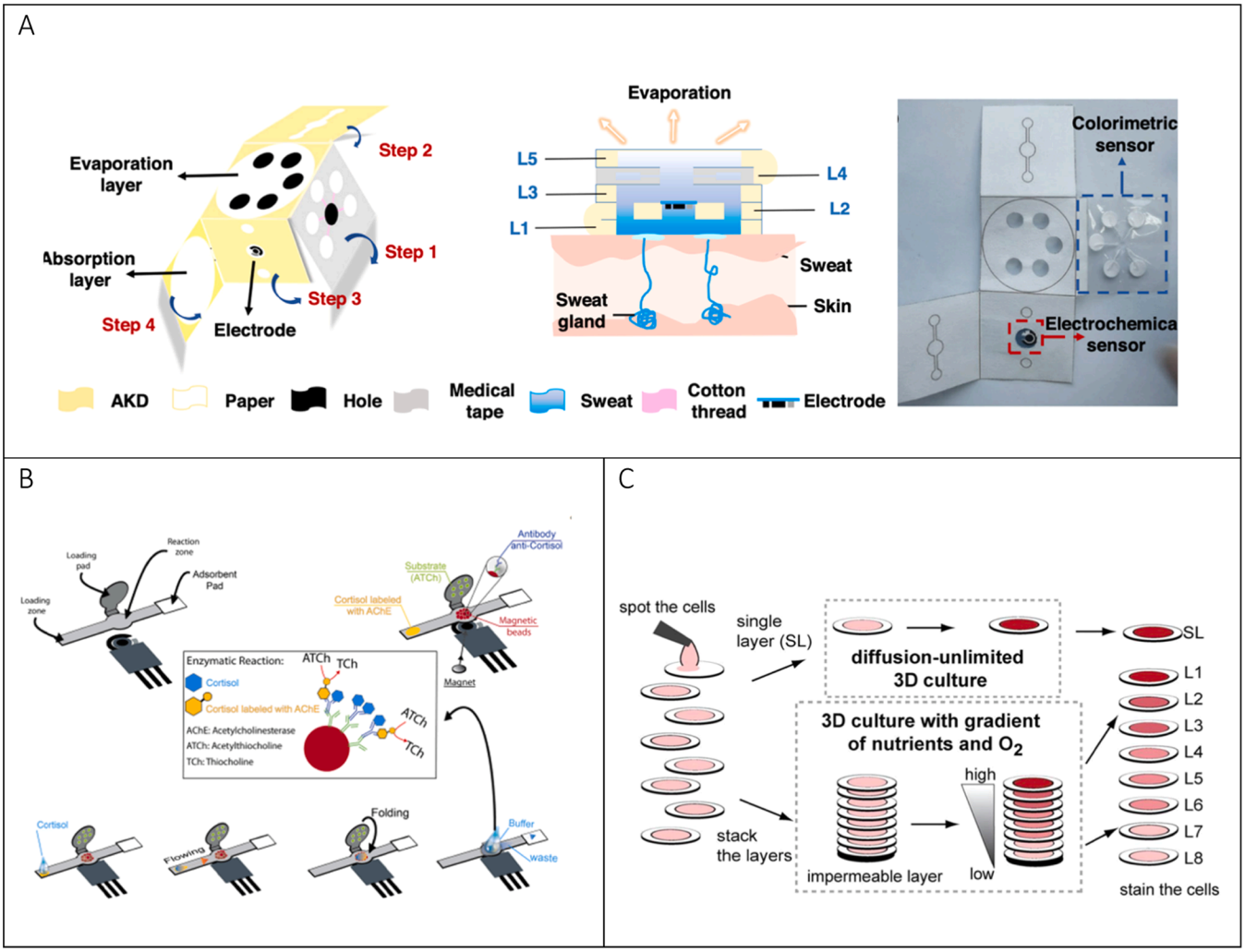

Fig. 5. A) MIP-based amperometric biosensor for cortisol detection in sweat. Reprinted from ref [53] under the terms of the Creative Commons license CC BY. B) Amperometric competitive immunosensor paper-based for the detection of cortisol in sweat. Reprinted with permission from ref [54] Copyright 2023 Elsevier. C) Paper-supported 3D cell culture for tissue-based bioassays. Reprinted with permission from ref [61].

(NFC) wireless module delivered flexible wearable analytical device for on-body cortisol monitoring with a dynamic range of 10 to 140 ng/mL. The applications reported were made during sports activity, but the combination with an iontophoresis sweat sampling system will allow for a non-invasive cortisol detection, which is a key POCT in the case of several drug administrations, such as hydrocortisone, prednisone, and dexamethasone, opening the way for the wearable e-PADs for precision medicine.

Research in POCT using electrochemical e-PADs is paving the way for the development of minimally or non-invasive, user-friendly, and rapid screening tools for patient-specific treatment monitoring. These devices can complement or even reduce the need for traditional, time-consuming, and expensive laboratory-based analyses offering on-site analyses with simpler instrumentation and protocols. However, a key challenge in advancing these technologies is ensuring reliable performance in complex biological matrices, while avoiding the need for extensive sample preparation or handling by the end-user. To address this, e-PADs must enable accurate analysis using small sample volumes, supporting minimally or non-invasive testing and potentially allowing direct integration into pharmaceutical packaging alongside the drug. Wearable devices represent an emerging frontier in POCT, offering continuous, real-time health monitoring with the potential for personalised data collection and early detection of clinical changes. Their integration with e-PADs could provide seamless monitoring of biomarkers in several biofluids such as serum [43–45], sweat [46, 48–54], and saliva [44]. Notably, by leveraging different types of paper and paper-based membranes, e-PADs have successfully utilised one of the most complex yet accessible biological matrices, namely capillary blood, for a wide range of POCT applications [40,41]. This advancement opens promising opportunities for real-world use and market-ready implementation, particularly when combined with wearable formats for decentralised and personalised healthcare.

5. e-PADs and Organ-on-a-Chip: the next future for precision medicine

Within drug development scene, different in vitro models are used to determine the adsorption, distribution, metabolism, excretion, and toxicity properties before conducting experiments in animals and humans. The in vitro parameters these models examine exemplify the entire body functions and are used as a starting point for in vivo measurements and evaluation [55]. This implies that an effective translation of results from in vitro to in vivo models rely on proper modelling of the physiological conditions. The choice of the most suitable model considers costs, complexity, ethics, experimental accessibility, and proper mimicry of the process of interest. The simplest model is the 2D monolayer culture, where cells isolated from a living tissue adhere to the surface of a treated culture layer, supplied by an appropriate cell culture

medium, the "blood surrogate", which contains all nutrients, growth and attachment factors, under carefully controlled physicochemical conditions. These 2D models are experimentally accessible both in terms of manipulation in experimental set-up and analysis, underlying the design of new models. Indeed, monolayer cultures sacrifice many aspects of in vivo microenvironments, including extracellular matrix and dynamic signalling [56]. Here lies the necessity of three-dimensional cell culture models. As reported by Low et al. [57], worldwide investment has enabled the development of several 3D tissue models, from simple cellular aggregates to tissue explants, and organoids. These 3D models can better mimic the three-dimensional architecture of human organs and tissues, providing an environment both chemically and physically suitable for cell differentiation, but still sacrifice some aspects of in vivo relevance to facilitate experimentation [58]. In this context, OoC technology could be a bridge between simple cell cultures and complex human architecture, providing optimized model to mimic human physiology. OoC gathers different scientific areas, merging recent technological achievements including induced pluripotent stem cells (iPS cells), co-cultures and 3D models, genome editing, 3D printing, sensing, microfluidics, and microfabrication engineering [57].

OoC research emerged in the early 2000s, in 2004 it has been reported the first work on a multi-OoC system, with a three-chamber (lung-liver-other) microscale device and integrated oxygen sensor, paving the way for including sensing to have a complete system for real-time testing [59]. Following these early concepts, in 2010, one of the pioneering works on lung OoC was published, a breathing-lung-on-a-chip responsive to bacteria and inflammatory cytokines and external mechanical stimuli [60]. Since these publications, research in OoC has grown exponentially, gaining interest with new challenges and opportunities in multiple scientific fields, merging expertise to fully realise the promising applications for the study of disease phenotypes and drug responses for personalised medicine.

To design sustainable OoC, paper represents a valid microfluidic substrate because of a variety of factors, including high flexibility, low cost, biocompatibility, commercial availability, ease of functionalisation, and degradability or incineration possibility to avoid complex handling of biologically risky or toxic material [55]. Furthermore, paper is a suitable material for cell seeding, as demonstrated by Derda and colleagues [61]. As depicted in Fig. 5C, stacking layers of fibre-supported hydrogels with each layer composed of chromatography paper impregnated with a hydrogel containing living cells, creating structured and heterogeneous 3D cultures both for in vitro and in vivo studies. In this overall scenario, the combination of e-PADs and paper-based cell cultures ~~is~~ represents a smart approach for the development of the next generation of sustainable and versatile OoCs [62], considering the advantages to work with a biocompatible materials for cells, to easily manage the fluid without any external instrument avoid the bubble problem, and to sense the cells byproducts in a simple, sensitive, and accurate manner.

The choice of materials based on their physicochemical properties is a crucial aspect in the development of 3D cell cultures, as it directly influences cell differentiation, viability, and the ability to mimic tissues and organs, and of the overall OoC device, which must integrate key features such as controlled microfluidics, efficient nutrient and waste exchange, mechanical stability, and a physiologically relevant microenvironment to ensure proper functionality. Paper, with its versatility, ease of functionalisation, and manipulability, presents both a challenge and a powerful opportunity for full exploration in this context, for example by leveraging its passive pumping capabilities to eliminate the need for external pumps and reduce bubble formation that often compromise device functionality. Integrating e-PADs into these systems opens new possibilities for the online monitoring of relevant biomarkers for cell viability monitoring and drug testing assessment. Since e-PADs must operate within the complex matrix of cell culture media, advances in POCT can be adapted to support their integration, paving the way for compact, all-in-one devices. The overarching challenge remains the development of clinically and physiologically relevant models that are comparable to traditional cultures, while also incorporating robust and sensitive (bio)sensors.

6. Conclusions

In the last decade, electrochemical paper-based analytical devices have been developed and applied in several fields, demonstrating the versatility of these ecodesigned analytical tools. The different multifaceted properties have been harnessed to deliver reagent-free, easy-to-carry-out, and accurate measurements. For drug analyses, the effort in recent years has been dedicated to designing electrochemical paper-based analytical devices to face the ongoing requirements in pharmaceutical fields, such as devices for sustainable analyses for quality control in pharmaceutical industries. Furthermore, the recent updating work related to European water legislation and the recent Food Contaminants Regulation (EU) No 2023/915 has identified drug residues as emerging contaminants, enlarging the measurements of the drugs to the environmental and agrifood sectors. The precision medicine vision has fostered easy-to-use, accurate, and robust point-of-care testing for drug self-administration at home, in which electrochemical paper-based analytical devices are the ideal candidates, considering the ease of use, accuracy, reagent-free measurement, cost-effectiveness, and environmentally friendly aspect. Furthermore, in the route of precision medicine, the future will encompass electrochemical paper-based analytical devices combined with Organ-on-a-Chip, conveying unprecedented, sustainable, and smart Organ-on-a-Chip devices, further extending the application of these devices in the growing field, such as drug studies and analyses.

CRediT authorship contribution statement

Laura Belcastro: Writing – original draft. **Fabiana Arduini:** Writing – original draft, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.electacta.2025.147084.

Data availability

No data was used for the research described in the article.

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