



Paper-based 2D configuration for the electrochemical and facile detection of paracetamol in wastewaters

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ABSTRACT

Since 2020, human pharmaceuticals were included in the list of emerging contaminants from the UNESCO and their detection and elimination were incorporated in the 2030 Agenda for Sustainable Development Goal Targets. Among these, analgesic and antipyretic drugs are the most widely used drugs worldwide and, despite their advantages, unused or expired pharmaceuticals are a potential source of water pollution. Paracetamol is one of the most common drugs used for analgesic and antipyretic purposes and has been found to have a much higher concentration in water streams in many European countries. Considering that, an all-in-one paper-based 2 dimensional (2D) fluidic configuration, able to detect paracetamol, was developed in order to deal with environmental matrices without complex/expensive analytical procedures. An ad-hoc paper-based testing area, coupled with a channel was designed and wax-printed onto a porous filter paper. Successively three electrodes were screen-printed, and the whole system was applied for the detection of paracetamol in wastewaters (prior and after the filtration system) without pretreating the sample. In order to detect paracetamol with the easiest approach, the configuration of the paper-based device was optimized in terms of type of substrate used for printing, microfluidic paper strip length/width and combination of them in an integrated architecture, capable to detect paracetamol in the matrices tested in few seconds with a detection limit down to micromolar range, ca. 1 μM . The integrated device shown great promise for simple, fast, sensitive, and sustainable detection of paracetamol in its role of emerging contaminant, especially in the environmental matrices.

1. Introduction

In recent years, environmental science has faced increasing challenges from emerging contaminants, diverse substances impacting ecosystems and human health [1–3]. The term "emerging contaminants" includes pharmaceuticals, personal care products, pesticides, and industrial chemicals [4–7]. These substances often evade traditional water treatment, and due to recent recognition, their full environmental and health implications are not fully understood [8–10].

Urban and industrial wastewater serves as a crucial case study for managing substances from human activities, industrial processes, and agriculture, raising concerns about the effectiveness of current water monitoring and treatment [4,6,9,11]. Monitoring and research efforts

aid regulatory authorities in informed decision-making about managing potential risks [12,13]. Pharmaceuticals have emerged as contaminants, infiltrating aquatic ecosystems and challenging traditional water quality concepts. Despite being designed to improve human well-being, pharmaceuticals contribute to a new environmental challenge. Improper disposal, incomplete metabolism, and inefficient removal during water treatment lead to pharmaceutical compounds entering wastewater [14–16]. Conventional water treatment struggles to effectively remove pharmaceuticals, posing concerns for long-term impacts on wastewater quality and habitats. Since 2020, UNESCO listed human pharmaceuticals as emerging contaminants, addressing their detection and elimination in Goal 6 of the 2030 Agenda for Sustainable Development [14,17–19].

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Paracetamol, or acetaminophen, is available over-the-counter and widely used as analgesic globally, known for relieving pain and reducing fever [20].

The presence of pharmaceuticals in the environment, including paracetamol, results from incomplete removal during wastewater treatment and improper disposal of medications; consequently, these compounds may persist in treated effluent, entering surface waters. Based on literature, the concentration of paracetamol in natural waters worldwide varies significantly due to factors such as local usage patterns, wastewater treatment efficiency, and environmental conditions. Concentrations ranging from ca. 1–100 $\mu\text{g/L}$ were found in wastewaters from Korea, Spain, and the Western Balkan, raising concerns about potential ecological consequences for aquatic organisms, long-term exposure, development of resistance, and human exposure through water consumption [21–23]. However, many countries have no specific regulation for the discharge limit of paracetamol, in particular close to the pharmaceutical factories [24].

Enhancements in wastewater treatment, public awareness on medication disposal, and advances in analytical techniques can improve the monitoring of pharmaceutical contaminants in water sources. Analyzing water samples for specific pharmaceutical compounds is a common approach in monitoring. The choice of analytical method depends on factors like the targeted pharmaceuticals, required sensitivity, and the sample type. These include titrimetric [25], chemiluminescent [26], high performance-liquid chromatography [27], liquid chromatography [28], liquid chromatography-mass spectroscopy [29], capillary electrophoresis [30], UV-Vis spectrometry [31], flow and batch injection analysis [32,33]. Commonly, these techniques are costly, complicated, time taking process and operated by highly skilled technicians. Incidentally, electrochemical methods provide a simple, rapid, selective detection with low-cost of systems and eco-friendly. Electrochemical sensors and biosensors are promising tools for in situ monitoring of paracetamol in water systems like wastewater [34]. These devices offer advantages such as real-time monitoring, high sensitivity, and the potential for miniaturization, making them suitable for on-site applications [35–38]. Different approaches were reported for paracetamol electrochemical sensing in several matrices thanks to its electroactivity at solid electrodes. P. A. Raymundo-Pereira et al., reported an electrochemical method using carbon SPEs pretreated with sulfuric acid solution, able to detect simultaneously the hydroquinone, paracetamol and estradiol in tap water in range between 0.1 and 0.8 μM [38]. Moreover, in the work of N. Karikalán et al., the electrochemical properties of paracetamol at the bare screen printed carbon electrode (BSPCE) were investigated and its electrochemistry was studied in various pHs, confirming that the mechanism of the electro-oxidation of paracetamol was not stable in strong acidic and strong alkaline media, while it is stable in intermediate pHs due to its dimerization [34,39]. Wan-Yu Su et al., reported electrocatalytic oxidation of paracetamol at screen-printed electrode (SPE) modified with electrogenerated poly(3,4-ethylenedioxythiophene) (PEDOT) film, obtaining a limit of detection of 1.39 μM [40]. These examples prove that advancements in analytical techniques continue to contribute to the development of more sensitive, selective, and efficient methods for monitoring pharmaceuticals as emerging contaminants in the environment. On the other hand, few examples are reported about the use of sustainable and green substrates for producing electrochemical sensors able to detect paracetamol in environmental matrices. Among these materials, paper is a valid alternative to the classic polyester because it is biodegradable, biocompatible, besides being convenient and easy to use [41,42]. Utilizing paper-based substrates, in particular when filter paper is used for manufacturing analytical strips, allow the preloading and preconcentration of reagents into the device due to its porous nature; moreover, the integration with paper allows to collect and filter real samples in order to avoid further treatments of the samples. For example, Oliveira et al., recently described a disposable electrochemical paper-based analytical device (ePAD), using a novel formulation of conductive ink that combines graphite powder, polyester

resin, and acetone, applied, as a proof of concept, for paracetamol (PAR) sensing. They achieved a LOD of 0.2 μM and applied their system to detect paracetamol in pharmaceutical tablets and in plasma samples, obtaining good correlation with traditional analytical methods [43]. In addition, paracetamol was also electrochemically detected by Dias et al., who optimized a system, based on vegetal paper, used as substrates for pencil drawing electrodes, for detecting metamizole, paracetamol and midazolam maleate in whiskey, obtaining a LOD equal to 298 μM [44]. Other examples of electrochemical paper-based devices for paracetamol detection in various pharmaceutical, biological, and food matrices, were reported in literature, even if none of them focus on the detection of paracetamol environmental matrices, including wastewaters [43–49]. In the present work, a novel electrochemical device, embedded into a 2D paper-based architecture for measuring paracetamol in wastewaters was reported. This is the first report which considers the electrochemical detection of paracetamol as an emerging pollutant. The adoption of porous paper-based channel, in strict combination with screen-printed electrode, provided an all-in-one platform which was capable to store the reagents necessary for the assay and to lower the matrix effect usually observed with traditional electrochemical measurements. Thanks to the collaboration with Acea Infrastructure, one of the Italian leading companies for the water management and remediation, the proposed device was characterized and applied to real wastewaters, prior and after the process of remediation, demonstrating the effect of whole sensing platform. The developed device allowed a detection limit equal to 0.7 micromolar, without the addition of any reagents because they were previously loaded on the channel, and also it highlighted an active role in limiting the interferences due to these real and complex matrices.

2. Experimental section

2.1. Materials and apparatus

Paracetamol, PBS tablets (140 mM NaCl, 10 mM phosphate buffer, 3 mM KCl), and potassium chloride were purchased from Sigma-Aldrich (St. Louis, MO, USA). All solutions were prepared in Milli-Q water. 0.1 M potassium chloride was employed as supporting electrolyte and all measurements were performed at room temperature. Incoming and outgoing water from drinking water treatment plants were purchased by Acea Infrastructure (Rome, Italy). Conductive inks (Ag/AgCl and graphite) were acquired from Acheson (Italy). Whatman No.1 chromatography paper was purchased from Merck (Italy). Scotch adhesive tape was purchased in the local market. Adobe Illustrator was used to design the wax pattern of both the testing area of the paper-based screen-printed electrode and paper-based channel. A solid ink printer, namely, ColorQube 8580 from Xerox (USA) was used to print the hydrophobic layer of wax onto paper-based substrates. All the electrochemical measurements were carried out with the use of a portable potentiostat, EmStat3 (PalmSens, The Netherlands), connected to a laptop. Currents were recorded and displayed on a laptop by using the software PStace 5.9.

2.2. Fully printed paper-based platform

The final pattern of the paper-based device was drawn on Adobe Illustrator and wax-printed onto a Whatman No. 1 chromatographic paper. Then, waxed paper was cured in an oven at 100 °C for 1 min, allowing the wax to diffuse through the paper, producing a hydrophobic layer all around the hydrophilic testing area. This step is very important to define the testing area and confine the solution in the delimited electrochemical cell area, avoiding its diffusion toward the electrical contacts and affecting the readout [50]. After that, the three-electrode system was manually screen-printed onto the hydrophilic zone using a spatula and two masks, first one for the Ag/AgCl ink (ElectroDag 477 SS), that was used to print the connections and the reference electrode,

and the other one for the carbon ink (Electrodag 421), that was used to print the working and counter electrodes. After each printing step, the screen-printed electrodes (SPEs) were cured at 60 °C for 30 min. Thermally curing was necessary to make the printed ink stable for electrochemical measurements [50]. A video illustrating the fabrication of paper-based 2D configuration was including in the SI. The diameter of the working electrode is 0.4 cm, the whole three-electrode system is ca. 2.5 cm (length) and 1 cm (width). Subsequently, the backside of the printing surface was covered with adhesive tape (without covering electrical connections) to prevent the solution leaking out. The complete platform consisted of a hydrophilic rectangular zone (microfluidic channel, 2.6 cm (length) x 0.2 cm (width)), connected to a hydrophilic semicircle zone (electrochemical cell, 1 cm diameter) where the electrodes were screen-printed as reported in the Fig. 1.

2.3. Paracetamol determination

Paracetamol was electrochemically oxidized to N-acetyl-p-benzoquinone-imine (NAPQI) within a quasi-reversible two-electron process at the electrode surface [34,39]. The electroanalytical technique adopted to measure paracetamol was the differential pulse voltammetry (DPV). In particular, 0.1 M potassium chloride was used as working solution and the technique parameters were optimized as follows: the measurement was carried out in a range potential from 0.0 V to 0.8 V, with an E step of 0.02 V, E pulse of 0.2 V, t pulse of 0.02 s and scan rate of 0.05 V/s. The final procedure to detect paracetamol within the 2D paper-based devices consisted in: 1) pre-load the channel with a solution of potassium chloride and let dry, 2) adding the sample containing paracetamol at the edge of the strip, and finally 3) waiting 1 min in order to let the sample re-dissolve KCl, mixing and reaching the working electrode surface to perform the measurement. The device was single-use, one electrode provided the result for one measurement.

3. Results and discussion

3.1. Optimization of the experimental set up

The first step of the optimization was focused on the selection of the

substrate for printing the carbon screen-printed electrodes. The substrates tested were polyester and chromatographic paper as reported in Fig. 2.

As shown Figs. 2A and 2C the efficiency of the two substrates was evaluated for increasing levels of paracetamol in a range from 0 to 100 μ M, obtaining a good linearity for both the substrate described by the following equations: $y = 0.23x - 0.29$ ($r^2=0.99$) and $y = 0.12x - 0.22$ ($r^2=0.99$) for polyester and chromatographic paper, respectively, where the y represents the anodic current in microampere and x represents the concentration of paracetamol expressed in micromolar. The sensitivity resulted higher using the polyester substrate because in this case the solution was in direct contact with the electrode area, while when paper was used the solution needed to diffuse the porous structure of paper prior to arrive the electrode: as observed in prior study, this might affect the sensitivity of detection [51]. However, we proceeded with paper-based substrate because of the final goal to have an all-in-one and more sustainable platform. Prior to realize the fully integrated device, two other configurations were characterized, e.g., polyester-based SPE combined with an external paper-based channel, and a fully paper-based SPE and channel, as shown in Figs. 2B and 2D. What is should be noted is that when the polyester was coupled to paper-based channel its sensitivity decreased, while the fully paper-based device still retained the initial sensitivity towards paracetamol. Whatman No. 1 chromatography paper was chosen in agreement with the satisfactory output obtained in previous works: Whatman No. 1 filter paper was tested several times to handle complex matrices and block gross impurities (lowering electrode fouling) and for pre-loading reagents [41,51,35]. Herein, the construction of the whole setup on paper, i.e. the three-electrode configuration and the channel, represented the best experimental condition considering both the flow rate and the interaction with the printed electrodes onto the porous substrate [52]. In addition to the analytical performance, the Whatman No.1 paper is widely available, low cost (it should be considered a 60 cm x 60 cm sheet costs ca. 2 Euro (Merck), and each of the developed device is ca. 2.5 cm x 1.5 cm) and easily adaptable with the wax printer. The choice of the voltammetric technique to be used to achieve a sensitive paracetamol detection and the optimization of the DPV electrochemical parameters were shown in Figure S1, S2 and S3 of the Supporting Info (SI). Pulse voltammetric techniques have been

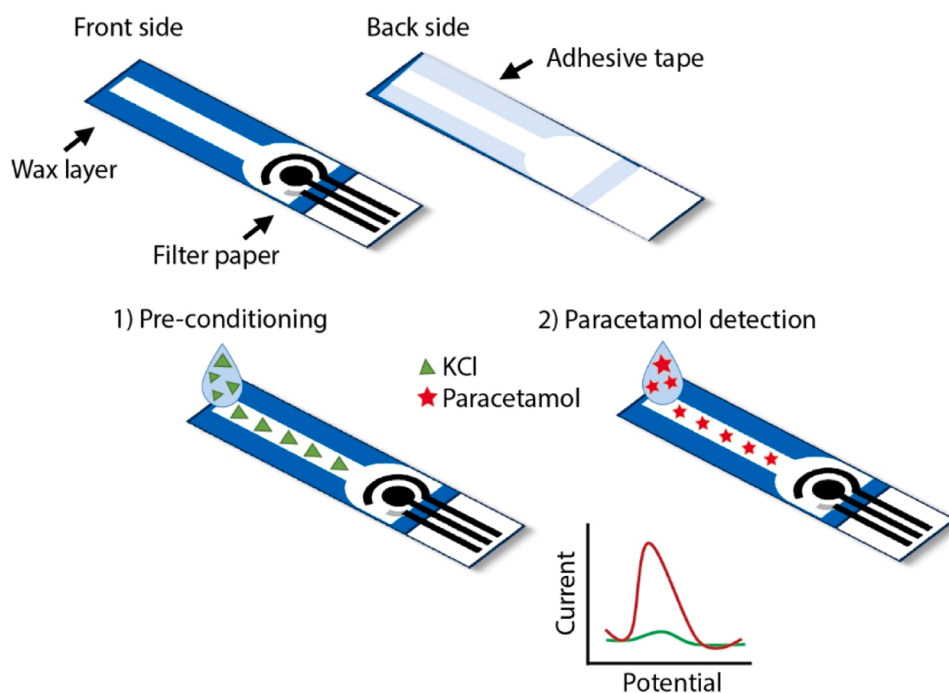


Fig. 1. Configuration of the paper-based 2D configuration for the electrochemical detection of paracetamol.

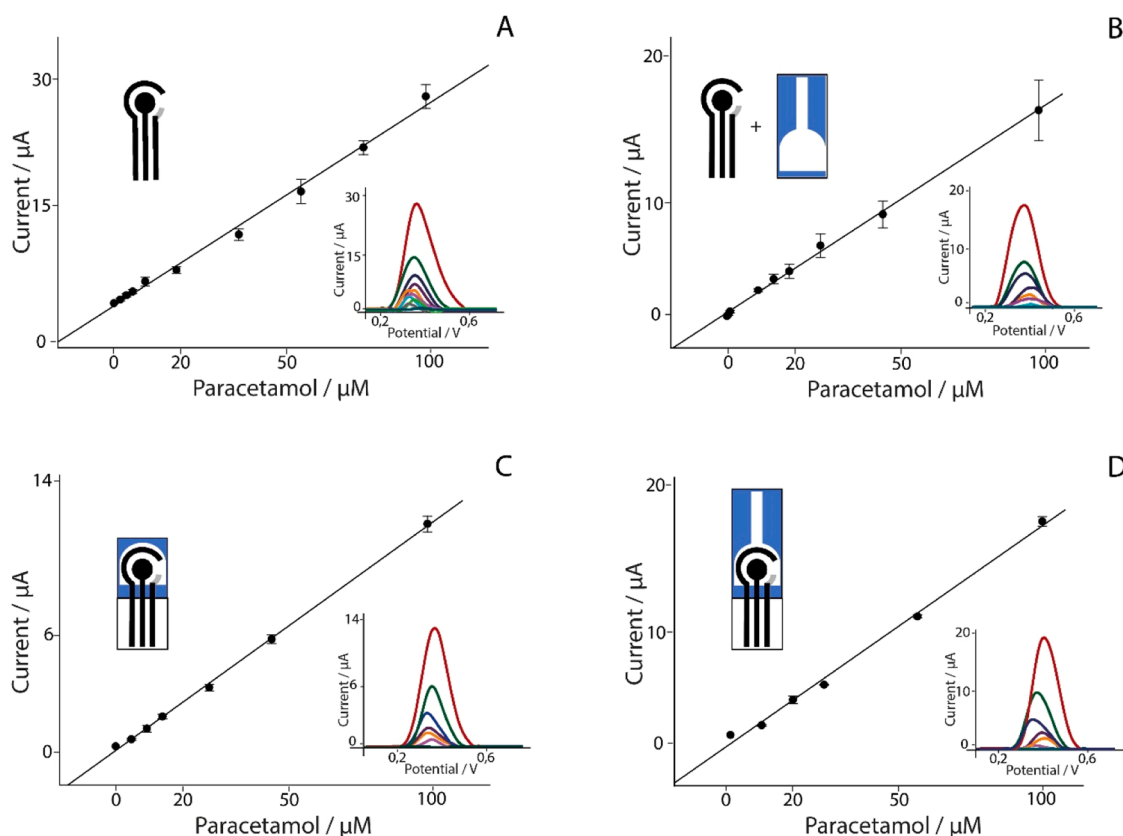


Fig. 2. Choice of the substrate evaluated at increasing concentration of paracetamol (0–100 μM) on A) polyester SPE, B) polyester SPE + filter paper strip, C) filter paper SPE, D) filter paper SPE + filter paper strip ($n = 3$). Experimental DPV parameters: E begin: 0.0 V, E end: 0.8 V, E step: 0.02 V, E pulse: 0.2 V, t pulse: 0.02 s, Scan rate: 0.05 V/s.

widely used because of their advantageous features, such as low detection limit, minimization of capacitive current and reduction of background currents by sampling the current immediately before the potential change [53].

Once the effectiveness of the obtained configuration in detecting paracetamol was satisfactory, we tried to improve our system evaluating different parameters such as the length of the channels, the run time of the solution within the channel and the working volume of solution to be placed on the edge of the channel. As shown in Fig. 3, different channel lengths were evaluated, namely 2.6, 4.8 and 6.0 cm.

As can be observed, the shortest strip gave the best results in terms of linearity and repeatability ($n = 3$), even if the length did not affect the sensitivity significantly. Using the chosen configuration, both the run time (Fig. 3D) and drop volume (Fig. 3E) were evaluated. With regard to the run time, in a range comprised between 1 and 5 min, 1 min gave the highest signal, and this was combined with the choice of a drop volume of 50 μL of solution to perform the measurements.

3.2. Analytical performance

Subsequently to the optimization of the experimental parameters, the fully printed paper-based device was tested for determination of paracetamol within the 0–50 μM range in 0.1 M KCl standard solution as reported in following Fig. 4.

As shown in Fig. 4, a linear correlation was obtained between the height of the current peaks and the concentration of paracetamol. The relationship was described by the following equation, $y = 0.14x - 0.05$, $r^2 = 0.99$, and each point on the curve was the result of three replicates using different electrodes. The detection limit, calculated as $3\sigma_B/\text{slope}$ (σ_B represents the standard deviation calculated for blank measurements, slope is the slope of the calibration curve), was calculated equal

to 0.7 μM and the limit of quantification resulted equal to ca. 2.1 μM, with a repeatability calculated as the relative standard deviation (RSD %) of ca. 7 %.

3.3. Application to real samples analysis

The analytical applicability and efficacy of the final device was demonstrated by applying it to the determination of paracetamol in wastewater samples. More specifically, the integrated system was tested firstly at known concentrations of paracetamol in incoming and outgoing water, from drinking water treatment plants purchased by Acea Group. The samples were spiked with different amount of paracetamol solution in order to evaluate both the linearity of the method and the effects of the matrices. A potential issue was given by the presence of many interferences species which can give an important matrix effect of suppression of the signal (and they can also interfere with SPE). The incoming and outgoing samples, without any kind of pretreatment, were drop cast at the edge of the paper-based channel as above described. Briefly, a chromatographic paper-based substrate was used to load all reagents together: the wastewater sample spiked with wide levels of paracetamol (0–50 μM) was added on the paper-based strip and, after 1 min, measurement was performed with the use of the optimized parameters, as reported in Fig. 5.

As shown in Figs. 5A and 5B, a good linearity was obtained both for incoming and outgoing wastewaters. It should be noted a good agreement between them, and a similar slope if compared with the results that have been obtained in standard solution. The relationship was described by the following equations, $y = 0.18x - 0.66$, $r^2 = 0.97$ for the incoming water and $y = 0.17x + 0.16$, $r^2 = 0.98$ for the outgoing. The detection limit resulted equal to ca. 1.5 and 1.3 μM for incoming and outgoing wastewaters, respectively, confirming the good efficacy of this kind of

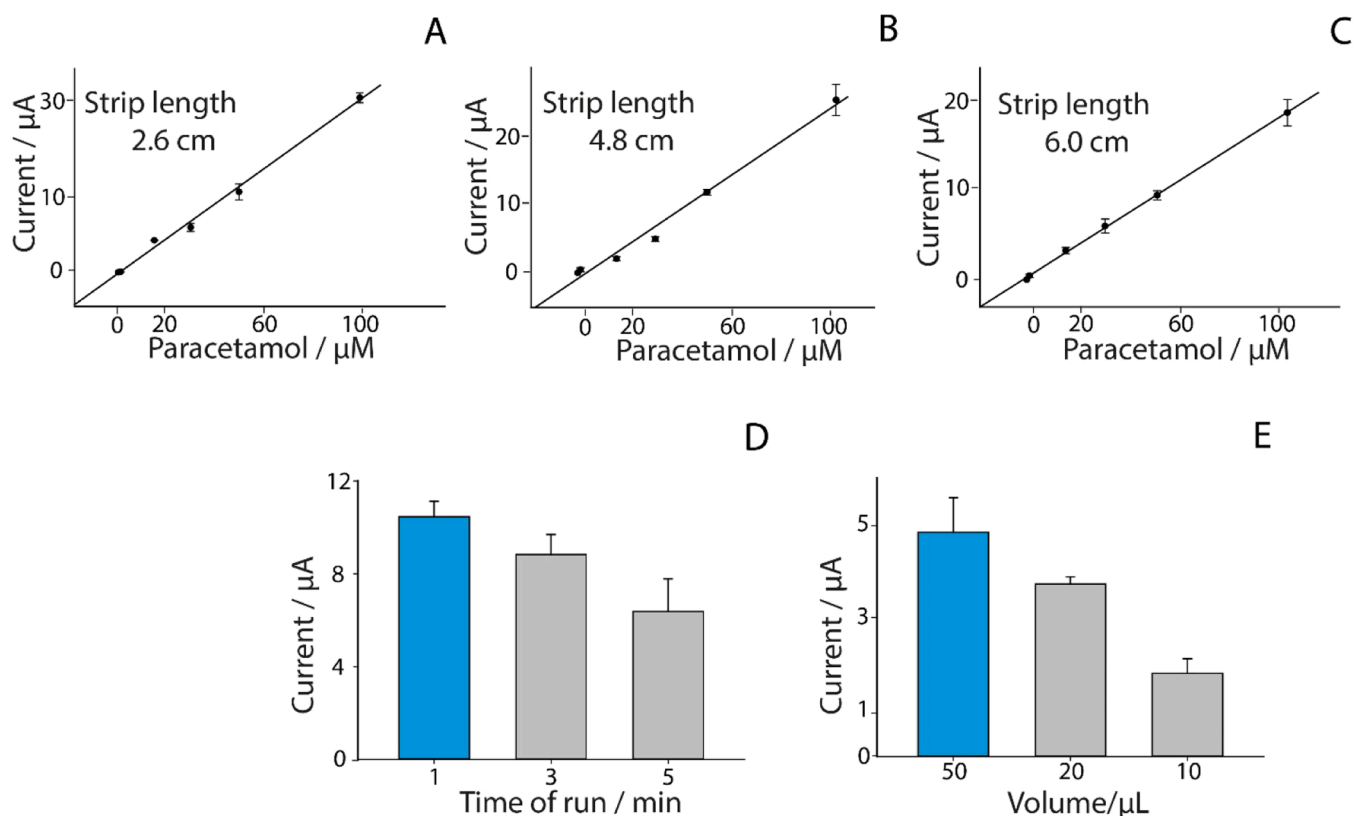


Fig. 3. Optimization of the filter paper strip length: A) 2.6 cm, B) 4.8 cm and C) 6.0 cm, D) Optimization of the time of run of the drop on the filter paper strip tested at 1, 3, 5 min in presence of 30 μM of paracetamol; E) Optimization of the volume of paracetamol solution to be placed onto the filter paper strip tested at 10, 20 and 50 μL in presence of 30 μM of paracetamol.

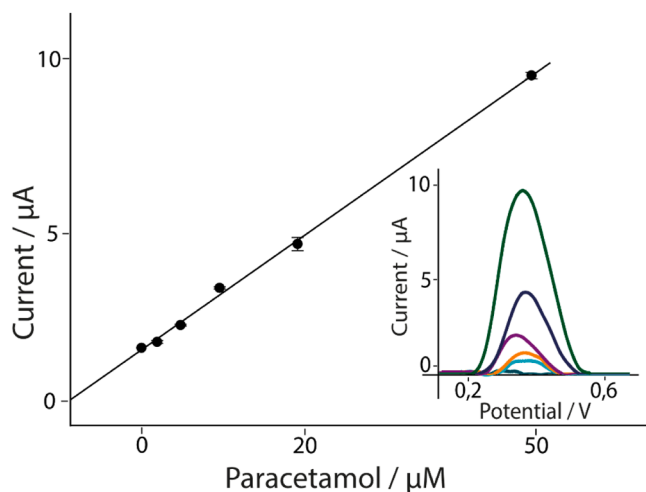


Fig. 4. Calibration curve from 0 to 50 μM of paracetamol in 0.1 M KCl, using the fully paper-based platform. Inset i: recorded DPV in absence and in presence of 2.5, 5, 10, 20 and 50 μM of paracetamol ($n = 3$). Experimental parameters: E begin: 0.0 V, E end: 0.8 V, E step: 0.02 V, E pulse: 0.2 V, t pulse: 0.02 s, Scan rate: 0.05 V/s.

architecture to handle complex environmental matrices such as wastewater, without a prior filtering of the sample because this step was already included in the configuration of the device. The effect of the paper-based channel toward the complex matrix should also be considered: if the wastewater was applied directly to the screen-printed electrode, either polyester or paper-based, a high signal due to the interfering species occurred, whereas if the paper-based channel was

used, this was effective with a lowering of the observed anodic peaks (Figure S4, Supporting Information).

Consequently, to improve the easiness of the system, exploiting the advantage of paper porosity to loads reagents, the potassium chloride was pre-loaded on the channel prior to analyze the solution. As shown in Fig. 6, three different experimental setup were taken into account, namely:

- Paracetamol in 0.1 M KCl solution
- Pre-conditioning of the strip with 1 M KCl solution, get dried and load of the paracetamol sample
- Paracetamol in ultrapure water solution

As shown in Fig. 6, the pre-loading of 1 M KCl solution on the filter paper strip, gave similar results in terms of sensitivity and repeatability than the ones obtained with the classical drop-casting method of paracetamol prepared in 0.1 M KCl solution. In this way we were able to obtain a pre-conditioned strip, where it was possible to load directly the paracetamol sample prepared in ultrapure water. In order to compare the present approach with existing literature, in Table 1 some of the experimental features, including the electrochemical technique used, the substrate adopted for realizing the electrodes, the analytical performance and the matrix of application, were reported. It was highlighted how this is the unique case of paper-based applied to wastewaters and also the substrate used does not need any modification, with a detection limit that is satisfactory.

As the last characterization of the paper-based device, recovery studies were carried out in presence of three paracetamol spiking levels, 4, 10 and 50 μM , in both incoming and outgoing wastewaters (voltammetric curves are reported in Supporting Information, Figure S5). With the use of the standard addition method, recoveries of 82, 90 and 98 % were obtained in incoming wastewater, respectively to 4, 10 and 50 μM ,

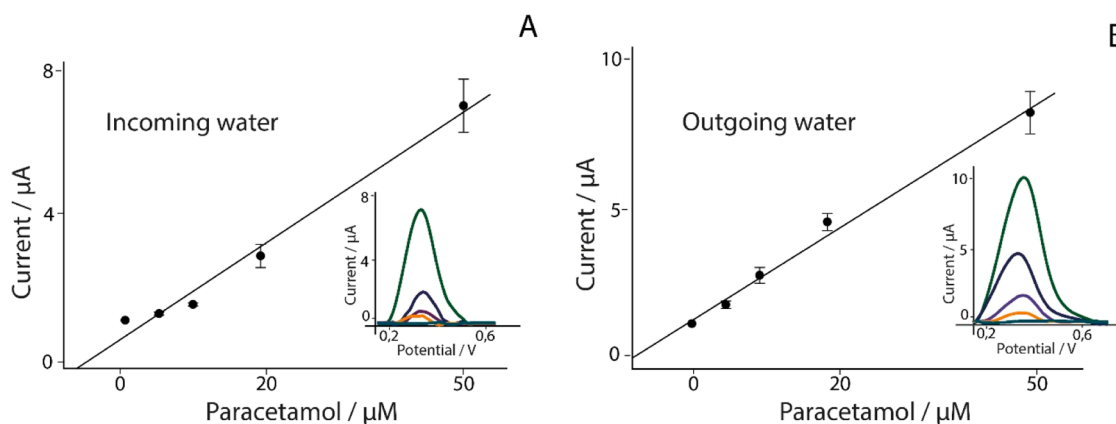


Fig. 5. Application of the fully paper-based platform for the detection of paracetamol in incoming and outgoing wastewaters. A) Matrix effect evaluation at increasing concentrations (0–50 μM) of paracetamol added in an incoming water sample. B) Matrix effect evaluation at increasing concentrations (0–50 μM) of paracetamol added in an outgoing water sample. Experimental parameters: E begin: 0.0 V, E end: 0.8 V, E step: 0.02 V, E pulse: 0.2 V, t pulse: 0.02 s, Scan rate: 0.05 V/s.

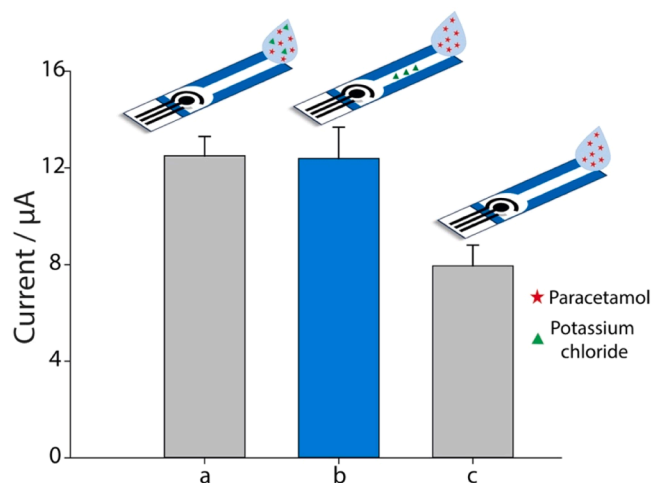


Fig. 6. Pre-conditioning evaluation by comparing b) 1 M KCl pre-conditioned filter paper strip (blue) with a) classical drop casting of paracetamol solution prepared in 0.1 M KCl and c) paracetamol prepared in ultrapure water.

Table 1
Comparison of paracetamol detection at paper-based electrochemical strips.

Electrode	Substrate	Technique	LOD	Application	Ref
Dual electrode detectors pencil-drawn	Whatman No.1 chromatography paper	CV and CA	6 μM	Tablets of Efferalgan drug	[45]
AuNP-PGA/SWCNT electrode	Nafion-modified nitrocellulose membrane	CV and DPV	15 μM	Pill-type pharmaceutical samples	[46]
GPT/WPE (ink composed of nail polish and graphite)	Waterproof paper	CV and DPV	5.4×10^{-8} M	Pharmaceuticals samples and saliva, urine, and sweat samples	[47]
ePADs using graphite pencil	Vegetal paper	SWV	298 μM	Whiskey	[44]
Fully PoP-drawn PADs	Filter paper	DPV	20.5 μM	Gin sample spiked with paracetamol	[48]
Stencil-printing Graphite and UPR ePADs	Vegetal paper	CV and SWV	0.2 μM	Pharmaceuticals samples and biological samples	[43]
Paper-based microfluidic analytical device (μPAD)	Whatman No.1 chromatography paper	Colorimetric	3.9 mg/L	Whiskey	[49]
Paper-based 2D configuration	Whatman No.1 chromatography paper	DPV	0.7 μM (std) 1.5 μM (real samples)	Wastewaters	This work

while recoveries of 86, 93 and 98 % were obtained in outgoing wastewater, respectively to 4, 10 and 50 μM , as reported in following Table 2.

4. Conclusions

In this work, an all-in-one paper-based portable device for the analysis of paracetamol in wastewaters was reported. In particular, a reagent-free platform was obtained merging a paper-based screen-printed electrode with a 2D paper-based channel. Our innovative platform was user-friendly and easy to fabricate, featuring a design that incorporates hydrophobic barriers to form a channel that supports the use of small sample volumes. The filter paper's porosity allowed for the direct application of wastewater samples, both incoming and outgoing, eliminating the need for pretreatment and reducing matrix effects. By

Table 2
Recovery studies in spiked wastewaters.

Incoming wastewater		
Spiked [Paracetamol]	Calculated [Paracetamol]	Recovery%
50 μM	48.9 ± 1.5	98
10 μM	9.0 ± 0.2	90
4 μM	3.3 ± 0.2	82
Outgoing wastewater		
50 μM	49.2 ± 1.1	98
10 μM	9.3 ± 0.6	93
4 μM	3.5 ± 0.3	86

integrating screen-printing, wax printing, and drop casting techniques, we can tailor the platform for specific uses in challenging matrices. The device was designed to be sustainable and reagent-free, with all necessary reagents included and the paper strip pre-conditioned, enabling on-site application with a limit of detection (LOD) of 0.7 μM in standard solution and ca. 1.5 μM in real samples. The cost-effective production process, combined with the system's simplicity that requires no specialized personnel, makes the device particularly suitable and user-friendly for use in various settings, including those with limited resources.

The method was applied towards wastewaters analysis and also the recoveries were characterized: in all the matrices tested, the recoveries of spiked solutions of paracetamol highlighted the satisfactory accuracy of the device. These results represent a significant step towards more effective and accurate detection of paracetamol in wastewater, redefining the concept of environmental analysis, making it more accessible, affordable and sustainable.

CRedit authorship contribution statement

Antonella Miglione: Writing – original draft, Methodology, Formal analysis. **Ada Raucci:** Writing – original draft, Methodology, Formal analysis. **Francesco Cristiano:** Methodology, Formal analysis. **Marco Mancini:** Conceptualization. **Valentina Gioia:** Resources. **Alessandro Frugis:** Resources, Project administration. **Stefano Cinti:** Writing – original draft, Supervision, Resources, Project administration, Methodology, 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.

Data availability

Data will be made available on request.

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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.2024.144255](https://doi.org/10.1016/j.electacta.2024.144255).

References

- X. Zhao, M. Jiang, W. Zhang, The impact of environmental pollution and economic growth on public health: evidence from china, *Front. Public Health* 10 (2022) 861157, <https://doi.org/10.3389/fpubh.2022.861157>. Mar.
- S. Khan, Mu. Naushad, M. Govarthanan, J. Iqbal, S.M. Alfadul, Emerging contaminants of high concern for the environment: current trends and future research, *Environ. Res.* 207 (2022) 112609, <https://doi.org/10.1016/j.envres.2021.112609>. May.
- M. Paszkiewicz, K. Godlewska, H. Lis, M. Caban, A. Bialk-Bielińska, P. Stepnowski, Advances in suspect screening and non-target analysis of polar emerging contaminants in the environmental monitoring, *TrAC Trends Anal. Chem.* 154 (2022) 116671, <https://doi.org/10.1016/j.trac.2022.116671>. Sep.
- B.S. Rathi, P.S. Kumar, P.L. Show, A review on effective removal of emerging contaminants from aquatic systems: current trends and scope for further research, *J. Hazard. Mater.* 409 (2021) 124413, <https://doi.org/10.1016/j.jhazmat.2020.124413>. May.
- R. Kumar, et al., A review on emerging water contaminants and the application of sustainable removal technologies, *Case Stud. Chem. Environ. Eng.* 6 (2022) 100219, <https://doi.org/10.1016/j.csee.2022.100219>. Dec.
- D. Prajapati, M. Shah, A. Yadav, J. Panchal, A critical review on emerging contaminants: origin, discernment, and remedies, *Sustain. Water Resour. Manag.* 9 (3) (2023) 69, <https://doi.org/10.1007/s40899-023-00853-y>. Apr.
- L.B. Barber, S. Ahuja, 1.13 - Emerging Contaminants. *Comprehensive Water Quality and Purification*, Elsevier, Waltham, 2014, pp. 245–266, <https://doi.org/10.1016/B978-0-12-382182-9.00015-3>.
- M. Puri, K. Gandhi, M.S. Kumar, Emerging environmental contaminants: a global perspective on policies and regulations, *J. Environ. Manage.* 332 (2023) 117344, <https://doi.org/10.1016/j.jenvman.2023.117344>. Apr.
- J. Wilkinson, P.S. Hooda, J. Barker, S. Barton, J. Swinden, Occurrence, fate and transformation of emerging contaminants in water: an overarching review of the field, *Environ. Pollut.* 231 (2017) 954–970, <https://doi.org/10.1016/j.envpol.2017.08.032>. Dec.
- B. Lopez, P. Ollivier, A. Togola, N. Baran, J.P. Ghestem, Screening of French groundwater for regulated and emerging contaminants, *Sci. Total Environ.* 518–519 (2015) 562–573, <https://doi.org/10.1016/j.scitotenv.2015.01.110>. Jun.
- S.F. Ahmed, et al., Recent developments in physical, biological, chemical, and hybrid treatment techniques for removing emerging contaminants from wastewater, *J. Hazard. Mater.* 416 (2021) 125912, <https://doi.org/10.1016/j.jhazmat.2021.125912>. Aug.
- L.C. Pereira, et al., A perspective on the potential risks of emerging contaminants to human and environmental health, *Environ. Sci. Pollut. Res.* 22 (18) (2015) 13800–13823, <https://doi.org/10.1007/s11356-015-4896-6>. Sep.
- X. Lin, et al., Occurrence and risk assessment of emerging contaminants in a water reclamation and ecological reuse project, *Sci. Total Environ.* 744 (2020) 140977, <https://doi.org/10.1016/j.scitotenv.2020.140977>. Nov.
- K. Samal, S. Mahapatra, M.Hibzur Ali, Pharmaceutical wastewater as Emerging Contaminants (EC): treatment technologies, impact on environment and human health, *Energy Nexus.* 6 (2022) 100076, <https://doi.org/10.1016/j.nexus.2022.100076>. Jun.
- P. Chaturvedi, et al., Prevalence and hazardous impact of pharmaceutical and personal care products and antibiotics in environment: a review on emerging contaminants, *Environ. Res.* 194 (2021) 110664, <https://doi.org/10.1016/j.envres.2020.110664>. Mar.
- M. Valdez-Carrillo, L. Abrell, J. Ramírez-Hernández, J.A. Reyes-López, C. Carreón-Diazconti, Pharmaceuticals as emerging contaminants in the aquatic environment of Latin America: a review, *Environ. Sci. Pollut. Res.* 27 (36) (2020) 44863–44891, <https://doi.org/10.1007/s11356-020-10842-9>. Dec.
- W. Colglazier, Sustainable development agenda: 2030', *Science* (1979) 349 (6252) (2015) 1048–1050, <https://doi.org/10.1126/science.aad2333>. Sep.
- B. Soergel, et al., A sustainable development pathway for climate action within the UN 2030 Agenda, *Nat. Clim. Chang.* 11 (8) (2021), <https://doi.org/10.1038/s41558-021-01098-3>. Art. no. 8, Aug.
- L. Guppy, P. Mehta, M. Qadir, Sustainable development goal 6: two gaps in the race for indicators, *Sustain. Sci.* 14 (2) (2019) 501–513, <https://doi.org/10.1007/s11625-018-0649-z>. Mar.
- C. Abdel Shaheed, et al., The efficacy and safety of paracetamol for pain relief: an overview of systematic reviews, *Med. J. Aust.* 214 (7) (2021) 324–331, <https://doi.org/10.5694/mja2.50992>.
- W.J. Lee, P.S. Goh, W.J. Lau, A.F. Ismail, Removal of pharmaceutical contaminants from aqueous medium: a state-of-the-art review based on paracetamol, *Arab. J. Sci. Eng.* 45 (9) (2020) 7109–7135, <https://doi.org/10.1007/s13369-020-04446-1>. Sep.
- V.K. Parida, D. Saidulu, A. Majumder, A. Srivastava, B. Gupta, A.K. Gupta, Emerging contaminants in wastewater: a critical review on occurrence, existing legislations, risk assessment, and sustainable treatment alternatives, *J. Environ. Chem. Eng.* 9 (5) (2021) 105966, <https://doi.org/10.1016/j.jece.2021.105966>. Oct.
- N. Agarwal, Paracetamol - A Contaminant of High Concern: existence in Environment and Adverse Effect, *Pharmaceut. Drug Regul. Affairs J.* 5 (2022), <https://doi.org/10.23880/pdraj-16000128>. Jan.
- W. Koagouw, Z. Arifin, G.W.J. Olivier, C. Ciocan, High concentrations of paracetamol in effluent dominated waters of Jakarta Bay, Indonesia, *Mar. Pollut. Bull.* 169 (2021) 112558, <https://doi.org/10.1016/j.marpolbul.2021.112558>. Aug.
- G. Burgot, F. Auffret, J.L. Burgot, Determination of acetaminophen by thermometric titrimetry, *Anal. Chim. Acta* 343 (1–2) (1997) 125–128, [https://doi.org/10.1016/S0003-2670\(96\)00613-7](https://doi.org/10.1016/S0003-2670(96)00613-7).
- W. Ruengsitagoon, S. Liawruangrath, A. Townshend, Flow injection chemiluminescence determination of paracetamol, *Talanta* 69 (4) (2006) 976–983, <https://doi.org/10.1016/j.talanta.2005.11.050>. Jun.
- I. Baranowska, B. Kowalski, The development of sp procedures and an UHPLC method for the simultaneous determination of ten drugs in water samples, *Water. Air. Soil. Pollut.* 211 (1) (2010) 417–425, <https://doi.org/10.1007/s11270-009-0310-7>. Sep.
- M.G. Gioia, P. Andreatta, S. Boschetti, R. Gatti, Development and validation of a liquid chromatographic method for the determination of ascorbic acid, dehydroascorbic acid and acetaminophen in pharmaceuticals, *J. Pharm. Biomed. Anal.* 48 (2) (2008) 331–339, <https://doi.org/10.1016/j.jpba.2008.01.026>. Sep.
- H. Lou, H. Yuan, Z. Ruan, B. Jiang, Simultaneous determination of paracetamol, pseudoephedrine, dextrophan and chlorpheniramine in human plasma by liquid chromatography–tandem mass spectrometry, *J. Chromatogr. B* 878 (7) (2010) 682–688, <https://doi.org/10.1016/j.jchromb.2010.01.005>. Mar.
- S. Zhao, W. Bai, H. Yuan, D. Xiao, Detection of paracetamol by capillary electrophoresis with chemiluminescence detection, *Anal. Chim. Acta* 559 (2) (2006) 195–199, <https://doi.org/10.1016/j.aca.2005.11.071>. Feb.

- [31] Sirajuddin, A.R. Khaskheli, A. Shah, M.I. Bhangar, A. Niaz, S. Mahesar, Simpler spectrophotometric assay of paracetamol in tablets and urine samples, *Spectrochim. Acta Part A Mol. Biomolecular Spectrosc.* 68 (3) (2007) 747–751, <https://doi.org/10.1016/j.saa.2006.12.055>. Nov.
- [32] D. Šatinský, et al., Sequential injection chromatographic determination of paracetamol, caffeine, and acetylsalicylic acid in pharmaceutical tablets, *J. Sep. Sci.* 27 (7–8) (2004) 529–536, <https://doi.org/10.1002/jssc.200301644>.
- [33] M.S.M. Quintino, K. Araki, H.E. Toma, L. Angnes, Batch injection analysis utilizing modified electrodes with tetra-ruthenated porphyrin films for acetaminophen quantification, *Electroanalysis*. 14 (23) (2002) 1629–1634, <https://doi.org/10.1002/elan.200290003>.
- [34] N. Karikalán, R. Karthik, S.M. Chen, M. Velmurugan, C. Karuppiah, Electrochemical properties of the acetaminophen on the screen printed carbon electrode towards the high performance practical sensor applications, *J. Colloid. Interface Sci.* 483 (2016) 109–117, <https://doi.org/10.1016/j.jcis.2016.08.028>. Dec.
- [35] A. Miglione, M. Spinelli, A. Amoresano, S. Cinti, Sustainable Copper Electrochemical Stripping onto a Paper-Based Substrate for Clinical Application, *ACS Meas. Au* (2022), <https://doi.org/10.1021/acsmearscia.1c00059>. Jan.
- [36] A. Raucci, A. Miglione, M. Spinelli, A. Amoresano, S. Cinti, A Hybrid Screen-Printed Strip for Enhanced Electroanalysis towards Lead and Cadmium in Multi-Matrices, *J. Electrochem. Soc.* 169 (3) (2022) 037516, <https://doi.org/10.1149/1945-7111/ac5c98>. Mar.
- [37] A. Cioffi, M. Mancini, V. Gioia, S. Cinti, Office Paper-Based Electrochemical Strips for Organophosphorus Pesticide Monitoring in Agricultural Soil, *Environ. Sci. Technol.* 55 (13) (2021) 8859–8865, <https://doi.org/10.1021/acs.est.1c01931>. Jul.
- [38] P.A. Raymundo-Pereira, N.O. Gomes, S.A.S. Machado, O.N. Oliveira, Simultaneous, ultrasensitive detection of hydroquinone, paracetamol and estradiol for quality control of tap water with a simple electrochemical method, *J. Electroanal. Chem.* 848 (2019) 113319, <https://doi.org/10.1016/j.jelechem.2019.113319>. Sep.
- [39] D. Nematollahi, H. Shayani-Jam, M. Alimoradi, S. Niroomand, Electrochemical oxidation of acetaminophen in aqueous solutions: kinetic evaluation of hydrolysis, hydroxylation and dimerization processes, *Electrochim. Acta* 54 (28) (2009) 7407–7415, <https://doi.org/10.1016/j.electacta.2009.07.077>. Dec.
- [40] W.Y. Su, S.H. Cheng, Electrochemical Oxidation and Sensitive Determination of Acetaminophen in Pharmaceuticals at Poly(3,4-ethylenedioxythiophene)-Modified Screen-Printed Electrodes, *Electroanalysis*. 22 (6) (2010) 707–714, <https://doi.org/10.1002/elan.200900455>.
- [41] S. Dortez, A.G. Crevillen, A. Escarpa, S. Cinti, Electroanalytical paper-based device for reliable detection and quantification of sugars in milk, *Sens. Actuators B Chem* 398 (2024) 134704, <https://doi.org/10.1016/j.snb.2023.134704>. Jan.
- [42] A. Faheem, S. Cinti, W.C. Mak, A.H. Pui Ho, Chapter 5 - Advanced techniques for manufacturing paper-based microfluidic analytical devices. *Microfluidic Biosensors*, Academic Press, 2023, pp. 159–170, <https://doi.org/10.1016/B978-0-12-823846-2.00009-2>.
- [43] L.C. Oliveira, D.S. Rocha, H.A. Silva-Neto, T.A.C. Silva, W.K.T. Coltro, Polyester resin and graphite flakes: turning conductive ink to a voltammetric sensor for paracetamol sensing, *Mikrochim. Acta* 190 (8) (2023) 324, <https://doi.org/10.1007/s00604-023-05914-9>. Jul.
- [44] A.A. Dias, et al., Detection of Analgesics and Sedation Drugs in Whiskey Using Electrochemical Paper-based Analytical Devices, *Electroanalysis*. 30 (10) (2018) 2250–2257, <https://doi.org/10.1002/elan.201800308>.
- [45] N. Dossi, R. Toniolo, E. Piccin, S. Susmel, A. Pizzariello, G. Bontempelli, Pencil-drawn dual electrode detectors to discriminate between analytes comigrating on paper-based fluidic devices but undergoing electrochemical processes with different reversibility, *Electroanalysis*. 25 (11) (2013) 2515–2522, <https://doi.org/10.1002/elan.201300374>.
- [46] S.H. Lee, et al., Determination of acetaminophen using functional paper-based electrochemical devices, *Sens. Actuators B Chem.* 232 (2016) 514–522, <https://doi.org/10.1016/j.snb.2016.03.169>. Sep.
- [47] J.R. Camargo, I.A.A. Andreotti, C. Kalinke, J.M. Henrique, J.A. Bonacin, B. C. Janegitz, Waterproof paper as a new substrate to construct a disposable sensor for the electrochemical determination of paracetamol and melatonin, *Talanta* 208 (2020) 120458, <https://doi.org/10.1016/j.talanta.2019.120458>. Feb.
- [48] V. Pagkali, E. Stavra, D. Soulis, A. Economou, Development of a High-Throughput Low-Cost Approach for Fabricating Fully Drawn Paper-Based Analytical Devices Using Commercial Writing Tools, *Chemosensors* 9 (7) (2021), <https://doi.org/10.3390/chemosensors9070178>. Art. no. 7Jul.
- [49] N.S. Moreira, K.M.P. Pinheiro, L.R. Sousa, G.D.S. Garcia, F. Figueredo, W.K. T. Coltro, Distance-based detection of paracetamol in microfluidic paper-based analytical devices for forensic application, *Anal. Methods* 16 (1) (2023) 33–39, <https://doi.org/10.1039/D3AY01739G>. Dec.
- [50] S. Cinti, D. Moscone, F. Arduini, Preparation of paper-based devices for reagentless electrochemical (bio)sensor strips, *Nat. Protoc.* 14 (8) (2019), <https://doi.org/10.1038/s41596-019-0186-y>. Art. no. 8Aug.
- [51] V. Ortone, L. Matino, F. Santoro, S. Cinti, Merging office/filter paper-based tools for pre-concentrating and detecting heavy metals in drinking water, *Chem. Commun.* 57 (58) (2021) 7100–7103, <https://doi.org/10.1039/D1CC02481G>. Jul.
- [52] P.M. Kalligosfyri, S. Cinti, Paper-Based Materials for Diagnostics, *ACS Mater. Lett.* 6 (2024) 1184–1198, <https://doi.org/10.1021/acsmaterialslett.3c01474>. March 2024.
- [53] J. Tu, W. Cai, X. Shao, Direct quantitative analysis from the current curve data of pulse voltammetric techniques, *J. Electroanal. Chem.* 725 (2014) 25–31, <https://doi.org/10.1016/j.jelechem.2014.05.001>. Jun.