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## Paraformaldehyde-coated electrochemical sensor for improved on-site detection of amphetamine in street samples

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## Abstract

The increasing illicit production, distribution and abuse of amphetamine (AMP) poses a challenge for law enforcement worldwide. To effectively combat this issue, fast and portable tools for the on-site screening of suspicious samples are required. Electrochemical profile (EP)-based sensing of illicit drugs has proved to be a viable option for this purpose as it allows rapid voltammetric measurements via the use of disposable and low-cost graphite screen-printed electrodes (SPEs). In this work, a highly practical paraformaldehyde (PFA)-coated sensor, which unlocks the detectability of primary amines through derivatization, is developed for the on-site detection of AMP in seized drug samples. A potential interval was defined at the sole AMP peak (which is used for identification of the target analyte) to account for potential shifts due to fluctuations in concentration and temperature, which are relevant factors for on-site use. Importantly, it was found that AMP detection was not hindered by the presence of common diluents and adulterants such as caffeine, even when present in high amounts. When inter-drug differentiation is desired, a simultaneous second test with the same solution on an unmodified electrode is introduced to provide the required additional electrochemical information. Finally, the concept was validated by analyzing 30 seized AMP samples (reaching a sensitivity of 96.7 %) and comparing its performance to that of commercially available Raman and Fourier Transform Infrared (FTIR) devices.

**Keywords:** amphetamine, electrochemical profile, square wave voltammetry, drug seizures, derivatization, forensics

## 1. Introduction

Amphetamine (AMP) is a synthetic drug and central nervous system stimulant that is part of the larger group of amphetamine-type stimulants (ATS), which also includes methamphetamine

(MET) and 3,4-methylenedioxyamphetamine (MDMA). Its enhancing effects on attention and cognitive performance, appetite suppression and mood elevation gave AMP several medical applications, including the treatment of narcolepsy and obesity, while also making it a popular drug for recreational use [1–4]. After recognition of AMP's adverse effects, most notably dependence and drug-induced psychoses, prescriptions declined and supply was restricted. Despite these restrictions, illegal use continued and today, AMP is the second most consumed stimulant drug in Europe behind cocaine [5].

Besides being a major consumer, Europe is also a key producer of AMP. Between 2015 and 2019, 85 % of the dismantled AMP laboratories worldwide were located in Europe [6,7]. Moreover, EU member states reported a total of 34 000 seizures of AMP, amounting to a record of 17 tons [5]. AMP is mostly manufactured as a sulphate salt and may occur as powders, tablets, pastes, crystals or liquids [7,8]. The average purity of AMP samples available at the retail level in the European Union varies widely, ranging from 13 wt. % to 67 wt. % in 2019, with half of the countries reporting an average purity between 20 wt. % and 35 wt. % [5]. Other substances present in these samples include by-products from the manufacturing process, diluents added by traffickers to increase profit and adulterants added to alter psychotropic effects [8,9]. Sugars such as lactose, creatine and most importantly caffeine are commonly encountered in seized AMP samples [8–10].

When a suspicious sample is encountered, it is important for law enforcement and security personnel to obtain an immediate indication of the sample's identity on the spot to determine further actions. Laboratory techniques such as gas chromatography coupled with mass spectrometry (GC-MS), which are regarded as the gold standard in drug analysis, are not suitable for on-site screening due to their low portability and high cost [4]. Presumptive color tests are widely used as they provide simple, low-cost and rapid analyses [11,12]. Specifically, Marquis, Simon's and Chen's tests are capable of detecting and distinguishing between

different types of ATS [12,13]. However, the lack of specificity of color tests has been reported to result in false positives and false negatives [14–16]. Moreover, interpretation of the colors is often subjective, while samples that are colored might also influence the test's results. More recently, portable spectroscopic techniques such as Raman and Fourier Transform Infrared (FTIR) have successfully been deployed for the detection of AMP in street samples [4,17–22]. These techniques are non-invasive, rapid and require limited or no sample preparation, which is advantageous for on-site use. Still, equipment remains expensive and the analysis of dark or colored samples can be challenging due to fluorescence interference, particularly for Raman devices [19,20]. Moreover, the presence of high concentrations of other substances (mainly caffeine) in strongly diluted AMP samples has been reported to hinder the detection of AMP with these techniques [22,23].

Electrochemical sensors have emerged as a promising alternative in the field of forensics and offer affordability, rapid measurements, strong analytical performance and potential for miniaturization [24–28]. Specifically, electrochemical profile (EP)-based sensing, which uses the characteristic electrochemical signal or profile of a compound in a given analytical context for its identification, is considered an inviting approach for this type of application [29]. In this, the identification of the target analyte is based on the oxidation or reduction potentials of its characteristic peaks. Several studies have successfully employed the direct electrochemical oxidation of illicit drugs such as cocaine [15,30], MDMA [31], heroin [32,33] and new psychoactive substances (NPS) [34,35] on screen-printed carbon electrodes (SPEs) for their detection in street samples. However, the direct electrochemical oxidation of AMP in aqueous media on carbon electrodes has proved to be complicated due to the high potentials required for primary amine oxidation [36–38]. Indeed, the on-site screening studies of other synthetic drugs such as 1-(3-chlorophenyl) piperazine (mCPP) [39] and 3,4-methylenedioxyethylamphetamine (MDEA) [40] reported no electroactivity for AMP (studied as an interferent) on carbon SPEs,

which are highly suitable for this purpose thanks to their portability and low cost. Using boron-doped diamond electrodes (BDDE), which offer a wide potential window, it was demonstrated by Teófilo et al. [41] that the direct oxidation of AMP is possible in alkaline environment, while it is not detectable in acidic conditions [42].

Alternative solutions have been developed by modifying the working electrode for direct potentiometric analysis [43] or by using a host-molecule-functionalized organic transistor [44]. A more affordable approach is the use of indirect detection methods such as derivatization into an electroactive compound. In particular, 1,2-naphthoquinone-4-sulfonate/sulfonic acid (NQS) has been utilized in several studies to improve the electrochemical detectability of AMP [45–47] and other molecules containing primary amines [48]. **Table S1** provides an overview of the reports on electroanalytical methods for AMP detection.

Our group has previously reported a proof-of-concept for the introduction of formaldehyde in solution (formalin), a simple and low-cost reagent, in the measuring conditions as a derivatization agent [49]. It was demonstrated that, by including formalin in the buffer solution, methylation is achieved via an Eschweiler-Clarke mechanism to unlock the detectability of primary amines and to enrich the EP of compounds containing secondary amines.

Building on this concept, this work reports the development of an innovative formaldehyde-based sensor for the qualitative on-site detection of AMP in seized samples. This sensor uses a coating of paraformaldehyde, which is dissolved and depolymerized upon contact with the buffer solution. The coating makes on-site deployment more straightforward and only requires a limited amount of derivatization reagent, thereby avoiding the need for significant quantities of formalin to be included in the buffer solutions. Furthermore, the proposed sensing approach offers low measurement times (1-2 minutes) and the use of affordable materials, while preserving strong analytical performance. After the optimization of the coating protocol and the measuring conditions, relevant factors for on-site use such as reproducibility, shelf life and the

influence of concentration, temperature and the presence of adulterants and diluents in drug samples are assessed. To achieve differentiation between different illicit drugs commonly encountered on-site, the potential of introducing a simultaneous second test with the same solution on an unmodified SPE (dual-sensor strategy) is explored. Finally, the concept's performance is validated by analyzing seized AMP samples, provided by European Forensic and Customs Laboratories, and the results are compared to those obtained by commercially available Raman and FTIR devices.

## 2. Experimental

### 2.1 Reagents and seized samples

Standards of d,l-amphetamine-sulfate, d-methamphetamine-HCl, d,l-MDMA-HCl and ketamine-HCl were purchased from Lipomed (Arlesheim, Switzerland). Standards of cocaine-HCl and heroin-HCl were purchased from Chiron AS (Trondheim, Norway). Standards of caffeine, lactose, maltose and glucose were purchased from VWR Chemicals (Leuven, Belgium), a standard of paracetamol was purchased from Sigma-Aldrich (Diegem, Belgium) and a standard of creatine monohydrate was purchased from J&K Scientific (Lommel, Belgium).

Seized amphetamine samples were provided by the National Institute for Criminalistics and Criminology (NICC) in Belgium, Dutch Customs Laboratory (the Netherlands) and Swedish Customs Laboratory (Sweden). Qualitative analysis of the seized samples was previously performed by these institutions using gas chromatography-mass spectrometry (GC-MS) [50]. Additionally, NICC performed quantitative analysis on their samples using GC-flame ionization detection (GC-FID). The applied chromatographic methods are ISO17025 accredited and are continuously evaluated through participation in international quality control programmes (United Nations Office on Drugs and Crime – UNODC, and European Network of Forensic Science Institutes – ENFSI).

Analytical grade salts of potassium phosphate, potassium chloride, sodium acetate and boric acid, as well as potassium hydroxide and hydrochloric acid, both used for pH-corrections, were purchased from Sigma-Aldrich (Overijse, Belgium). Paraformaldehyde powder (96 %, extra pure) was purchased from Acros Organics (Geel, Belgium). Ethanol (99.8 %, absolute) was acquired from Fisher Scientific (Loughborough, United Kingdom). All solutions were prepared in  $18.2 \text{ M}\Omega \text{ cm}^{-1}$  doubly deionized water (Milli-Q water systems, Merck Millipore, Germany). Monitoring of the pH was performed with a 914 pH/conductometer from Metrohm (Herisau, Switzerland). All electrochemical measurements were performed in 100 mM buffer solutions containing 100 mM KCl (i.e. phosphate buffer saline [PBS] and Britton-Robinson buffers [BRB]).

**Preparation protocol for PFA-coated SPEs.** A  $25 \text{ mg mL}^{-1}$  suspension of PFA powder in a 70 % ethanol 30 % water solution is prepared and continuously vortexed. Subsequently, a  $3 \mu\text{L}$  drop of the suspension is applied on the working electrode of the SPE, which is then left to dry at ambient temperature for 30 minutes.

## 2.2. Instrumentation and methods

**Electrochemical measurements.** All square wave voltammetry (SWV) measurements were carried out using MultiPalmSens4 or EmStat Pico potentiostats (PalmSens, Houten, The Netherlands) with PStace/MultiTrace software. Disposable carbon Italsens IS-C screen printed electrodes (SPEs) containing a graphite working electrode ( $\varnothing = 3 \text{ mm}$ ), a carbon counter electrode, and an internal silver (pseudo) reference electrode were used for all measurements (single use) and were also provided by PalmSens. All experiments were performed by applying an  $85 \mu\text{L}$  drop of solution onto the SPE. The SWV parameters used: potential range of  $-0.1$  to  $1.5 \text{ V}$ , frequency  $10 \text{ Hz}$ ,  $25 \text{ mV}$  amplitude and  $5 \text{ mV}$  step potential. All square wave voltammograms (SWVs) shown were background corrected using the “moving average

iterative background correction” (peak width = 1) tool in the PSTrace software. All electrochemical measurements included in this manuscript were performed three times (N = 3).

**Temperature measurements.** Temperature experiments were performed using a Mistral oven heater (Spark Holland B.V., the Netherlands) for exact and reproducible temperature control. An SPE connector cable (PalmSens, Houten, The Netherlands) was fixed inside the oven and connected to a portable EmStat3 Blue potentiostat (PalmSens, Houten, The Netherlands) located outside the oven. The steel probe of a digital thermometer (VWR, Leuven, Belgium) was fixed in the proximity of the SPE to obtain an accurate indication of the temperature. When the temperature in the oven had reached the desired temperature, the coated SPE was inserted. Subsequently, the solution was prepared and applied to the SPE. Finally, the measurement was started after the optimized reaction time (1 minute) had ended.

**Portable Raman measurements.** A Bruker Bravo Handheld Raman spectrometer (Bruker Optik GmbH, Ettlingen, Germany) was used for all Raman measurements. The instrument uses a dual laser excitation feature with two laser diodes (wavelengths: 785 nm and 852 nm). Spectra were recorded from  $170\text{ cm}^{-1}$  to  $3200\text{ cm}^{-1}$ . OPUS 8.2.28 (Bruker Optik GmbH, Ettlingen, Germany) software was used for data acquisition and analysis. All seized samples were processed by the partnered institutes into powdered form and kept in transparent Eppendorf tubes. All measurements were performed by placing the Eppendorf tubes containing the sample on the measuring tip. Identification was performed using the TICTAC Drug Library (TICTAC Communications Ltd., London, United Kingdom).

**Fourier Transform IR measurements.** A Bruker Alpha II spectrometer (Bruker Optik GmbH, Ettlingen, Germany) was used for the analysis of the seized samples provided by NICC (Belgium) and Dutch Customs Laboratory (the Netherlands), while a Bruker Tensor 27 (Bruker Optik GmbH, Ettlingen, Germany) was used for the samples from Swedish Customs Laboratory (Sweden). All measurements were performed in attenuated total reflectance (ATR) mode, using

a diamond crystal. For each measurement, a small amount of sample was placed directly on the crystal. The spectra were recorded from  $4000\text{ cm}^{-1}$  to  $400\text{ cm}^{-1}$  with a spectral resolution of  $4\text{ cm}^{-1}$  and consisting of 128 co-added scans (analysis time: ca. 170 s). A background scan (128 scans) was run against air before the measurements. Data acquisition and analysis were also performed using OPUS 8.2.28 software. The TICTAC Drug Library (for ATR spectra) was used for identification.

**Analysis of seized samples.** For the analysis of seized samples, two Emstat Pico potentiostats were coupled to a laptop with PSTrace software. For each measurement, a PFA-coated SPE was connected to one potentiostat and an unmodified SPE to the other. Using a disposable spatula, approximately 4-5 mg of sample was added to a 5 mL tube containing 2 mL of buffer solution. The tube was then vortexed thoroughly and an  $85\text{ }\mu\text{L}$  drop of the solution was applied to both of the SPEs. After a waiting time of 1 min, the SWV scan was started.

### 3. Results and discussion

#### 3.1. Proof-of-concept and optimization of the sensor

The derivatization reaction unlocks the detectability of the target analyte (AMP) and is, therefore, an essential part of this sensor. Furthermore, to maintain the aspect of highly practical deployment in the field, the derivatization reagent is deposited on the SPE. This way, the need for a separate derivatization step is avoided as immediate detection can take place due to the interaction between AMP and the coating. Hence, several parameters regarding the preparation of the PFA-coated SPEs and the used measuring conditions such as pH, reaction time and PFA concentration were optimized.

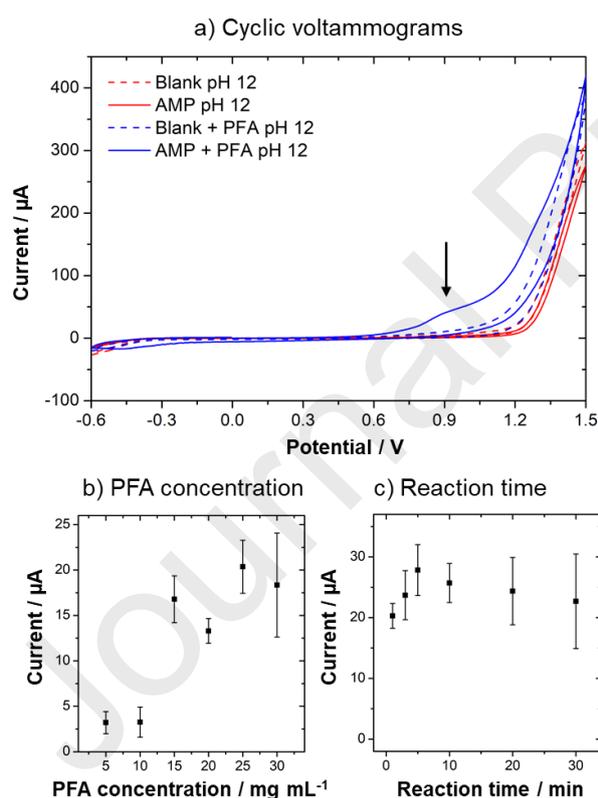
After the application of the aqueous solution containing AMP on the PFA-coated SPE, the PFA needs to be depolymerized into formaldehyde to become available for the derivatization reaction. This can easily be achieved by using alkaline conditions in the measuring buffer.

Indeed, it was demonstrated that the use of alkaline conditions (PBS pH 12) resulted in higher yields for the reaction compared to neutral conditions (PBS pH 7) [49]. However, to find the most suitable conditions for analysis using PFA-coated SPEs, 1 mM solutions of AMP were prepared and subsequently measured in the pH-range 8-12 using SWV, which is chosen due to its sensitivity, fast analysis and straightforward peak identification (**Fig. S1**). In BRB pH 8, the SWV of the AMP solution overlaps that of the blank and no signals which could be attributed to the (derivatized) analyte are observed. In BRB pH 9-11, the AMP solutions produce a single peak, which undergoes a cathodic shift in peak potential and obtains higher peak currents as the pH increases ( $1.21 \pm 0.02$  V and  $0.05 \pm 0.03$   $\mu$ A in pH 9,  $1.00 \pm 0.02$  V and  $0.31 \pm 0.07$   $\mu$ A in pH 11, N = 3). The SWV recorded in PBS pH 12 contains two oxidation signals with peak potentials at  $0.92 \pm 0.02$  V and  $1.32 \pm 0.02$  V (N = 3), with the latter being discarded as it is also present for in the blank solution. Cyclic voltammograms recorded in PBS pH 12 confirm the occurrence of an irreversible oxidation process in the AMP solution which is not observed on unmodified SPEs (**Fig. 1a**). As it was proven in previous work that methamphetamine is formed in these conditions [49], the observed signal is linked to the oxidation of the secondary amine of methamphetamine [38,51], which leads to the formation of the corresponding primary amine (AMP) and formaldehyde [38]. This peak (also observed in BRB pH 9-11) is characteristic of AMP in these conditions and can be used for its detection, proving that the concept is viable. As PBS pH 12 yields the most intense signal ( $1.3 \pm 0.1$   $\mu$ A, N = 3), this supporting electrolyte will be used for all further experiments.

Within this established framework, two more parameters were optimized: (i) the concentration of PFA in the suspension used for the preparation of the coated SPEs, and (ii) the reaction time.

The effect of the PFA concentration used for the preparation of the coated SPEs is shown in **Fig. 1b**. The characteristic AMP peak reaches its highest peak current ( $20.4 \pm 2.7$   $\mu$ A, N = 3) for a PFA concentration of  $25 \text{ mg mL}^{-1}$ , which is further used for the preparation of all coated

SPEs. Thereafter, 3 mM AMP solutions were analyzed on PFA-coated SPEs at different reaction times (i.e. the time between application of the buffer solution on the SPE and the start of the measurement) being varied between 1 and 60 minutes (**Fig. 1c**). It can be observed that 5 minutes is the optimal reaction time to obtain a maximal peak current ( $27.8 \pm 4.5 \mu\text{A}$ ,  $N = 3$ ). Longer reaction times result in lower average currents and larger standard deviations (e.g. 30 min:  $22.7 \pm 7.8 \mu\text{A}$ ,  $N = 3$ ) as, in these conditions (pH 12), formaldehyde is further converted into formate over time and the occurrence of side reactions is possible. However, a reaction time of 1 minute (which already produces an intense peak and obtains the smallest current variation,  $20.3 \pm 2.1 \mu\text{A}$ ,  $N = 3$ ) is selected for further measurements as a compromise between sensitivity and the timeframe for a feasible on-site screening (1-2 minutes).



**Fig. 1.** Cyclic voltammograms and optimization of parameters related to the preparation of the PFA-coated SPEs for the detection of AMP. (a) Cyclic voltammograms of 3 mM solutions of AMP (full lines) and blanks (dashed lines) on unmodified SPEs (red) and PFA-coated SPEs (blue) in PBS pH 12. (b) Optimization of the PFA concentration used during preparation and (c) of the reaction time after applying the buffer solution. Measurements in (b) and (c) were performed using SWV on 3 mM solutions of AMP in PBS pH 12.

### 3.2. Reproducibility and shelf life of PFA-coated SPEs

The reproducibility of the PFA-coated SPEs was assessed by analyzing 3 mM solutions of AMP in PBS pH 12 on five occasions, intraday (1 hour between) and interday (1 day between). For each measurement, a new PFA-coated SPE is used. The precision is described using the relative standard deviation (RSD). The obtained RSD values for peak currents (**Table S12**) range between 5.9 % and 11.8 % for the intraday measurements and between 7.1 % and 17.1 % for the interday measurements. For the interday measurements, it is observed that, after several days, the average peak current decreases and the RSD increases. Since PFA is sensitive to moisture and tends to sublime, the coating degrades over time. This process can be slowed down by storing the coated SPEs in dry and cool conditions. The peak potentials vary between 0.83 and 0.85 V, both intraday (RSD values: 2.4-2.8 %) and interday (RSD values: 1.7-2.9 %). As the peak potentials are used for the identification of AMP, it is an important observation that the variation in these values is limited.

To assess how the performance of PFA-coated SPEs evolves as a function of time since preparation, a shelf life experiment was conducted over 18 weeks. A batch of coated SPEs was prepared using optimized parameters and stored in dark and dry conditions at 4 °C. Measurements (N = 5, each on a different coated SPE) were performed every two weeks using 3 mM solutions of AMP in PBS pH 12 and the resulting average peak potentials and currents are displayed in **Fig. S2**. Over 18 weeks, the peak potentials remain relatively stable and increase slightly (week 0:  $0.84 \pm 0.01$  V, week 18:  $0.86 \pm 0.01$  V, N = 5), which will be taken into account when defining detection conditions for AMP based on peak potentials. A general decreasing trend is observed for the peak currents, with large variations starting to occur after 10 weeks. These variations in resulting peak current will be considered when defining a

sampling procedure for seized samples with unknown compositions to ensure that even the low purity samples will produce a measurable signal.

### *3.3. Evaluation of the sampling and environmental conditions*

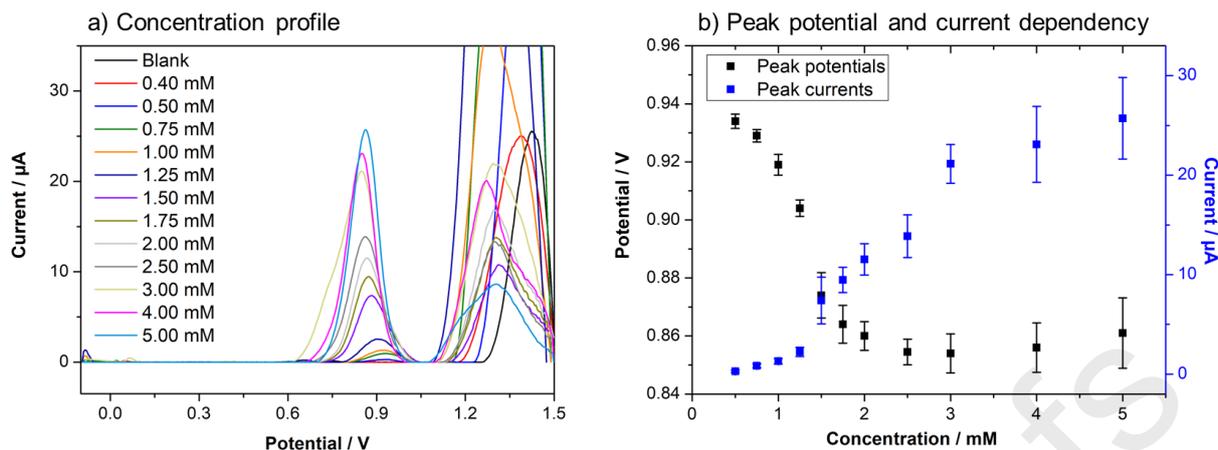
#### *3.3.1 Effect of concentration*

When analyzing seized samples, the concentration of AMP in the solution can differ strongly due to variations in the purity of the AMP street samples or the sampled amount [5]. As the potential of the AMP peak is used for its identification, the influence of the AMP concentration on the potential and shape of the characteristic peak was studied.

**Fig. 2a** displays the voltammograms and **Fig. 2b** the dependency of peak potential and current of AMP solutions between 0.4 mM and 5 mM in PBS pH 12 measured on PFA-coated SPEs. The concentration that was determined to yield the lowest detectable voltammetric signal was 0.5 mM. Although this concentration is relatively high due to the need for a derivatization reaction, this factor poses no issue as this sensor aims at the qualitative analysis of bulk powders. A suitable sampling procedure for seized samples will further be proposed based on these findings. The peak observed for 0.5 mM is also characterized by the highest peak potential:  $0.93 \pm 0.02$  V ( $N = 3$ ). As the AMP concentration increases, the peak potential gradually decreases to a minimum value of  $0.85 \pm 0.02$  V ( $N = 3$ ) for 3 mM. The voltammogram of the 3 mM AMP solution also shows a shoulder to the left side of the main peak (**Fig. 2a**). Our previous work proved that this derivatization reaction in PBS pH 12 produces both the mono-methylated (main) and di-methylated (minor) product of AMP [49]. Thus, it is proposed that this shoulder is caused by the oxidation of the di-methylated product and that, for other concentrations, the contributions of both products overlap and form one peak. Therefore, only one peak composes the characteristic EP of AMP in these conditions. Above 3 mM, the peak potential shifts to more positive potential values again. Regarding the peak currents, the linear relationship ( $R^2 = 0.97$ ) between concentration of AMP and current of its single peak was

limited to 0.50 – 1.25 mM (**Fig. S3**), with linear equation:  $I(\mu\text{A}) = 2.3 (\pm 0.2) C_{\text{AMP}} (\text{mM}) - 0.9 (\pm 0.2)$ . The calculated LOD and LOQ values are 0.3 and 0.9 mM respectively. The LOD and the lowest detectable concentration (0.5 mM) will later be taken into consideration when determining the sampling procedure for seized samples to safeguard the detectability of low purity samples. The signals obtained at higher concentrations are characterized by a non-linear increase, which complicates quantification purposes. While other electrochemical methods for the detection of AMP obtain a better analytical performance (**Table S1**), the proposed method offers a combination of short analysis times, a lack of sample preparation, low-cost materials and straightforward deployment for on-site analysis.

When developing a sensor based on the detection of characteristic EPs, potential intervals around the characteristic peak(s) of the target compound are defined to account for small variations due to temperature, concentration or electroactive adulterants present in drug samples. If peaks are detected in all the intervals defined for a target compound, it is thus successfully detected. As the effect of AMP concentration on the potential of the single AMP peak is strong (80 mV difference between 0.5 mM and 3 mM), a wide interval of ca 120 mV is required for accurate detection. By providing an additional 20 mV on either side of the potential zone in which pure AMP occurs, a potential interval ranging from 0.83 V to 0.95 V is selected. If the recorded voltammogram contains a peak within this interval that exceeds the threshold current of 0.1  $\mu\text{A}$  (defined to avoid the inclusion of artefacts in the EP of an analyzed sample), the measurement is positive for AMP.



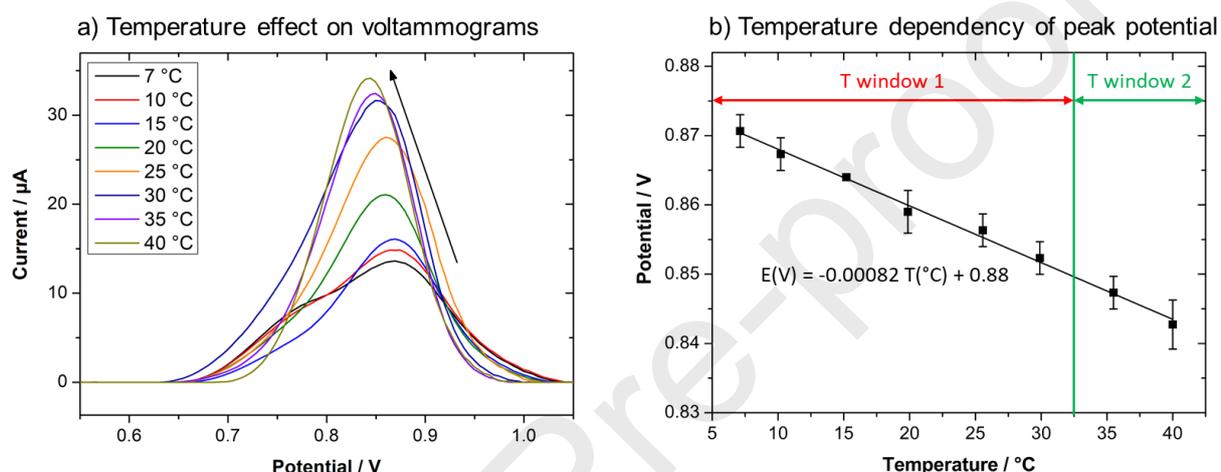
**Fig. 2.** The effect of AMP concentration on its EP. a) Baseline corrected SWVs showing the concentration profile of AMP solutions in PBS pH 12 on PFA-coated SPEs. b) Dependency of the peak potential (black) and peak current (blue) on the concentration of AMP in PBS pH 12, tested on PFA-coated SPEs. Reaction time: 1 min.

### 3.3.2. Effect of temperature

The ambient temperature is another experimental parameter that influences the analytical performance of the sensor. The conditions in which on-site analysis is performed can vary strongly and temperature fluctuations could affect the obtained results. Therefore, the dependency of the peak potential on the temperature was studied by analyzing 3 mM AMP solutions at measuring temperatures between 7 and 40 °C. The resulting plot and corresponding voltammograms are displayed in **Fig. 3**.

As the temperature increases, the peak potential of the AMP peak decreases linearly (slope: -0.82 mV °C<sup>-1</sup>, R<sup>2</sup> = 0.99) (**Fig. 3b**). Since the previously defined potential interval for AMP (0.83 – 0.95 V) was selected for an ambient temperature of 20 °C, potential shifts due to divergent temperatures could cause peaks to fall outside this interval. If the temperature at the time of the analysis can be measured (e.g. through a temperature sensor in the device), a different potential interval can be defined for different temperature windows (**Fig. 3b**). In this work, temperature window 1 is defined as all temperatures below 32.5 °C and is linked to the

original potential interval (0.83 – 0.95 V). Temperature window 2 covers temperatures of 32.5 °C and above using an adjusted interval. As the difference between the peak potentials measured at 20 °C and 40 °C is 16 mV, this adjusted interval is shifted by 16 mV towards lower potentials (0.814 – 0.934 V). If an ambient temperature of 32.5 °C or above is measured at the time of analysis, the adjusted potential interval is employed in the detection conditions for AMP.



**Fig. 3.** The effect of temperature on the EP of AMP. a) Baseline corrected SWVs showing the effect of temperature on the voltammetric response of a 3 mM AMP solution in PBS pH 12 on PFA-coated SPEs. b) Dependency of the peak potential on temperature for 3 mM AMP solutions measured on PFA-coated SPEs.

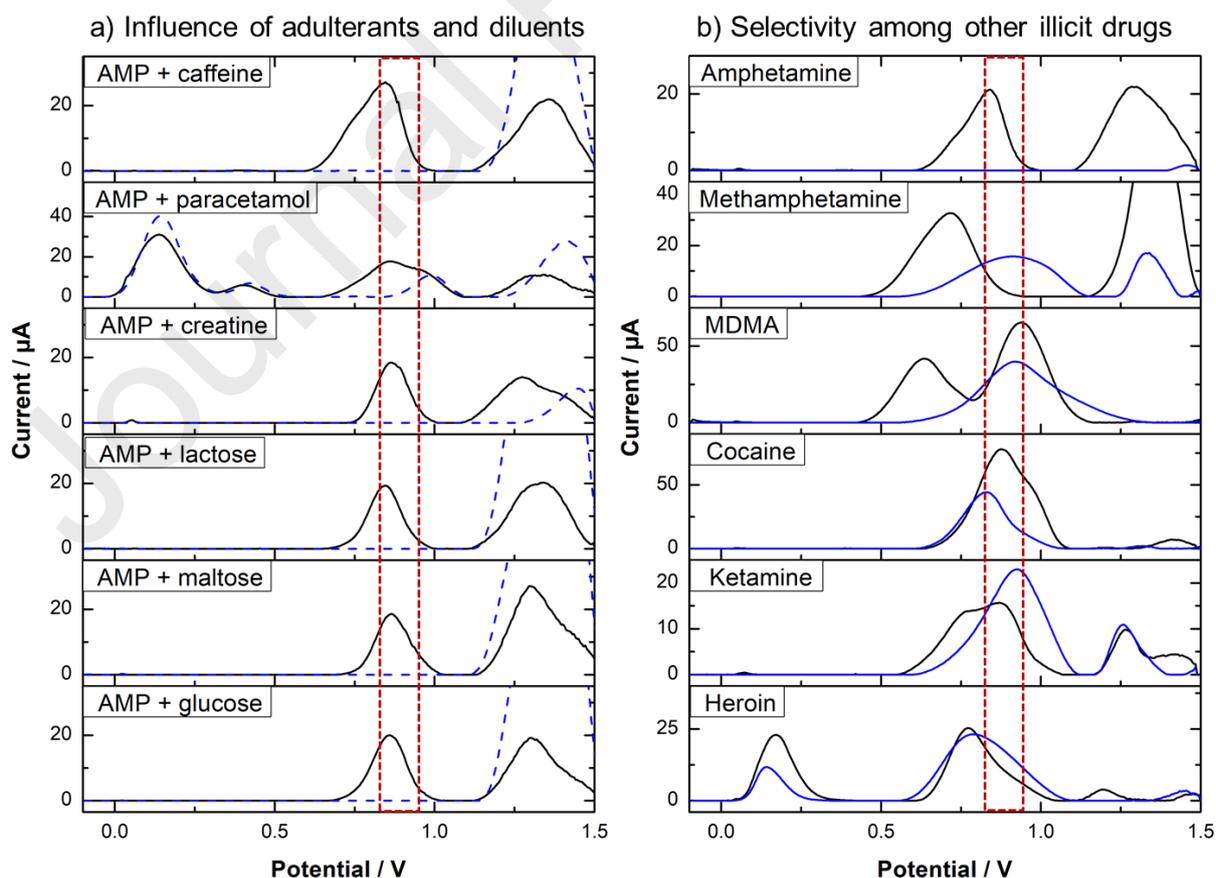
### 3.4. Evaluation of the sensor's selectivity

#### 3.4.1. Study of the influence of adulterants and diluents

AMP street samples tend to contain a variety of other substances. Since the presence of these compounds could influence the analysis, binary mixtures were prepared between AMP and the following commonly encountered adulterants and diluents: caffeine, paracetamol, creatine, lactose, maltose and glucose [8–10]. The mixtures were prepared in equimolar concentrations and subsequently analyzed on PFA-coated SPEs.

**Fig. 4a** displays the voltammograms of the pure adulterants and diluents, as well as their binary mixtures with AMP. For the analysis to be positive for AMP, a peak maximum needs to be

located in the defined potential interval (indicated with a red dashed frame, from 0.83 V to 0.95 V) and exceed the defined threshold current of 0.1  $\mu\text{A}$ . This condition is fulfilled for all the binary mixtures and for none of the pure adulterants/diluents, thus avoiding false negatives and false positives, respectively. In our previous research on illicit drug detection, it was shown that caffeine (1.27 V) and paracetamol (0.10 V) each produce one oxidation peak in PBS pH 12 [32,52]. The introduction of PFA in the reaction conditions does not appear to change the EP of caffeine (**Fig. 4a**, dashed blue line), as its single characteristic peak is overlapped by the intense signal already observed in the blank. For paracetamol, besides its expected peak at  $0.14 \pm 0.02$  V, two additional signals are observed at  $0.42 \pm 0.02$  V and  $0.99 \pm 0.02$  V ( $N = 3$ ). Although the latter is located close to the AMP potential interval (0.83 – 0.95 V) and forms a shoulder on the AMP peak in the binary mixture, AMP is successfully detected (**Fig. 4a**, full black line). Creatine, lactose, maltose and glucose are not electroactive in these conditions (**Fig. 4a**, dashed blue lines) and do not interfere with the detection of AMP.



**Fig. 4.** Evaluation of the sensor's ability to detect AMP in the presence of common adulterants and diluents, as well as to differentiate AMP from other illicit drugs. a) Baseline corrected SWVs of mixtures between AMP and adulterants and diluents. Black full lines – 1:1 mixtures (concentration 3 mM) in PBS pH 12 measured on PFA-coated SPEs. Blue dashed lines – 3 mM solutions of the pure adulterants and diluents in PBS pH 12 on PFA-coated SPEs. Red dashed frame – potential interval in which AMP peak is expected. b) Baseline corrected SWVs of pure solutions of common illicit drugs. Black lines – 3 mM solutions of the pure drugs in PBS pH 12 measured on PFA-coated SPEs. Blue lines – 3 mM solutions of the pure drugs in PBS pH 12 on unmodified SPEs. Red dashed frame – potential interval in which AMP peak is expected. AMP detection is achieved when a peak exceeding the threshold current ( $0.1 \mu\text{A}$ ) is located within the defined potential interval.

#### 3.4.2. Assessment of the selectivity among other illicit drugs.

AMP street samples may be encountered in various sample types, including tablets, powders, pastes, and crystals. Moreover, due to the addition of dyes and other excipients, these samples occur in numerous different colors. This makes it difficult to visually differentiate AMP samples from other illicit drugs in circulation in the same settings. Therefore, the on-site screening has to provide this selectivity. To assess the ability of the sensor to differentiate, 3 mM solutions of some of the most commonly encountered illicit drugs were analyzed in PBS pH 12 on PFA-coated SPEs (**Fig. 4b**). The potential interval defined for AMP is displayed on the voltammograms to facilitate identifying the illicit drugs that may interfere with the detection of AMP.

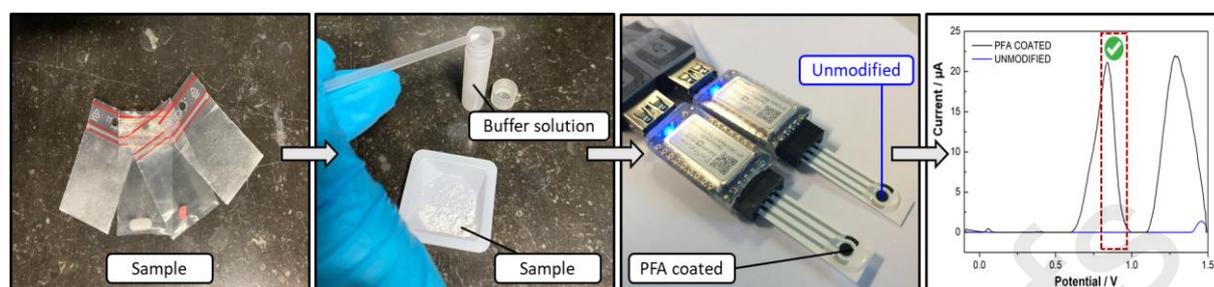
The EPs of heroin ( $0.17 \pm 0.01 \text{ V}$  and  $0.77 \pm 0.02 \text{ V}$ ,  $N = 3$ ) and methamphetamine ( $0.72 \pm 0.02 \text{ V}$ ,  $N = 3$ ) (**Fig. 4b**, black lines) contain no signals in the defined AMP potential interval and the detection of these drugs, therefore, poses no issue for AMP identification. However, several other drugs (i.e. MDMA, cocaine and ketamine) also do obtain a peak maximum within the AMP potential interval in these conditions. MDMA yields a peak in this interval ( $0.94 \pm 0.02 \text{ V}$ ,  $N = 3$ ) but the presence of a second characteristic MDMA peak at  $0.63 \pm 0.02 \text{ V}$  ( $N = 3$ ) (**Fig. 4b**, black lines) makes its EP sufficiently different from AMP so discrimination between the two is possible. Cocaine ( $0.88 \pm 0.02 \text{ V}$ ,  $N = 3$ ) and ketamine ( $0.87 \pm 0.02 \text{ V}$ ,  $N =$

3) both produce a single oxidation peak containing a shoulder on opposite sides. However, shoulders are not sufficiently reliable over wide concentration ranges and in the presence of electroactive adulterants for inclusion in the EP of a target drug. Therefore, differentiation between AMP, cocaine and ketamine proves to be difficult on a single PFA-coated SPE and more electrochemical information is required to achieve this.

Simultaneously performing a second test with the same solution on an unmodified SPE, in parallel with the first test (dual-sensor strategy), could provide this (**Fig. 5**). The voltammograms of 3 mM solutions of these illicit drugs analyzed in PBS pH 12 on unmodified SPEs (**Fig. 4b**, blue lines) show that the EP of cocaine contains one peak ( $0.83 \pm 0.02$  V,  $N = 3$ ), that ketamine yields two peaks ( $0.92 \pm 0.02$  V and  $1.26 \pm 0.02$  V,  $N = 3$ ) and that AMP produces no peaks. Moreover, in previous reports, the concentration studies performed on cocaine [15] and ketamine [52] in the same measuring conditions (PBS pH 12, unmodified graphite SPEs) showed no strong variations in peak potential as a function of concentration. Thus, the EPs of AMP, cocaine and ketamine (**Fig. 4b**, blue lines) in these conditions are considered sufficiently different to allow inter-drug differentiation. Based on this, another condition for the identification of AMP can be added: in the parallel test on unmodified SPEs, no peak maximum should be located in the potential interval 0.82 – 0.98 V, where the EPs of other illicit drugs do contain signals. Only if the conditions on both SPEs are fulfilled, the analysis is positive for AMP. AMP also occasionally occurs in small amounts as adulterant in ecstasy samples [8,9]. To avoid the occurrence of false negative results for this type of samples, detection conditions can be included in the sensor for MDMA (i.e. the two characteristic signals on PFA-coated SPEs and one on unmodified SPEs), as well as for AMP.

Importantly, this approach requires no additional sampling (both tests use the same buffer solution) and the parallel performance preserves the short analysis time (1-2 min). Moreover,

straightforward expansion towards the detection of other illicit drugs is possible by adapting the detection conditions according to the EP of the other drug.



**Fig. 5.** Concept of the dual-sensor and the workflow for the analysis of seized samples. The sample is first diluted in buffer solution, subsequently, a drop is applied to both a PFA-coated SPE and an unmodified SPE. Two voltammograms are recorded simultaneously, and a positive result is shown when the defined conditions for AMP detection are fulfilled on both sensors.

### 3.5. Seized samples analysis and comparison with other commercial techniques

According to the latest European Drug Report, the average purity of AMP samples in the European Union at the retail level varied from 13 wt. % to 67 wt. % in 2019 [5]. Half of the countries reported an average purity between 20 wt. % and 35 wt. %. Moreover, these purities and sample compositions change as a function of time and location. Therefore, the analysis of unknown samples requires a fixed sampling procedure capable of covering strongly varying purities. Based on the findings in the concentration study, a target concentration range of 2-2.5 mg mL<sup>-1</sup> is proposed. This takes into account variations in sampling when performed on-site. Using this concentration range, low purity samples remain detectable (e.g. 5 wt. % corresponds to 0.54 mM of AMP when 2 mg mL<sup>-1</sup> is sampled), while typical purities (20 – 35 wt. %) give AMP concentrations between 2 and 4 mM (for 2 mg mL<sup>-1</sup> sampling). As the peak potentials of AMP reach a minimum value at a concentration of 3 mM, samples with higher purities (which can reach AMP concentrations above 10 mM using the proposed sampling procedure) are still expected to occur within the defined potential interval.

The performance of the analytical concept was validated by analyzing 30 seized AMP samples previously analyzed by standard methods (i.e. GC-MS and GC-FID), provided by three European Forensic and Customs Laboratories, and compared to a commercially available portable Raman and FTIR device. The compositions of the samples, as well as their sample types and appearances, are summarized in **Table S3**. The strong variations in purity (4.9 – 100 wt. %), sample type and color demonstrate the diversity of AMP street samples.

The voltammograms that result from applying the electrochemical sensor (dual-sensor strategy) to the seized samples are displayed in **Fig. S4**. It can be observed that the two conditions previously defined for AMP detection are fulfilled for 29/30 of the seized samples, representing a test sensitivity of 96.7 %. The only sample not correctly identified was SS10 (**Fig. S4**), which produces a double peak pattern with potentials of  $0.82 \pm 0.02$  V and  $0.97 \pm 0.02$  V ( $N = 3$ ). It appears that this sample contains an electroactive compound (the second test on unmodified SPE contains a peak at  $0.80 \pm 0.02$  V,  $N = 3$ ) that was not identified in the GC-MS analysis. The signal of this compound shifts the peak of AMP to a more positive potential ( $0.97 \pm 0.02$  V,  $N = 3$ ), which is outside of the defined potential window for AMP. Although it is expected that the presence of this particular compound in AMP street samples is exceptional (as it is not detected in any of the other seized samples), it is possible to adjust the limits of the potential intervals used for identification when unexpected potential shifts (e.g. due to the rise of new adulterants) are observed in analyzed samples. For example, it could be defined that the potential interval for AMP expands if two peaks are detected between 0.80 – 1.00 V (as is the case for SS10). This demonstrates the flexibility of the approach, which is an important asset in a drug market that is becoming increasingly dynamic.

The same set of seized AMP samples was subsequently analyzed with two spectroscopic devices commercially available for on-site use: a handheld Raman (Bravo) device and an ATR-FTIR (Alpha II) spectrometer. To best mimic the conditions that apply during the deployment

in the field by non-specialized personnel, the data analysis is limited to finding the two main components (no manual mixture analysis was performed). Therefore, the results do not necessarily reflect the full capabilities of the technique, but rather those of the device for the specific purpose.

**Table 1** contains the results of the two spectroscopic devices, as well as those of the electrochemical sensor. Raman and FTIR obtained sensitivities of 56.7 and 70.0 % respectively, values considerably lower than that of the electrochemical sensor (96.7 %). For 9/30 samples, the Raman device identified a compound with a similar chemical structure compared to AMP (i.e. pseudoephedrine, norephedrine, phenethylamine). Depending on the legal status of these compounds in the country of the analysis, a law enforcement officer could decide to further investigate these samples with other techniques. Other false negatives were likely caused by the presence of large amounts of other compounds (caffeine, creatine, sugars) in strongly diluted samples (**Table S3**), which are then identified by the devices as the primary components of the sample. In practice, law enforcement often uses a combination of FTIR/Raman and other techniques to prevent these false negatives from remaining undetected.

For the electrochemical sensor, it is advantageous that caffeine (high oxidation potential) and sugars (non-electroactive) do not interfere with the measurements as it allows a more straightforward identification of the target analyte (AMP) in the case of strongly diluted or adulterated samples (e.g. SS4-6). These findings demonstrate that this practical electrochemical sensor, unaffected by sample type or color, also offers strong performance and provides a promising alternative for the on-site analysis of suspicious samples.

**Table 1.** Comparison of the performance of two commercially available spectroscopic devices for on-site deployment and of the electrochemical sensor developed in this work. For the Raman and FTIR analyses, the two main components resulting from the library search were considered. The result shown in the table is the most relevant one according to the analysis by the standard method of those two results. **Green** = AMP detected (true positive). **Red** = AMP not detected (false negative).

Sample name	Result Raman (Bruker Bravo)	Result FTIR (Bruker Alpha II)	Result electrochemical sensor
SS1	Norephedrine	Amphetamine	Amphetamine
SS2	Phenethylamine	Amphetamine	Amphetamine
SS3	Norephedrine	Amphetamine	Amphetamine
SS4	Amphetamine	Caffeine	Amphetamine
SS5	Amphetamine	Caffeine	Amphetamine
SS6	Caffeine	Caffeine	Amphetamine
SS7	Amphetamine	Amphetamine	Amphetamine
SS8	Amphetamine	Amphetamine	Amphetamine
SS9	Amphetamine	Amphetamine	Amphetamine
SS10	Amphetamine	Amphetamine	Unknown
SS11	Norephedrine	Amphetamine	Amphetamine
SS12	Norephedrine	Amphetamine	Amphetamine
SS13	Creatine	Amphetamine	Amphetamine
SS14	Norephedrine	Amphetamine	Amphetamine
SS15	Norephedrine	Amphetamine	Amphetamine
SS16	Norephedrine	Amphetamine	Amphetamine
SS17	Amphetamine	Amphetamine	Amphetamine
SS18	Amphetamine	Amphetamine	Amphetamine
SS19	Pseudoephedrine	Amphetamine	Amphetamine
SS20	1-phenyl-1-propanol	Amphetamine	Amphetamine
SS21	Sugar	Amphetamine	Amphetamine
SS22	Amphetamine	Amphetamine	Amphetamine
SS23	Amphetamine	Amphetamine	Amphetamine

SS24	Amphetamine	Amphetamine	Amphetamine
SS25	Amphetamine	Caffeine	Amphetamine
SS26	Amphetamine	Unknown	Amphetamine
SS27	Amphetamine	Caffeine	Amphetamine
SS28	Amphetamine	Caffeine	Amphetamine
SS29	Amphetamine	Caffeine	Amphetamine
SS30	Amphetamine	Caffeine	Amphetamine
<b>Results</b>	17/30 (56.7 %)	21/30 (70.0 %)	29/30 (96.7 %)

#### 4. Conclusion

In this work, a paraformaldehyde-coated sensor for the rapid (ca. 1.5 min) and straightforward on-site qualitative analysis of AMP in seized drug samples was developed and validated. The combination of a PFA-coating on the working electrode of a graphite SPE and PBS pH 12 proved to be suitable conditions for the derivatization and subsequent electrochemical detection of AMP, which is otherwise non-electroactive at an unmodified graphite SPE. After assessing the influence of important on-site factors such as concentration and temperature on the electrochemical behavior, a potential interval around the single characteristic AMP peak was defined (0.83 – 0.95 V) to account for potential shifts due to fluctuations in these on-site factors. The sensor proved capable of detecting AMP in the presence of the most commonly encountered diluents and adulterants, including caffeine, which is known to cause issues for the Raman/FTIR analysis of AMP samples when present in high amounts. To discriminate AMP from cocaine and ketamine, a simultaneous second test with the same solution on an unmodified SPE was successfully introduced to provide the necessary additional electrochemical information (dual-sensor strategy).

The concept was finally validated by analyzing 30 seized AMP samples, provided by several European Forensic and Customs Laboratories, and compared to the performance of commercially available Raman and FTIR devices. The electrochemical sensor obtained the highest test sensitivity and combined with its affordability and rapid nature proved its potential value as an alternative sensing technique for the on-site analysis of a wide variety of suspicious samples.

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## References

- [1] N. Rasmussen, Amphetamine-Type Stimulants: The Early History of Their Medical and Nonmedical Uses, in: *International Review of Neurobiology*, 1st ed., Elsevier Inc., 2015: pp. 9–25. <https://doi.org/10.1016/bs.irn.2015.02.001>.
- [2] S.K. Bell, J.C. Lucke, W.D. Hall, Lessons for Enhancement From the History of Cocaine and Amphetamine Use, *AJOB Neuroscience*. 3 (2012) 24–29. <https://doi.org/10.1080/21507740.2012.663056>.
- [3] M. Morelli, E. Tognotti, Brief history of the medical and non-medical use of amphetamine-like psychostimulants, *Experimental Neurology*. 342 (2021) 113754. <https://doi.org/10.1016/j.expneurol.2021.113754>.
- [4] A.-M. Dragan, M. Parrilla, B. Feier, R. Oprean, C. Cristea, K. De Wael, Analytical techniques for the detection of amphetamine-type substances in different matrices: A comprehensive review, *TrAC Trends in Analytical Chemistry*. 145 (2021) 116447. <https://doi.org/10.1016/j.trac.2021.116447>.
- [5] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), *European Drug Report 2021: Trends and Developments*, Publications Office of the European Union, 2021. <https://doi.org/10.1093/tandt/9.1.4>.

- [6] United Nations Office on Drugs and Crime (UNODC), World Drug Report 2021, 2021.
- [7] European Monitoring Centre for Drugs and Drug Addiction, EMCDDA – Europol joint publications: Amphetamine, 2011. <https://doi.org/10.2810/49525>.
- [8] C. Cole, L. Jones, J. Mcveigh, A. Kicman, Q. Syed, M. a Bellis, CUT. A guide to adulterants, bulking agents and other contaminants found in illicit drugs, Liverpool, 2010. <http://www.cph.org.uk/wp-content/uploads/2012/08/cut-a-guide-to-the-adulterants-bulking-agents-and-other-contaminants-found-in-illicit-drugs.pdf>.
- [9] C. Cole, L. Jones, J. McVeigh, A. Kicman, Q. Syed, M. Bellis, Adulterants in illicit drugs: a review of empirical evidence, *Drug Testing and Analysis*. 3 (2011) 89–96. <https://doi.org/10.1002/dta.220>.
- [10] M.F. Andreasen, C. Lindholst, E. Kaa, Adulterants and Diluents in Heroin, Amphetamine, and Cocaine Found on the Illicit Drug Market in Aarhus, Denmark, *The Open Forensic Science Journal*. 2 (2009) 16–20. <https://doi.org/10.2174/1874402800902010016>.
- [11] E. Cuypers, A.-J. Bonneure, J. Tytgat, The use of presumptive color tests for new psychoactive substances, *Drug Testing and Analysis*. 8 (2016) 136–140. <https://doi.org/10.1002/dta.1847>.
- [12] M. Philp, S. Fu, A review of chemical ‘spot’ tests: A presumptive illicit drug identification technique, *Drug Testing and Analysis*. 10 (2018) 95–108. <https://doi.org/10.1002/dta.2300>.
- [13] United Nations Office on Drugs and Crime (UNODC), Recommended Methods for the Identification and Analysis of Amphetamine, Methamphetamine and Their Ring-Substituted, 2006.
- [14] R.A. Murray, P.L. Doering, L.A. Boothby, M.L. Merves, R.R. McCusker, C.W. Chronister, B.A. Goldberger, Putting an Ecstasy Test Kit to the Test: Harm Reduction or Harm Induction?, *Pharmacotherapy*. 23 (2003) 1238–1244. <https://doi.org/10.1592/phco.23.12.1238.32704>.
- [15] M. de Jong, A. Florea, J. Eliaerts, F. van Durme, N. Samyn, K. de Wael, Tackling Poor Specificity of Cocaine Color Tests by Electrochemical Strategies, *Analytical Chemistry*. 90 (2018) 6811–6819. <https://doi.org/10.1021/acs.analchem.8b00876>.
- [16] S. Thiruvottriyur Shanmugam, R. Van Echelpoel, G. Boeye, J. Eliaerts, M. Samanipour, H.Y.V. Ching, A. Florea, S. Van Doorslaer, F. Van Durme, N. Samyn, M. Parrilla, K. De Wael, Towards Developing a Screening Strategy for Ecstasy: Revealing the Electrochemical Profile, *ChemElectroChem*. 8 (2021) 4826–4834. <https://doi.org/10.1002/celec.202101198>.
- [17] S.E.J. Bell, D.T. Burns, A.C. Dennis, J.S. Speers, Rapid analysis of ecstasy and related phenethylamines in seized tablets by Raman spectroscopy, *The Analyst*. 125 (2000) 541–544. <https://doi.org/10.1039/a908091k>.
- [18] E. Katainen, M. Elomaa, U.-M. Laakkonen, E. Sippola, P. Niemelä, J. Suhonen, K. Järvinen, Quantification of the Amphetamine Content in Seized Street Samples by Raman Spectroscopy, *Journal of Forensic Sciences*. 52 (2007) 88–92. <https://doi.org/10.1111/j.1556-4029.2006.00306.x>.
- [19] M.D. Hargreaves, K. Page, T. Munshi, R. Tomsett, G. Lynch, H.G.M. Edwards, Analysis of seized drugs using portable Raman spectroscopy in an airport environment—a proof of principle study, *Journal of Raman Spectroscopy*. 39 (2008) 873–880. <https://doi.org/10.1002/jrs.1926>.

- [20] E. Gerace, F. Seganti, C. Luciano, T. Lombardo, D. Di Corcia, H. Teifel, M. Vincenti, A. Salomone, On-site identification of psychoactive drugs by portable Raman spectroscopy during drug-checking service in electronic music events, *Drug and Alcohol Review*. 38 (2019) 50–56. <https://doi.org/10.1111/dar.12887>.
- [21] K.W. Tupper, K. McCrae, I. Garber, M. Lysyshyn, E. Wood, Initial results of a drug checking pilot program to detect fentanyl adulteration in a Canadian setting, *Drug and Alcohol Dependence*. 190 (2018) 242–245. <https://doi.org/10.1016/j.drugalcdep.2018.06.020>.
- [22] E. Deconinck, C. Ait-Kaci, A. Raes, M. Canfyn, J. Bothy, C. Duchateau, C. Mees, K. De Braekeleer, L. Gremaux, P. Blanckaert, An infrared spectroscopic approach to characterise white powders, easily applicable in the context of drug checking, drug prevention and on-site analysis, *Drug Testing and Analysis*. 13 (2021) 679–693. <https://doi.org/10.1002/dta.2973>.
- [23] C. Weyermann, Y. Mimoune, F. Anglada, G. Massonnet, P. Esseiva, P. Buzzini, Applications of a transportable Raman spectrometer for the in situ detection of controlled substances at border controls, *Forensic Science International*. 209 (2011) 21–28. <https://doi.org/10.1016/j.forsciint.2010.11.027>.
- [24] L. Shaw, L. Dennany, Applications of electrochemical sensors: Forensic drug analysis, *Current Opinion in Electrochemistry*. 3 (2017) 23–28. <https://doi.org/10.1016/j.coelec.2017.05.001>.
- [25] H. Teymourian, M. Parrilla, J.R. Sempionatto, N.F. Montiel, A. Barfidokht, R. Van Echelpoel, K. De Wael, J. Wang, Wearable Electrochemical Sensors for the Monitoring and Screening of Drugs, *ACS Sensors*. 5 (2020) 2679–2700. <https://doi.org/10.1021/acssensors.0c01318>.
- [26] P.C. Ferreira, V.N. Ataíde, C.L. Silva Chagas, L. Angnes, W.K. Tomazelli Coltro, T.R. Longo Cesar Paixão, W. Reis de Araujo, Wearable electrochemical sensors for forensic and clinical applications, *TrAC Trends in Analytical Chemistry*. 119 (2019) 115622. <https://doi.org/10.1016/j.trac.2019.115622>.
- [27] E. De Rycke, C. Stove, P. Dubruel, S. De Saeger, N. Beloglazova, Recent developments in electrochemical detection of illicit drugs in diverse matrices, *Biosensors and Bioelectronics*. 169 (2020) 112579. <https://doi.org/10.1016/j.bios.2020.112579>.
- [28] B. Zanfrognini, L. Pigani, C. Zanardi, Recent advances in the direct electrochemical detection of drugs of abuse, *Journal of Solid State Electrochemistry*. 24 (2020) 2603–2616. <https://doi.org/10.1007/s10008-020-04686-z>.
- [29] G. Moro, H. Barich, K. Driesen, N. Felipe Montiel, L. Neven, C. Domingues Mendonça, S. Thiruvottriyur Shanmugam, E. Daems, K. De Wael, Unlocking the full power of electrochemical fingerprinting for on-site sensing applications, *Analytical and Bioanalytical Chemistry*. 412 (2020) 5955–5968. <https://doi.org/10.1007/s00216-020-02584-x>.
- [30] R.G. Rocha, J.S. Stefano, I.V.S. Arantes, M.M.A.C. Ribeiro, M.H.P. Santana, E.M. Richter, R.A.A. Munoz, Simple Strategy for Selective Determination of Levamisole in Seized Cocaine and Pharmaceutical Samples Using Disposable Screen-printed Electrodes, *Electroanalysis*. 31 (2019) 153–159. <https://doi.org/10.1002/elan.201800716>.
- [31] G. Murilo Alves, A. Soares Castro, B.R. McCord, M.F. Oliveira, MDMA Electrochemical Determination and Behavior at Carbon Screen-printed Electrodes: Cheap Tools for Forensic Applications, *Electroanalysis*. 33 (2021) 635–642. <https://doi.org/10.1002/elan.202060080>.

- [32] N. Felipe Montiel, M. Parrilla, V. Beltrán, G. Nuyts, F. Van Durme, K. De Wael, The opportunity of 6-monoacetylmorphine to selectively detect heroin at preanodized screen printed electrodes, *Talanta*. 226 (2021) 122005. <https://doi.org/10.1016/j.talanta.2020.122005>.
- [33] A. Florea, J. Schram, M. de Jong, J. Eliaerts, F. Van Durme, B. Kaur, N. Samyn, K. De Wael, Electrochemical Strategies for Adulterated Heroin Samples, *Analytical Chemistry*. 91 (2019) 7920–7928. <https://doi.org/10.1021/acs.analchem.9b01796>.
- [34] J. Schram, M. Parrilla, N. Slegers, F. van Durme, J. Berg, A.L.N. Nuijs, K. de Wael, Electrochemical profiling and liquid chromatography–mass spectrometry characterization of synthetic cathinones: From methodology to detection in forensic samples, *Drug Testing and Analysis*. (2021) dta.3018. <https://doi.org/10.1002/dta.3018>.
- [35] M.O.B. Arriero, L.C. Arantes, D.A.R. Moreira, D.M. Pimentel, C.D. Lima, L.M.F. Costa, R.M. Verly, W.T.P. dos Santos, Electrochemical detection of eutylone using screen-printed electrodes: Rapid and simple screening method for application in forensic samples, *Electrochimica Acta*. 412 (2022) 140106. <https://doi.org/10.1016/j.electacta.2022.140106>.
- [36] M. Masui, H. Sayo, Y. Tsuda, Anodic oxidation of amines. Part I. Cyclic voltammetry of aliphatic amines at a stationary glassy-carbon electrode, *Journal of the Chemical Society B: Physical Organic*. (1968) 973. <https://doi.org/10.1039/j29680000973>.
- [37] A. Adenier, M.M. Chehimi, I. Gallardo, J. Pinson, N. Vilà, Electrochemical Oxidation of Aliphatic Amines and Their Attachment to Carbon and Metal Surfaces, *Langmuir*. 20 (2004) 8243–8253. <https://doi.org/10.1021/la049194c>.
- [38] E.M.P.J. Garrido, J.M.P.J. Garrido, N. Milhazes, F. Borges, A.M. Oliveira-Brett, Electrochemical oxidation of amphetamine-like drugs and application to electroanalysis of ecstasy in human serum, *Bioelectrochemistry*. 79 (2010) 77–83. <https://doi.org/10.1016/j.bioelechem.2009.12.002>.
- [39] W.P. Silva, R.G. Rocha, L.C. Arantes, C.D. Lima, L.M.A. Melo, R.A.A. Munoz, W.T.P. dos Santos, E.M. Richter, Development of a simple and rapid screening method for the detection of 1-(3-chlorophenyl)piperazine in forensic samples, *Talanta*. 233 (2021) 122597. <https://doi.org/10.1016/j.talanta.2021.122597>.
- [40] A. dos S. Novais, L.C. Arantes, E.S. Almeida, R.G. Rocha, C.D. Lima, L.M. de A. Melo, E.M. Richter, R.A.A. Munoz, W.T. Pio dos Santos, R.A.B. da Silva, Fast on-site screening of 3,4-methylenedioxyethylamphetamine (MDEA) in forensic samples using carbon screen-printed electrode and square wave voltammetry, *Electrochimica Acta*. 403 (2022) 139599. <https://doi.org/10.1016/j.electacta.2021.139599>.
- [41] K.R. Teófilo, L.C. Arantes, P.A. Marinho, A.A. Macedo, D.M. Pimentel, D.P. Rocha, A.C. de Oliveira, E.M. Richter, R.A.A. Munoz, W.T.P. dos Santos, Electrochemical detection of 3,4-methylenedioxymethamphetamine (ecstasy) using a boron-doped diamond electrode with differential pulse voltammetry: Simple and fast screening method for application in forensic analysis, *Microchemical Journal*. 157 (2020) 105088. <https://doi.org/10.1016/j.microc.2020.105088>.
- [42] D.M. Pimentel, L.C. Arantes, L.M. Santos, K.A.O. Souza, R.M. Verly, S.L. Barbosa, W.T.P. dos Santos, Rapid and simple voltammetric screening method for Lysergic Acid Diethylamide (LSD)

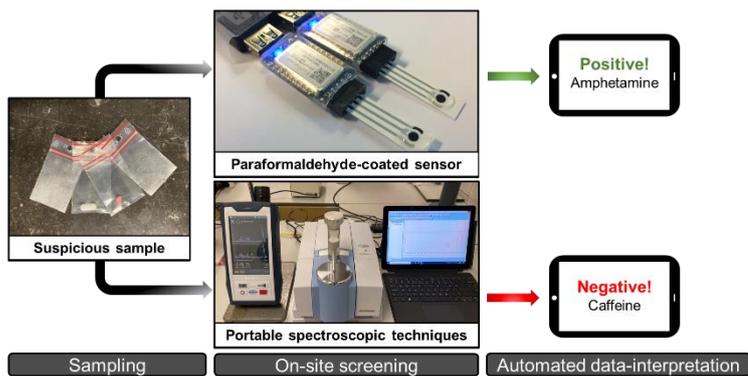
- detection in seized samples using a boron-doped diamond electrode, *Sensors and Actuators, B: Chemical*. 344 (2021). <https://doi.org/10.1016/j.snb.2021.130229>.
- [43] J. Gallardo-Gonzalez, A. Saini, A. Baraket, S. Boudjaoui, A. Alcácer, A. Streklas, F. Teixidor, N. Zine, J. Bausells, A. Errachid, A highly selective potentiometric amphetamine microsensor based on all-solid-state membrane using a new ion-pair complex, [3,3'-Co(1,2-closo-C2B9H11)2]- [C9H13NH]<sup>+</sup>, *Sensors and Actuators B: Chemical*. 266 (2018) 823–829. <https://doi.org/10.1016/j.snb.2018.04.001>.
- [44] Y. Jang, M. Jang, H. Kim, S.J. Lee, E. Jin, J.Y. Koo, I.-C. Hwang, Y. Kim, Y.H. Ko, I. Hwang, J.H. Oh, K. Kim, Point-of-Use Detection of Amphetamine-Type Stimulants with Host-Molecule-Functionalized Organic Transistors, *Chem*. 3 (2017) 641–651. <https://doi.org/10.1016/j.chempr.2017.08.015>.
- [45] F.M. Iverson, J.W. Kane, J.E. Pearson, J. Kenny, P. Vadgama, Development of a redox mediated amperometric detection system for immunoassay. Application to urinary amphetamine screening, *Electroanalysis*. 12 (2000) 778–785. [https://doi.org/https://doi.org/10.1002/1521-4109\(200006\)12:10<778::AID-ELAN778>3.0.CO;2-%23](https://doi.org/10.1002/1521-4109(200006)12:10<778::AID-ELAN778>3.0.CO;2-%23).
- [46] A. Goodwin, C.E. Banks, R.G. Compton, Tagging of Model Amphetamines with Sodium 1,2-Naphthoquinone-4-sulfonate: Application to the Indirect Electrochemical Detection of Amphetamines in Oral (Saliva) Fluid, *Electroanalysis*. 18 (2006) 1833–1837. <https://doi.org/10.1002/elan.200603596>.
- [47] M. Parrilla, N. Felipe Montiel, F. van Durme, K. de Wael, Derivatization of amphetamine to allow its electrochemical detection in illicit drug seizures, *Sensors and Actuators B: Chemical*. 337 (2021) 129819. <https://doi.org/10.1016/j.snb.2021.129819>.
- [48] M. Parrilla, A. Vanhooydonck, R. Watts, K. De Wael, Wearable wristband-based electrochemical sensor for the detection of phenylalanine in biofluids, *Biosensors and Bioelectronics*. 197 (2022) 113764. <https://doi.org/10.1016/j.bios.2021.113764>.
- [49] J. Schram, S.T. Shanmugam, N. Slegers, A. Florea, N. Samyn, A.L.N. van Nuijs, K. de Wael, Local conversion of redox inactive molecules into redox active ones: A formaldehyde based strategy for the electrochemical detection of illicit drugs containing primary and secondary amines, *Electrochimica Acta*. 367 (2021) 137515. <https://doi.org/10.1016/j.electacta.2020.137515>.
- [50] A. Slosse, F. Van Durme, N. Samyn, D. Mangelings, Y. Vander Heyden, Evaluation of data preprocessings for the comparison of GC–MS chemical profiles of seized cannabis samples, *Forensic Science International*. 310 (2020) 110228. <https://doi.org/10.1016/j.forsciint.2020.110228>.
- [51] M. Haghghi, M. Shahlaei, M. Irandoust, A. Hassanpour, New and sensitive sensor for voltammetry determination of Methamphetamine in biological samples, *Journal of Materials Science: Materials in Electronics*. 31 (2020) 10989–11000. <https://doi.org/10.1007/s10854-020-03647-6>.

- [52] J. Schram, M. Parrilla, N. Slegers, N. Samyn, S.M. Bijvoets, M.W.J. Heerschop, A.L.N. van Nuijs, K. de Wael, Identifying Electrochemical Fingerprints of Ketamine with Voltammetry and Liquid Chromatography–Mass Spectrometry for Its Detection in Seized Samples, *Analytical Chemistry*. 92 (2020) 13485–13492.  
<https://doi.org/10.1021/acs.analchem.0c02810>.

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**Research Highlights:**

- Rapid and user-friendly electrochemical sensor for amphetamine detection.
- Deposition of a paraformaldehyde-coating as a derivatization reagent.
- Assessment of on-site parameters such as fluctuating temperature and concentration.
- Additional test on unmodified electrode needed for inter-drug differentiation.
- Sensor validation through analysis of 30 seized samples containing amphetamine.



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**Declaration of interests**

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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