Investigating the electrochemical profile of methamphetamine to enable fast on-site detection in forensic analysis

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Highlights

- Investigation of the electrochemical behavior of MA over a wide concentration range
- Selective detection of MA in mixtures with other illicit drugs and adulterants
- Voltammetric sensing of MA in confiscated samples using screen-printed electrodes
- Fast and portable device with high sensitivity, specificity and acurracy

Abstract

Methamphetamine (MA) is a synthetic psychoactive drug which is consumed both licitly and illicitly. In some countries it is prescribed for attention-deficit and hyperactivity disorder, and short-term treatment of obesity. More often though, it is abused for its psychostimulant properties. Unfortunately, the spread and abuse of this synthetic drug have increased globally, being reported as the most widely consumed synthetic psychoactive drug in the world in 2019. Attempting to overcome the shortcomings of the currently used on-site methods for MA detection in suspected cargos, the present study explores the potential of electrochemical

identification of MA by means of square wave voltammetry on disposable graphite screen-printed electrodes. Hence, the analytical characterization of the method was evaluated under optimal conditions exhibiting a linear range between 250 µM and 2.5 mM MA, a LOD of 66.4 µM, a LOQ of 201.2 µM and a sensitivity of 5.3 µA mM^{-1}. Interestingly, two zones in the potential window were identified for the detection of MA, depending on its concentration in solution. Furthermore, the oxidative pathway of MA was elucidated employing liquid chromatography – mass spectrometry to understand the change in the electrochemical profile. Thereafter, the selectivity of the method towards MA in mixtures with other drugs of abuse as well as common adulterants/cutting agents was evaluated. Finally, the described method was employed for the analysis of MA in confiscated samples and compared with forensic methods, displaying its potential as a fast and easy-to-use method for on-site analysis.

Keywords:
electrochemical profile; methamphetamine; redox pathway; on-site forensic analysis; Raman spectrometer; FTIR spectrometer.

1. Introduction

Methamphetamine (MA) is a synthetic psychoactive drug belonging to the class of amphetamine-type stimulants (ATS), together with amphetamine and MDMA (3,4-methylenedioxymethamphetamine, ecstasy) [1] and can exist in two forms (base - a colorless volatile oil, and hydrochloride salt - a crystalline solid) [2]. It is classified as an internationally controlled drug [3] and can be used both licitly and illicitly. It is approved by the FDA (Food and Drugs Administration) as a second-line treatment of attention-deficit and hyperactivity disorder (ADHD) [3,4] and short-term treatment of obesity. More commonly, MA is illicitly used for its psychostimulant properties, generating euphoria, entactogenic effects, the stimulation of the reward centers, increased level of wakefulness, sexual arousal and hallucinations [3,5,6]. These effects are a result of the increased levels of monoaminergic neurotransmitters, namely dopamine, adrenaline, and noradrenaline [5]. The increased levels of these neurotransmitters are also responsible for the adverse toxic effects of MA, such as addiction, psychosis, serotonin syndrome, and cardiovascular conditions, among many others [4,6].

Globally, ATS accounted for 19 % of the drug seizure cases between 2017 and 2019 (13% being appointed to MA alone), being the second most common seized group of illicit drugs after cannabis [7]. It was reported that 0.5 % of the worldwide population aged between 15 and 64 (27 million people) used amphetamines in 2019 [7]. This was also the percentage of the

European population that used amphetamines in 2019 in the same age range, while for North America and Oceania the values recorded were higher (2% and 1%, respectively) [7]. The most recent World Drug Report showed that MA was the predominant ATS on the illicit drug market in 2019 (72% of the total ATS seized cargos), while the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) reported in the same year that MA was the most widely used synthetic psychoactive drug in the world [8]. Furthermore, in the last 10 years, MA presented an important increase in its spread around the globe, reaching 111 countries by 2019 from 79 in 2009 [9], as well as the largest increase in the quantities seized in Europe (+931%). The numbers for illicit drugs consumption remain high, although the synthetic drugs demand decreased during the COVID-19 pandemic, which could be explained by the closing of clubs and many other social gathering locations [10].

It is well-known that the drugs sold on the illicit market may contain other substances besides the drug itself, namely adulterants and cutting agents which could hinder the detection of the suspected illicit drug. The available reports showed that MA sold on the illicit drugs market has an inconsistent purity, varying between 92% and 97% in the United States (predominantly crystal methamphetamine) [9] and between 20% and 100% in Europe (crystal methamphetamine and other forms) [1]. The most encountered adulterants in MA samples are dimethyl sulfone, which can be a co-ingredient of the precursors used for MA synthesis [11,12], and caffeine [13–16], which also presents nervous system stimulant proprieties, which could explain the choice of this adulterant. Other MA adulterants/cutting agents, as well as their proportion reported in MA samples, are presented in **Table 1**.

Table 1. Adulterants/cutting agents and their proportions in methamphetamine samples

Adulterant/cutting agent	Concentration (%)	Ref
Dimethyl sulfone	0 - ≥90	[11,12]
Caffeine	3 - 60	[13–16]
Paracetamol	2 - 10	[13,15]
Creatine	1 - 5	[16]
Levamisole	4	[13]
Quinine/quinidine	2	[13]
Lidocaine	1	[13]
Xylazine	1	[13]
Procaine	NM	[17]
Dextromethorphan	NM	[14]
Sugars (sucrose, lactose, dextrose, mannitol)	NM	[2,11]

NM=not mentioned

Regarding the identification of MA, as in the case of the other illicit drugs, the detection methods can be grouped in two categories: on-site detection methods, for screening of suspected cargos, and methods used in toxicological laboratories as confirmatory analysis. Belonging to the latter category, are the traditional methods, mainly chromatographic techniques coupled to mass spectrometry (MS) or tandem mass spectrometry (MS/MS) such as gas-chromatography or liquid chromatography and capillary electrophoresis [6]. Besides, spectroscopic techniques such as Fourier transform infrared (FTIR) and Raman spectroscopy are widely used in laboratory settings [6].

The screening of suspicious samples is an important step for the on-site identification of illicit drugs since law enforcement agents decide if the suspected cargo needs to be confiscated or not. Hence, the analytical tools used for the screening step play an important role in the outcome of the confiscation of the illicit drugs and require specific characteristics: (i) portability and miniaturization, (ii) low rate of false positive and false negative results, (iii) ease of use by the personnel, (iv) fast outcome delivery, (v) ease of output interpretation and (vi) low cost. The currently used on-site methods are (i) the presumptive color tests, based on the Marquis reagent, and (ii) immunoassays, while (iii) portable Raman and FTIR represent more expensive alternative choices [6].Presumptive color tests and portable Raman devices, although being simple and quick tests, show low accuracy and high false positive or false negative rates [6].

An emerging technique for on-site testing of suspected cargos is depicted by electrochemical methods [6,18,19]. The constant development conducted in this field has permitted the replacement of the laboratory setting equipment consisting of a three separate electrodes configuration (reference, counter and working electrodes) and a bulky potentiostat connected to a computer or a laptop, with single screen-printed electrodes (SPE) and miniaturized portable potentiostats connected to smartphones [20–23]. This switch, together with fast electrochemical techniques such as square wave voltammetry (SWV) facilitated the use of electrochemical sensors for on-site detection. Importantly, electrochemical tests comply with the requirements mentioned above for on-site testing devices while maintaining excellent analytical performance in terms of both sensitivity and selectivity. Recently, an interesting approach was proposed by Vannoy *et al.,* describing the use of an electrochemical cell consisting of a graphite microwire, a platinum wire and a soap bubble wall for the detection of MA from liquid aerosols [24]. Besides, literature reports on electrochemical sensors for the detection of MA mainly based on electrode's modifications with various nanomaterials (gold nanoparticles, multiwalled carbon nanotubes, graphene oxide) or artificial receptors (molecularly imprinted polymers and aptamers), while using SWV, differential pulse voltammetry (DPV) and electrochemical

impedance spectroscopy (EIS) as the most common electrochemical techniques (**Table 2**). However, these sensors aim to detect MA in different biological matrices while avoiding its application in cargos analysis.

The present work describes the electrochemical behavior of MA on a graphite SPE, aiming to investigate the potential of electrochemistry as an alternative method for decentralized analysis of suspected cargos (**Fig. 1**). In order to reach this aim, several steps were systematically assessed. Firstly, the electrochemical characterization of MA on graphite SPEs was performed by cyclic voltammetry (CV) and SWV as a fast electroanalytical technique. During this step, a pH study was conducted to evaluate the influence of this variable on the electrochemical oxidation of MA. Besides, the oxidative pathway of MA under electrochemical interrogation was elucidated using liquid chromatography coupled to a quadrupole time-of-flight mass spectrometer (LC-QTOF-MS) to understand the products formed after the electrochemical analysis. Subsequently, the analytical characterization of the method and the evaluation of its selectivity towards MA in mixtures with other drugs of abuse as well as common adulterants/cutting agents were evaluated. Finally, the portable device (i.e. disposable SPE and portable potentiostat) was employed for the assessment of confiscated street samples, displaying its potential for implementation in the field as a fast and easy-to-use method for on-site analysis.

2. Experimental section

The present study systematically followed several steps:

(i). Electrochemical characterization of methamphetamine on graphite SPEs

a. The pH study for the electrochemical characterization of MA was performed by SWV in 0.5 mM solutions in the pH range from 6 to 12.
b. The assessment of the MA redox behavior was performed by CV in a 0.5 mM solution at pH 12. For a 10 mM MA standard solution, a scan rate study by CV was carried out.

(ii) Analytical performance

The analytical characterization of the electrochemical method was evaluated by SWV at pH 12 through the concentration (µM) range (using solutions with the following concentrations: 50, 100, 250, 500, 750, 1000, 2500, 5000, 6000, 7000, 7500, 8000, 9000 and 10000), the limit of detection (LOD), the limit of quantification (LOQ) and sensitivity. Triplicates were performed for each point of the linear range and the average was used for the construction of the calibration curve. The LOD and LOQ were determined according to the formulas: LOD = $3.3(S_y/S)$ and

LOQ = 10(S_y/S), where S_y is the standard deviation of the response and S is the slope of the calibration curve; the sensitivity represents the slope of the linear curve.

(iii) The elucidation of the MA oxidative pathway

The elucidation of the MA oxidative pathway was performed by LC-QTOF-MS on 200 µM MA solutions which were electrolyzed in PBS pH 12, at 0.95 V (vs int. ref). Besides, 10 mM solution was also electrolyzed at 0.69 V (vs. int. ref) in PBS pH 12. After 60 minutes, the electrolyzed samples were diluted to 20 ng μL^{-1} with ultrapure water and injected directly.

(iv) Evaluation of the selectivity in MA mixtures

The selectivity was assessed by SWV at pH 12 in binary and complex mixtures: the binary mixtures tested contained equal concentrations of MA and either another illicit drug (MDMA, mephedrone, heroin, cocaine, and ketamine) or an adulterant/cutting agent (DMS, caffeine, paracetamol, creatine, and levamisole); two concentration levels were investigated, 0.5 mM and 7.5 mM, for all binary mixtures. Three complex mixtures were tested which contained MA in combination with (i) paracetamol, creatine and caffeine, (ii) paracetamol and creatine, and (iii) caffeine and creatine, in equal concentrations (0.5 mM) for each component.

(v) Detection and validation of the electrochemical device in confiscated samples

The electrochemical evaluation of confiscated samples was performed at NICC, Belgium. Two sampling methods were investigated by dissolving the suspected powder in 15 mL of buffer: (i) underloading, when a very small amount of powder (by filling the tip of the spatula which accounts for ca. 1 mg), and (ii) overloading, when a larger amount of powder (by filling the whole area of the spatula which accounts to ca. 5 mg). A drop of the obtained solution was afterward cast on the disposable SPE inserted into a miniaturized portable potentiostat (EmStatBlue) connected to a laptop through Bluetooth. A schematic illustration of the configuration for on-site electrochemical analysis using a SensitSmart potentiostat (PalmSens, The Netherlands) connected to a smartphone with the android “PStouch” application is shown in **Fig. 1**.

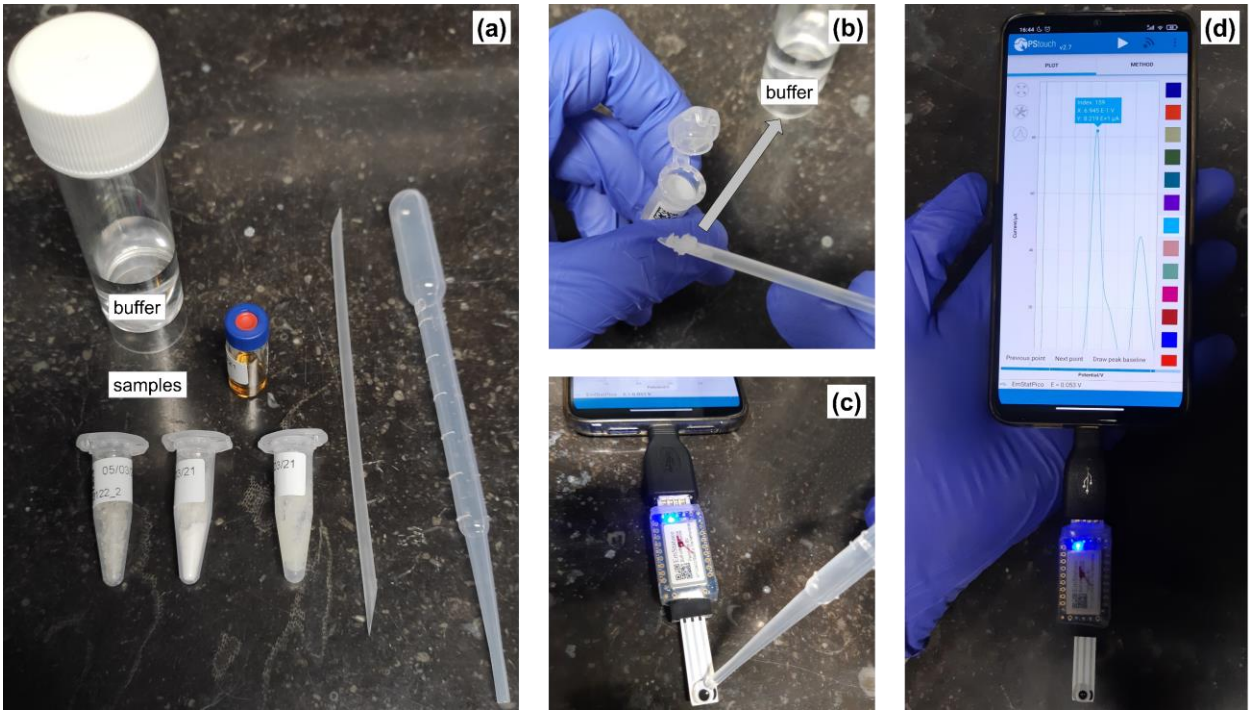

Fig. 1. *Schematic representation of the electrochemical screening of confiscated samples using the portable test:* ***a)*** *The different types of samples that can be tested (powder, crystal, paste or liquid, white, colored or transparent), a disposable spatula as a sampling tool, a disposable Pasteur pipette and a recipient with buffer;* ***b)*** *Sampling of a few crystals to be dissolved in the buffer;* ***c)*** *Casting a drop of the obtained solution to the disposable SPE connected to a miniaturized portable potentiostat powered by and controlled with a smartphone;* ***d)*** *The recording of the electrochemical profile using the android "PSTouch" app installed on the smartphone.*

Reproducibility studies for the electrochemical method were performed for intra- and inter-day analysis of MA standard solutions (N=3, and N=5, respectively) of 0.5 mM and 7.5 mM and for the assessment of seized samples in each sampling method (N=3) on SPEs at pH 12.

The CV parameters were: potential range from -0.2 V to 1.5 V with a scan rate of 0.10 V s^{-1} for the assessment of MA redox behaviour and from 0.025 V s^{-1} to 0.60 V s^{-1} (0.025, 0.050, 0.10, 0.20, 0.40, 0.60) for the scan rate study. The SWV parameters were: equilibration time of 5 s, potential range from 0.005 V to 1.5 V, step potential of 5 mV, amplitude of 25 mV and frequency of 10.0 Hz; when employed, the cathodic pretreatment consisted in an integrated application of a -0.8 V potential for 10 s, 120 s and 300 s right before starting the SWV.

The sensitivity, specificity and accuracy of the portable methods were calculated according to the following formulas:

$$Sensitivity = \frac{TP}{TP+FN}\ x\ 100;\ Specificity = \frac{TN}{TN+FP}\ x\ 100;\ Accuracy = \frac{TP+TN}{TP+TN+FP+FN}\ x\ 100;$$

where TP: true positive; TN: true negative; FP: false positive; FN: false negative.

All materials and instruments used in this study as well as LC-QTOF-MS parameters can be found in the supplementary data.

3. Results and discussion

3.1. Electrochemical characterization of methamphetamine on graphite SPEs

The electrochemical characterization of MA was performed using two electrochemical techniques: SWV and CV. Firstly, the influence of the pH on the behavior of 0.5 mM MA was assessed by SWV in the pH range from 6 to 12. As can be seen in **Fig. 2a**, in the pH range of 6 - 8, no electrochemical signal was observed, suggesting that MA is not redox-active in the considered potential window (0 - 1.2 V). Towards more alkaline conditions (starting with pH 9 and up to pH 12), a redox peak was registered in the electrochemical profile of MA, corresponding to the electrochemical oxidation of the secondary amine from the MA structure (**Fig. S1**). It is suggested that the electro-oxidation of MA at the SPE is facilitated due to its deprotonation (pK_a=9.9). Furthermore, this peak registered a cathodic shift of the peak potential (E_p) from 1.04 V to 0.91 V, as well as an increase of the current intensity (I_p) from 0.34 µA to 3.50 µA, with the variation of the pH from pH 9 to pH 12 (**Fig. 2b**). This behavior suggests the involvement of protons in the electro-oxidation mechanism of MA. Hence, considering both peak parameters (the lowest E_p and the highest I_p), pH 12 was considered optimal for further experiments. Consequently, the electrochemical reversibility of MA was evaluated using CV at pH 12. **Fig. 2c** shows the cyclic voltammogram of 0.5 mM MA, where the irreversible oxidation of MA was registered at the potential of 0.88 V.

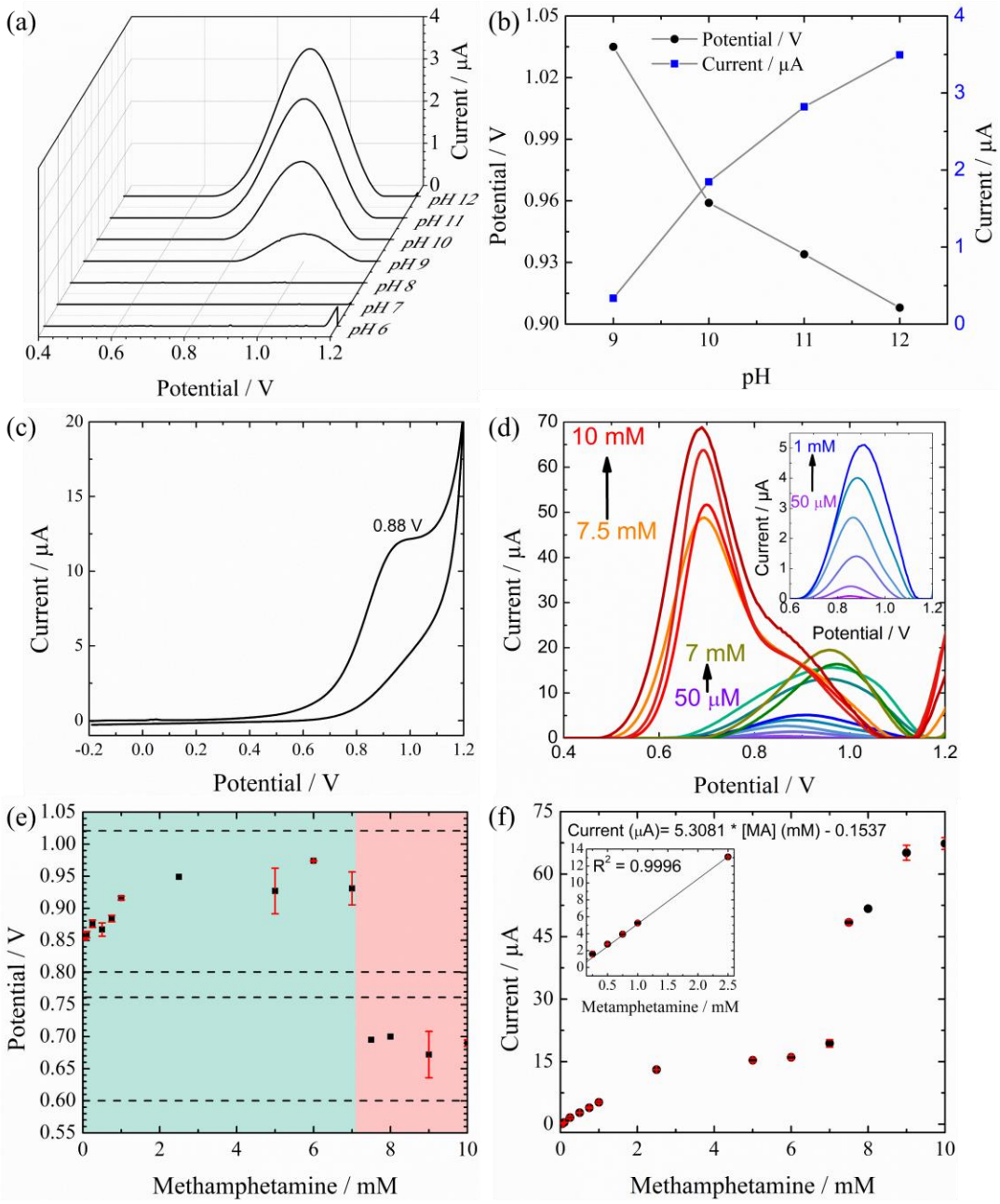

Fig. 2. *Electrochemical characterization of methamphetamine (MA) on graphite screen-printed electrodes (SPEs):* ***(a)*** *baseline corrected square wave voltammograms (SWV) of 0.5 mM MA in PBS 20 mM at pH ranging from 6 to 12;* ***(b)*** *the shift of 0.5 mM MA peak potential (**black points**) and current intensity (**blue squares**) at different pH values (6 - 12);* ***(c)*** *cyclic voltammogram for the redox activity assessment of 0.5 mM MA;* ***(d)*** *baseline corrected square wave voltammograms upon increasing concentrations of MA (50 µM - 10 mM);* ***(e)*** *the shift of MA peak potential upon increasing concentrations: with **faded green** - the high potential zone and with **faded red** - the low potential zone;* ***(f)*** *the current intensity response with increasing concentration (50 µM - 10 mM µM); inset: calibration curve from 250 µM to 2.5 mM (N = 3) with the corresponding equation: current (µA)= 5.3081 * [MA] (mM) + 0.1537, R^2 = 0.99. All experiments were performed in PBS 20 mM pH 12 except for the pH study.*

3.2. Analytical performance

The evaluation of the analytical performance of the method was carried out by the analysis of increasing concentrations of MA solutions in PBS pH 12 within the range from 50 µM to 10 mM. Importantly, high concentrations were also evaluated as the amount of analyte is not an issue in suspected samples, as unfortunately, grams or kilograms of the sample are usually encountered. Besides, the method described here is intended to be applied outside of laboratory conditions and without the employment of laboratory instruments (e.g., micropipettes or analytical balances) or trained personnel. **Fig. 2d** shows the SWVs of the MA solutions for the entire concentration range. It can be seen that the electrochemical profile of MA changed across the concentration range: for low concentrations (below 7 mM), MA exhibited a single well-defined peak, whilst at higher concentrations, the peak registered a shift to lower potential values of ~0.3 V and its shape changed, displaying a shoulder in addition to the main peak. This change in the electrochemical behavior of MA in high concentrations could be due to its adsorption on the electrode's surface, as previously observed for paracetamol, aspirin and caffeine [25]. To verify this hypothesis, a scan rate study was carried out in which a linear relationship between the I_p and the scan rate was obtained (**Fig. S2**), suggesting that the electrochemical reaction is indeed governed by an adsorption-controlled process and not a diffusion-controlled process (which is usually the case for the MA oxidation in low concentration solutions [26]). Furthermore, in the logarithmic plot of the current intensity response with increasing scan rate, the slope of the obtained equation was higher than 0.5 (**Fig. S2c)**. Hence, for high concentration solutions, the oxidation of MA is more favorable due to the adsorption-controlled phenomenon which generates the cathodic shift of the oxidation peak to lower potentials. Overall, the two peak profile of MA at high concentration could be explained by simultaneously occurring two processes, being the first peak oxidized due to adsorption phenomenon and the second peak due to diffusion-controlled process. Thus, depending on the concentration range, two potential zones were identified for MA detection: for low concentration solutions the potential window is defined from 0.80 V to 1.02 V, and for high concentration solutions the potential window is from 0.60 V to 0.76 V (**Fig. 2e)**. A 5% error was considered in the potential zone to overcome changes that might appear due to changes in temperature or concentration.

For quantitative purposes, the current intensities obtained for the MA solutions were plotted against the corresponding MA concentration (**Fig. 2f**). The corresponding linear equation was current (µA) = 5.1 * [MA] (mM) + 0.18, R^2 = 0.99, and the linearity plot can be seen in the inset of **Fig. 2f**. The linearity range obtained was within 250 µM and 2500 µM, with a LOD of 66.4 µM,

a LOQ of 201.2 and a sensitivity of 5.1 μA mM^{-1}. LOD value is slightly higher than the ones reported in the literature (**Table 2**), but this should not be a concern since the method described here aimed to qualitatively detect MA in suspected cargos where the obtained solutions are in the mM range. On the other hand, the literature screening showed that none of the papers describing MA electrochemical detection explored the electrochemical behavior of MA in such a wide range of concentrations as we have done in this study, particularly not for concentrations above 1 mM. Hence, to the best of our knowledge, the modification in the MA electrochemical behavior with the cathodic shift of the peak potential for high concentrations (above 7 mM) is herein reported for the first time. Finally, the reproducibility of the method was evaluated for two concentrations: (i) 0.5 mM (**Fig. S3a**; **Table S1a**) and (ii) 7.5 mM (**Fig. S3b**; ; **Table S1b**), both showing good intra- and inter-day reproducibility: (i) $RSD_{intra\text{-}day}$: 2 %, N = 3; $RSD_{inter\text{-}day}$: 6 %, N = 5; (ii) $RSD_{intra\text{-}day}$: %, N = 3; $RSD_{inter\text{-}day}$: 7 %, N = 5.

Table 2. Electrochemical techniques described in the literature for MA detection in different matrices.

Platform	Technique	LOD (μM)	Linear range (μM)	Sample	Duration (s)	Ref.
graphite microwire	CV	-	-	liquid aerosols	-	[24]
SPGE/G-PEG-dial/GA/BMIM TFSI/mAb	DPV	0.004	0.027 – 5.38	saliva	-	[27]
EDOT-BTDA-Pala/Ab GCE	DPV	87.58	67 - 670	urine, serum, saliva	-	[28]
PPGE	DPV	0.05	0.075 - 54	seized samples, serum, urine	>600	[29]
BDDE	DPV	0.05	0.07 - 80	human blood, urine	-	[30]
AgNDs/CNOs/GCE	DPV	0.03	0.099 - 59.88	serum urine	-	[31]
GCE	ECL & CV	5	10 - 500	urine	-	[32]
$Ru(bpy)_3]^{2+}$ – Nafion composite GCE	ECL	$0.05*10^{-3}$	0.005 - 1000	seized samples	15	[33]
AuNPs/APTMS/ITO	ECL	0.002	0.013 - 3.35	serum	-	[34]
anti-MA/AuNPs/MPS/ PB/LC GE	AMP	$7.5*10^{-3}$	0.01 - 5	human blood	-	[35]
anti-MA/3-MPA/SAM GE	EIS	$0.677*10^{-7}$	$1.34*10^{-7}$ - $13.4*10^{-7}$	serum	-	[36]

Platform	Technique	LOD (µM)	Linear range (µM)	Sample	Duration (s)	Ref.
BSA-MA/AuNPs conjugates glassy electrode	EIS	$6.7*10^{-3}$	-	-	-	[37]
aptaMETH/AuNPs/GE	EIS	-	-	-	-	[38]
AuNPs/MWCNTs SPE	EIS	$0.3*10^{-3}$	$1.15*10^{-3}$ - 0.027	-	>200	[39]
	SWSV	0.006	0.2 - 0.1	-	>200	[39]
			3.0 - 50			
MIPs/MWCNTs CPE	FFT-SWV	$0.83*10^{-3}$	0.01 - 1	urine	>20	[40]
			3 - 100	serum		
CeO_2NP/rGO/GCE	SWV	8.75	25-166.6	plasma	-	[41]
MWCNTs/AuNPs-$SH(CH_2)_3$-Si-SiO_2@Fe_3O_4 GCE	SWV	0.016	0.05 - 50	urine	-	[42]
C-SPE	SWV	2.15	0 - 26.93	saliva	55	[43]
dsDNA modified GE	SWV	$17*10^{-9}$	0.001 – 0.1	serum, urine	-	[44]
Apt-38/MB GE	SWV	0.02	0.02 - 20	serum, urine, saliva	-	[45]
graphite SPE	SWV	66.4	250 - 2500	seized samples	30	This work

Platforms: **AgNDs/CNOs/GCE**: glassy caron electrode modified with nanodiamond-derived carbon nano-onions decorated with silver nanodendrites; **anti-MA/AuNPs/MPS/PB/LC GE**: methamphetamine antibody- gold nanoparticles-(3-mercaptopropyl trimethoxysilane)- persian blue- L-cysteine modified gold electrode; **anti-MA/3-MPA/SAM GE**: 3-mercaptopropionic acid bonded methamphetamine antibody on Self-assembled molecular monolayer gold electrode; **Apt-38/MB GE**: gold electrode modified with a methylene blue-labeled 38-base aptamer sequence; **aptaMETH/AuNPs/GE**: gold electrode modified with methamphetamine aptamer and gold nanoparticles; **AuNPs/APTMS/ITO**: gold nanoparticles/ (3-aminopropyl)trimethoxysilane modified indium tin oxide coated glass; **AuNPs/MWCNTs SPE**: screen printed electrode modified with multi-walled carbon nanotubes and gold nanoparticles; **BDDE**: boron doped diamond electrode; **BSA-MA/AuNPs**: methamphetamine-antibody/ gold nanoparticles conjugates; **C-SPE**: carbon screen printed electrode; **CeO_2NP/rGO/GCE**: cerium oxide-reduced graphene oxide glassy carbon electrode; **dsDNA modified GE**: double-straned DNA modified gold electrode; **EDOT-BTDA-Pala/Ab GCE**: glassy carbon electrode modified with a selective methamphetamine antibody immobilized by a fluorescent-labeled peptide; **GCE**: glassy carbon electrode; **GPH-SPE**: graphene modified screen printed electrode; **MIPs/MWCNTs CPE**: carbon paste electrode modified with MIPs and multi-walled carbon nanotubes; **MWCNTs/AuNPs-$SH(CH_2)_3$-Si-SiO_2@Fe_3O_4 GCE**: multi-walled carbon nanotubes-gold nanoparticles linked to nanomagnetic core shells modified glassy carbon electrode; **PPGE**: pretreated pencil graphite electrode; **$Ru(bpy)_3]^{2+}$ – Nafion composite GCE**: Tris(bipyridine)ruthenium(II) - Nafion nanocomposite coated glassy carbon electrode; **SPGE/G-PEG-dial/GA/BMIM TFSI/mAb**: screen-printed gold electrode modified with a ionogel composed of gelatine-polyethylene glycol-dialdehyde hydrogel, glutaraldehyde and 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide (ionic liquid) and methamphetamine-specific monoclonal antibodies.
Techniques: **AMP**: Amperometry; **CV**: cyclic voltammetry; **DPV**: differential pulse voltammetry; **ECL**: electrochemiluminescence; **EIS**: electrochemical impedance spectroscopy; **FFT-SWV**: fast Fourier transform square wave voltammetry; **SWV**: square wave voltammetry; **SWSV**: square wave stripping voltammetry.

3.3. The elucidation of the MA oxidative pathway

LC-QTOF-MS analysis on the partially electrolyzed solutions of MA for both high (7.5 mM) and low (0.5 mM) concentrations were performed to identify possible differences in the oxidation products. The obtained chromatograms were compared to a 0.1 mM standard of MA (**Fig. 3a and 3b, black**) and amphetamine (**Fig. 3a, blue**).

3.3.1 Low concentration electrolysis

One main oxidation product was formed during the electrolysis at 0.5 mM in PBS pH 12 at 0.91 V. Product M1 elutes at 3.59 min (*m/z* 136.1121, $C_9H_{13}N$), just before the remaining non-oxidized MA at 3.94 min (*m/z* 150.1226, $C_{10}H_{15}N$). After comparing the elution time, mother-ion and fragmentation pattern (**Fig. S4b**) of product M1 and amphetamine (*m/z* 136.1121, $C_9H_{13}N$), the main oxidation product of MA is amphetamine (the major electrolysis compounds of MA are shown in **Table S2a**). In **Fig. 2c**, the suggested oxidation mechanism for MA involving two electrons and two protons is shown.

3.3.2 High concentration electrolysis

Three main oxidation products were observed: Dimer1 (*m/z* 295.2169, $C_{20}H_{26}N_2$), Dimer2 (*m/z* 293.2012, $C_{20}H_{24}N_2$) and Dimer3 (*m/z* 309.1961, $C_{20}H_{26}N_2O$), eluting at 7.45 min, 7.36 min and 7.82 min, respectively, while in low concentration only the oxidative formation of amphetamine was observed. All three products possess m/z-values higher than MA (**Fig. 3b**, **Table S2b**), indicating that these are probably dimers formed during electrolysis. Additionally, the observed dimers exhibit common ions with MA (**Fig. S4c,d,e**), thereby confirming that the newly observed products are dimers of MA (m/z 91.0545, m/z 119.0852 for Dimer1, m/z 91.0545 for Dimer2 and m/z 91.0545, m/z 119.0852, m/z 150.1274 for Dimer3).

Overall, the formed products in high concentration differ from the products formed during electrolysis in low concentration, suggesting a high concentration of MA at the surface which is in line with the switch from diffusion to the adsorption-controlled process shown by the electrochemical data.

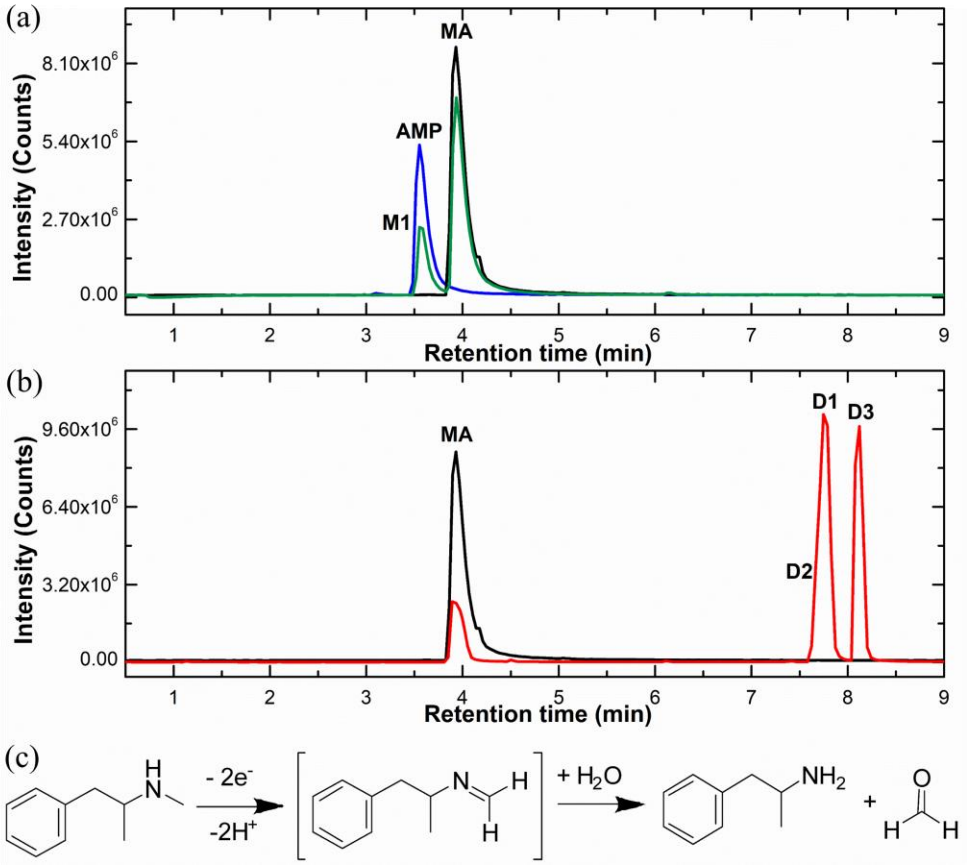

Fig. 3. Elucidation of the MA oxidative pathway: **(a)** Extracted ion chromatogram of 20 ng/µL solutions of MA (**black**), amphetamine (**blue**) and directly injected low concentration electrolysis sample of MA in PBS pH 12 (0.95V vs int. ref for 60 min) (**green**); **(b)** Extracted ion chromatogram of 20 ng/µL solutions of MA (**black**) and directly injected high concentration electrolysis sample of MA in PBS pH 12 (0.95V vs int. ref for 60 min) (**red**); **(c)** The proposed mechanism of MA electrochemical oxidation. *AMP: amphetamine; D1, D2, D3: dimer 1, dimer 2 and dimer 3.*

3.4. Evaluation of the selectivity in MA mixtures

The selectivity of the method towards MA was assessed by analyzing binary mixtures with other illicit drugs (i.e. MDMA, mephedrone, heroin, cocaine, and ketamine). Furthermore, since MA sold on the illicit market is characterized by variable adulteration, binary and complex mixtures of MA with common adulterants/cutting agents (i.e. dimethyl sulfone, caffeine, paracetamol, creatine, and levamisole, as shown in **Table 1**) were evaluated. All tested mixtures had equimolar concentrations for each component, two concentrations being tested: 0.5 mM and 7.5 mM, aiming to assess the optimal concentration for qualitative purposes. For a proper evaluation of the influence of these molecules on the MA signal, their electrochemical behavior was first investigated by SWV in 0.5 mM and 7.5 mM solutions at pH 12 on SPEs (**Fig. 4**). All tested molecules registered oxidation peaks in the potential range tested, except dimethyl

sulfone, caffeine and creatine which had no electrochemical signal. The values stating the E_p and the I_p of each tested solution are shown in **Table S3**, while the SWVs are shown in **Fig. 4** (blue dotted lines).

3.4.1. Low concentration (0.5 mM) mixtures

Binary mixtures with a concentration of 0.5 mM for each component (MA and another illicit drug or an adulterant/cutting agent) were evaluated. As it can be observed in **Fig. 4**, MA could not be distinguished in any of the mixtures containing other illicit drugs (**Fig. 4a**) as most of the drugs presented oxidation peaks close to the peak potential of MA at this concentration at pH 12 (**Fig. 4a** - blue dotted lines; **Table S3**). This is due to the deprotonation at the secondary and tertiary amines present in the structures of the tested illicit drugs at pH 12 (**Fig. S1**) which facilitates the electrooxidation of these molecules on SPE, enabaling the detection of all these illicit drugs in the same window of potential. On the other hand, MA could be detected in the presence of all tested adulterants/cutting agents (with anodic shifts of 22 mV to 42 mV - **Table S4**), except for levamisole (**Fig. 4b**), which suppressed the signal of MA. The suppression effect of levamisole was reported before by researchers from our group for other illicit drugs such as heroin [46] and cocaine [47], in the latter case being stated that this suppression could be due to the fouling of the electrode surface by the oxidized (and even partly oxidized) forms of levamisole [47].

As MA could be adulterated with more than just one molecule, several complex mixtures were tested in the same conditions. The components of these mixtures were selected according to the data found in the literature [16], while the concentration for each component was kept to 0.5 mM. MA could be detected in all tested mixtures (**Fig. S5**).

For the elimination of the effect of levamisole, we investigated two strategies: (i) testing the mixture at 7.5 mM, while maintaining the 1:1 ratio between the components, since at this high concentration the signal of MA shifted in the cathodic direction as shown in **Fig. 2d**; and (ii) pretreatment of the electrode, a strategy that was described before as a solution for the interferences brought by levamisole [47], ketamine [21] or paracetamol [48]. The results of both strategies are discussed in section 3.4.2 and 3.4.3, respectively.

3.4.2. High concentration (7.5 mM) mixtures

Binary mixtures of MA with adulterants/cutting agents and other illicit drugs with an equimolar concentration of 7.5 mM were tested. In this case, the expected cathodic shift of ~0.3 V of the peak potential was registered only for MA and not for the other molecules tested. Hence, MA could be distinguished in the presence of all tested illicit drugs and adulterants/cutting agents (with shifts of 5 mV to 49 mV and of 4 mV to 10 mV, respectively - **Table S4**). The only problematic mixtures were with heroin (**Fig. 4c**) as the MA peak at this concentration is still in

the potential range of heroin peak, and with paracetamol which seemed to suppress the signal of MA at this high concentration (**Fig. 4d**). The same cathodic pretreatment was tested in these cases as well and the results are discussed in the following section.

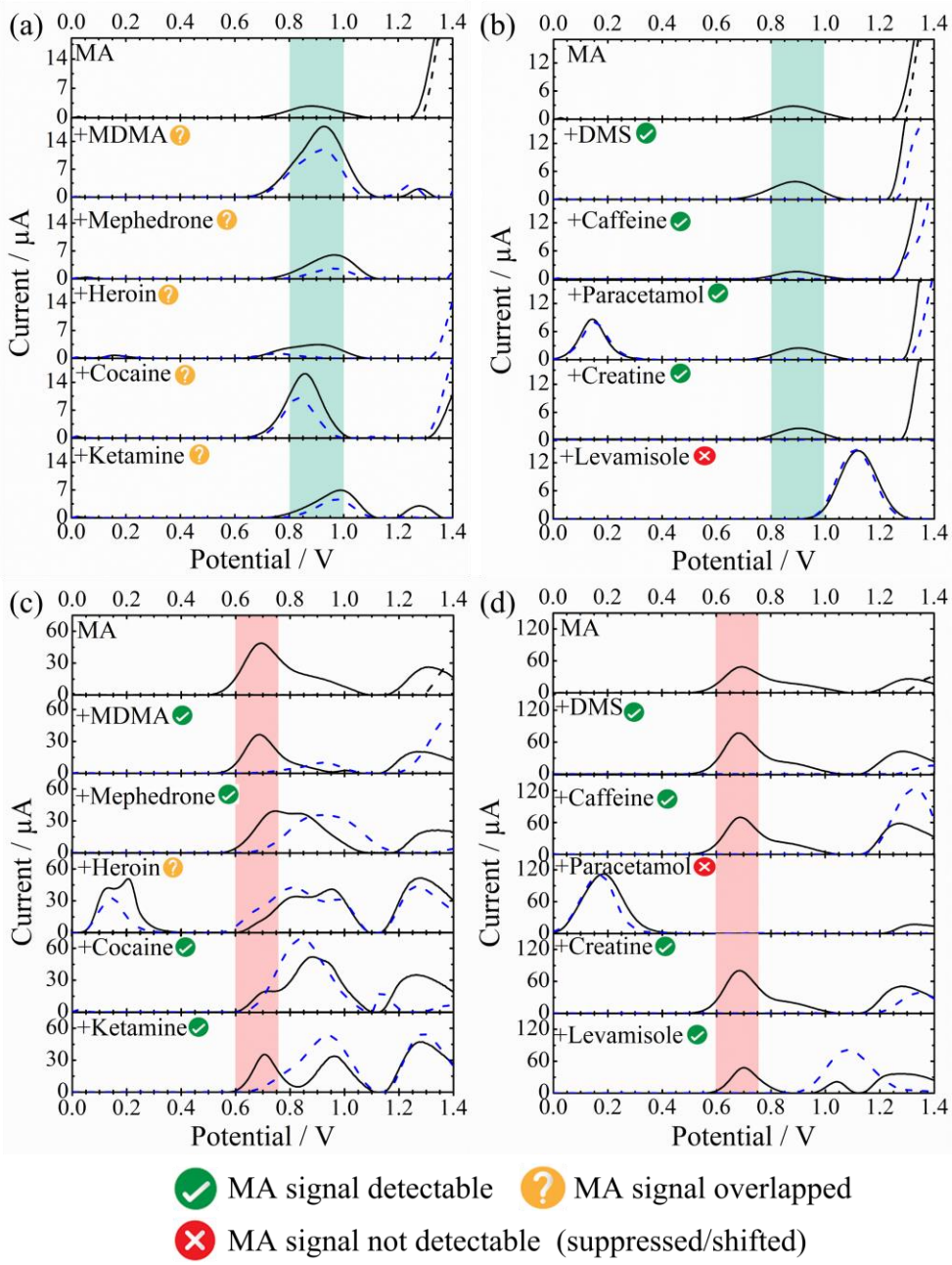

Fig. 4. *Baseline corrected square wave voltammograms (SWVs) of MA in binary mixtures with other illicit drugs – at 0.5 mM* ***(a)*** *and 7.5 mM* ***(c)****, and with adulterants/cutting agents – at 0.5 mM* ***(b)*** *and 7.5 mM* ***(d)****, in a 1:1 ratio in PBS 20 mM pH 12 on graphite screen-printed electrodes.* ***On the first layer****: the continuous black SWVs correspond to pure MA; the dashed black SWVs correspond to the blank.* ***On the 2nd to the 6th layers****: the continuous black SWVs*

correspond to the binary mixtures; the dashed blue SWVs correspond to the electrochemical behavior of the pure illicit drugs (other than MA) or pure adulterants/cutting agents. The faded green and faded red columns represent the potential range of the pure MA oxidation peak at 0.5 mM and 7.5 mM, respectively.

3.4.3. Assessment of binary mixtures after the pretreatment of the electrodes

A cathodic pretreatment was applied for the analysis of four problematic binary mixtures: (i) MA and levamisole in 0.5 mM equimolar concentration, (ii) MA and paracetamol in 7.5 mM equimolar concentration, and (iii) MA and heroin in 0.5 mM and 7.5 mM equimolar concentrations. As can be seen in **Fig. 5a**, after the cathodic pretreatment of the MA/levamisole mixture at 0.5 mM, the MA peak shifted to lower potentials (0.80 V, 0.82 V and 0.72 V after 10 s, 120 s and 300 s, respectively) and even after only 10 s, the signal of MA, although low, could be observed on the square wave voltammogram. Besides, the signal increased when the pretreatment was applied for longer times showing the effect of the cathodic pretreatment. A cathodic shift of the levamisole peak was also registered after the cathodic pretreatment (1.05 V, 1.06 V and 1.01 V after 10 s, 120 s and 300 s, respectively), but the peak potential ranges for the two molecules did not overlap, hence the pretreatment allowed the detection of MA in the presence of levamisole. It was stated that the electrochemical pretreatments clean the surface of the electrodes, have an effect on the oxygen-functional groups on the surface of the electrode and may create rupture sites on the surface, making it more reactive [47]. This increased reactivity could explain the oxidation of MA at a lower potential after the cathodic pretreatment, allowing the separation of this peak from the peak of levamisole.

The detection of MA in the high concentration mixture with paracetamol was possible after the cathodic pretreatment as well (**Fig. 5b**). As in the previous case, the signal of MA could be detected after 10 s of pretreatment and the intensity of the current increased for longer pretreatment times; a significant shift of the MA peak was not observed in this case, although the current intensity of the peak was rather low (7.81 µA, 14.91 µA and 40.63 µA after 10 s, 120 s and 300 s, respectively) considering the high concentration of MA (7.5 mM) in the mixture and the current generated by a solution with the same concentration of MA alone and under the same conditions (e.g., 55.24 µA after 300 s).

In the case of MA/heroin mixture, the cathodic pretreatment allowed the identification of MA in neither the low concentration nor the high concentration mixture (data not shown). However, this is not an issue as heroin is not usually encountered with MA in suspected samples. Overall, the cathodic pretreatment overcomes the issues posed by levamisole and paracetamol and can be a fast and easy solution for MA identification.

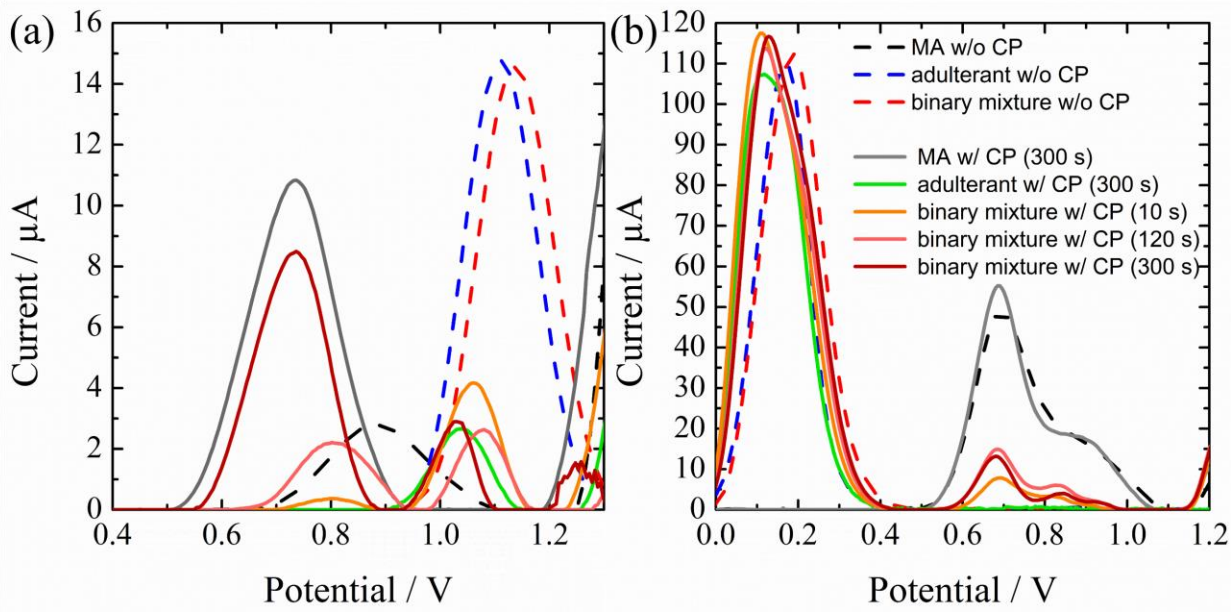

Fig. 5. *Baseline corrected square wave voltammograms (SWVs) of MA in binary mixtures of 1:1 ratio after a cathodic pretreatment (- 0.8 V for 10 s to 300 s) of the graphite SPEs:* ***(a)*** *with* ***levamisole****, 0.5 mM each component, and* ***(b)*** *with* ***paracetamol****, 7.5 mM each component (w/o: without cathodic pretreatment; w/ CP: with cathodic pretreatment).*

3.5. Detection and validation of the electrochemical device in confiscated samples

Finally, the suitability of the electrochemical method for on-site screening of suspected cargos was evaluated at NICC, Belgium on several seized samples containing MA (sample 1-19) or other illicit drugs (sample 20-34). Two sampling methods were investigated: (i) underloading and (ii) overloading as explained in the **"Experimental section**". For the first approach, the electrochemical profile of the samples was compared with the electrochemical profile of 0.5 mM MA standard solution (**Fig. 6a**), while for the second approach the comparison was done with the electrochemical profile of 7.5 mM MA standard solution (**Fig. 6b**). For samples containing other illicit drugs (sample 20-34), only the second approach was considered, since the tests on the standards showed that the profile of MA at low concentrations was not suited for discriminating the target analyte from the other illicit drugs tested. The test was considered positive for MA if an electrooxidation peak (**Table S5**) was obtained in the potential range of 0.80 V to 1.02 V in case of the underloading approach, and of 0.60 V to 0.76 V in case of the overloading approach (the potential zones are shown in **Fig. 1e**).

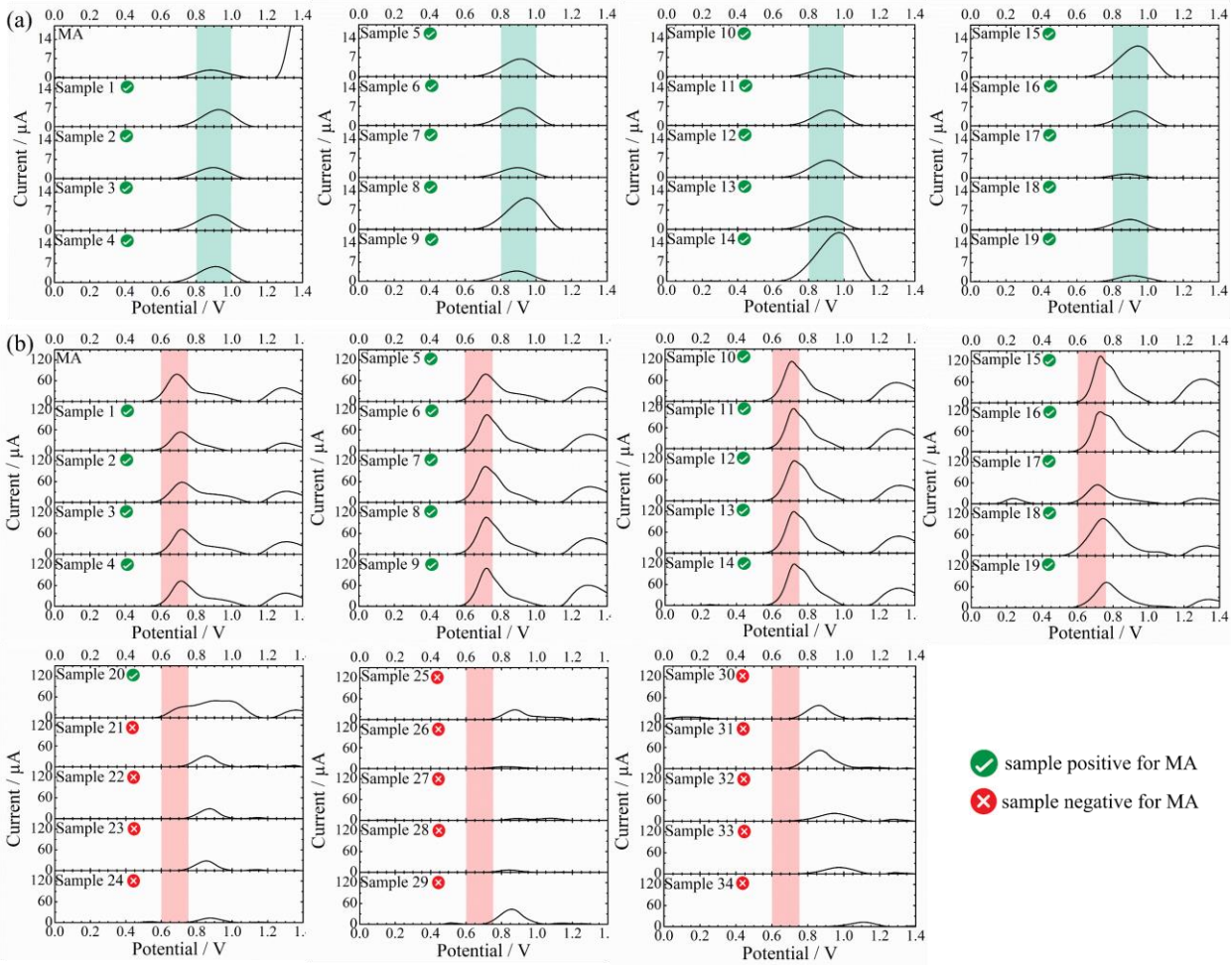

Fig. 6. Baseline corrected square wave voltammograms (SWVs) of seized samples analyzed in PBS 20 mM pH 12 on graphite screen-printed electrodes using the underloading method **(a)** and the overloading method **(b)**. The faded green and faded red columns represent the potential range of the pure MA oxidation peak at 0.5 mM (i) and 7.5 mM (ii), respectively. Table S6 contains a list of the identified compounds in the samples by the standard method. Samples 1-19 contain MA, while samples 20-34 contain other illicit drugs.

The results obtained with the electrochemical technique and two other on-site techniques (i.e. Raman and FTIR spectrometer) were compared with the results gathered by GC-MS and GC-FID (**Table S6)**. The GC-MS method confirmed the presence of MA in 19 out of 34 tested samples (among which two oil samples and 17 solid samples, including paste samples) with various MA concentrations (between 22 % and 100 %), among which 6 (32 %) were adulterated with dimethyl sulfone and benzyl methyl ketone (a precursor) was present in 3 (16 %) samples. When the portable Raman spectrometer was employed (on-site by untrained operators, not in a laboratory setting), none of the samples tested positive for MA. However, the Raman device identified 12 samples (63 % of the MA containing samples) containing ephedrine hydrochloride

(on the 1st or 2nd hit), whose chemical structure is similar to MA. The FTIR device identified 18 out of the 19 MA samples (95 %) and it managed to identify DMSO as an adulterant in 6 samples, all in agreement with the GC-MS analysis. For the electrochemical method, all samples containing MA tested positive for MA (100 % true positive rate) for both sampling methods. Only one of the samples containing other illicit drugs generated a false positive response (a MDMA sample), testing positive for MA (93 % true negative rate). A comparison of the sensitivity, specificity and accuracy of the portable methods is shown in **Table 4**.

Table 4. Sensitivity, specificity and accuracy for MA detection by the portable methods used in this study for the screening of confiscated samples.

Method	TP	TN	FP	FN	Sensitivity	Specificity	Accuracy
Electrochemical reader*	19	14	1	0	100	93.33	97.06
Raman device	0	15	0	19	0	100.00	44.12
FTIR device	18	15	0	1	94.74	100.00	97.06

*overloading sampling; FN: false negative; FP: false positive; TN: true negative; TP: true positive

The reproducibility of the seized samples using the electrochemical method was also evaluated employing both sampling methods: (i) underloading (**Fig. S6a**; **Table S7a**) and (ii) overloading (**Fig. S6b**; **Table S7b**). The results exhibited excellent values (N = 3) for each sampling method: (i) RSD_{Ep} of 0.3 % - 0.8 %; RSD_{Ip} of 0.09 % - 5.6 %; (ii) RSD_{Ep} of 0 % - 1.4 %; RSD_{Ip} of 2 % - 3.4 %. Hence, the electrochemical device proved to be a suitable method for the detection of MA in confiscated samples of different nature including oils, crystals and pastes.

4. Conclusions

The increasing spread and abuse of illicit drugs such as MA urge the constant development of new analytical tools to be employed by the law enforcement agencies for the fast and accurate screening of suspected cargos. In this regard, the present study explored and characterized the potential of SWV as an electrochemical method for the detection of MA in seized samples. Furthermore, the influence exerted by different factors such as the pH of the electrolyte, the presence of other illicit drugs or adulterants/cutting agents and the sampling method were investigated. Two potential zones for the identification of MA corresponding to two sampling methods were proposed and successfully applied for the screening of several confiscated samples. Additionally, the results obtained with the electrochemical setting were compared with the laboratory standard method (GC - MS) and with regular portable devices used by law

enforcement agencies (based on Raman and FTIR spectroscopy). After the analysis of 34 samples of MA and other illicit drugs, the electrochemical device, Raman and FTIR spectrometer exhibited an accuracy of 97 %, 44 % and 97 %, respectively. All in all, the electrochemical method showed excellent reliability, presenting similar analytical performance to the FTIR spectrometer and improved results than the currently used Raman device, proving the applicability of this strategy for the fast on-site screening of MA suspected samples.

Graphical abstract

Declaration of Competing Interest

The authors declare that they have no known competing financial interests.

Author Contributions

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

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