Electrochimica Acta 354 (2020) 136728

Contents lists available at ScienceDirect

Electrochimica Acta

journal homepage: www.elsevier.com/locate/electacta

Electrochemical detection of the synthetic cathinone 3,4-methylenedioxypyrovalerone using carbon screen-printed electrodes: A fast, simple and sensitive screening method for forensic samples

Camila D. Lima[a], Rosa A.S. Couto[b], Luciano C. Arantes[c], Pablo A. Marinho[d], Dilton M. Pimentel[a], M. Beatriz Quinaz[b], Rodrigo A.B. da Silva[e], Eduardo M. Richter[e], Sandro L. Barbosa[f], Wallans T.P. dos Santos[a,f,*]

[a] Departamento de Química, Universidade Federal dos Vales do Jequitinhonha e Mucuri, 39100-000 Diamantina, MG, Brazil
[b] REQUIMTE, LAQV, Laboratory of Applied Chemistry, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal
[c] Seção de Perícias e Análises Laboratoriais, Instituto de Criminalística, Polícia Civil do Distrito Federal, 70610-970 Brasília, DF, Brazil
[d] Instituto de Criminalística, Polícia Civil de Minas Gerais, 30180-060 Belo Horizonte, MG, Brazil
[e] Instituto de Química, Universidade Federal de Uberlândia, 38400-902 Uberlândia, MG, Brazil
[f] Departamento de Farmácia, Universidade Federal dos Vales do Jequitinhonha e Mucuri, 39100-000 Diamantina, MG, Brazil

ARTICLE INFO

Article history:
Received 21 April 2020
Revised 8 June 2020
Accepted 4 July 2020
Available online 9 July 2020

Keywords:
Synthetic cathinone
Bath salts
Forensic analysis
Novel psychoactive substances (NPS)
Voltammetry

ABSTRACT

In this work, the electrochemical detection of 3,4-methylenedioxypyrovalerone (MDPV), a synthetic cathinone used as a stimulant drug, is presented for the first time. The electrochemical behavior of MDPV was studied by cyclic voltammetry (CV) at the surface of an unmodified glassy carbon electrode and a carbon graphite screen-printed electrode (SPE-Gr), where three irreversible oxidation processes were identified. The quantification of MDPV in seized drug samples was optimized for the first oxidation process (at + 0.6 V *vs* Ag) in 0.1 mol L^{-1} Britton Robison (BR) buffer solution pH 6.0 at SPE-Gr, using adsorptive stripping differential pulse voltammetry (AdSDPV) detection. The proposed method exhibited a limit of detection (LOD) of 0.5 µmol L^{-1} and suitable electrochemical response stability using the same ($N = 5$) or different ($N = 3$) electrodes, both presenting a RSD lower than 1.6%. Additionally, interference studies and application to MDPV sensing in reference samples provided by United Nations Office on Drugs and Crime (UNODC) were performed, confirming the potential of the proposed sensor for application in forensic analysis as a simple, fast and cost-effective screening method for MDPV.

1. Introduction

Over the last thirteen years, there has been an increasing trend towards the misuse of Novel Psychoactive Substances (NPS), also known as designer drugs, for recreational purposes [1]. NPS became highly attractive for users since they can mimic the effects of some traditional illegal substances as cocaine, amphetamine-type stimulants (amphetamine, methamphetamine, and ecstasy-like substances) or lysergic acid diethylamide (LSD), but are often not scheduled under drug control conventions and consequently not internationally controlled [2,3]. Not surprisingly, in recent years the NPS market became very dynamic, and the 2019 World Drug Report listed the emergence of more than 200 different stimulant NPS [3,4]. Among these, the consumption of synthetic cathinones in the form of “bath salts” is prominent and, together with phenethylamines, represent the majority of NPS identified worldwide and reported by the United Nations Office on Drugs and Crime (UNODC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [5,6].

Indeed, "bath salts" is a term commonly used to refer to the group of synthetic substances chemically related to the psychoactive alkaloid cathinone found in the leaves of the kath (*Catha edulis*) plant [7], being usually marketed on the internet and in head and smart-shops. Although labeling several legal compounds, such as amino acids, phosphate, and magnesium salts [8], their actual content are synthetic cathinones such as 4-methylmethcathinone (mephedrone), 3,4-methylenedioxy-*N*-

* Corresponding author.
E-mail address: wallanst@ufvjm.edu.br (W.T.P. dos Santos).

https://doi.org/10.1016/j.electacta.2020.136728
0013-4686/

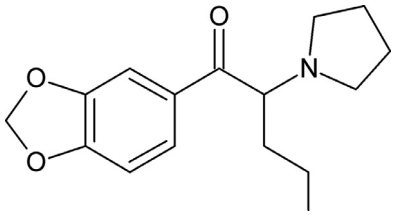


Fig. 1. Chemical structure of 3,4-methylenedioxypyrovalerone (MDPV).

methylcathinone (methylone) and 3,4-methylenedioxypyrovalerone (MDPV) [9], which are already included in the list of controlled substances in the United States since 2013 [10], and under international control since 2015 [11]. In Brazil, mephedrone and MDPV are already scheduled since 2012, and the synthetic cathinones' class was included in 2017 [12].

The use of MDPV as a stimulant substance was firstly reported by the United States Drug Enforcement Administration (DEA) in 2008 [13] and, along with mephedrone, has recently become one of the most widely used synthetic cathinones in the world [14,15]. As illustrated in Fig. 1, MDPV is characterized by the presence of a propyl side chain, a phenyl ring substitution of 3,4-methylenedioxy, similar to 3,4-methylenedioxymethamphetamine (MDMA), and an amine-positioned pyrrolidine ring [16], being classified as a β-ketophenethylamine [17].

Although some methods for the detection of MDPV have been published, they are mainly based on chromatography, such as liquid chromatography-mass spectrometry (LC-MS) [18-21] and gas chromatography-mass spectrometry (GC-MS) [8,22]. Such methodologies are time-consuming and expensive and are not appropriate for a point-of-care detection of MDPV, being eventually reserved for the definitive characterization of seized samples. Undoubtedly, the development of a fast screening test for NPS, as a viable alternative to select samples containing illegal substances, would be of foremost interest. Currently, the Zimmermann reagent assay is used as a screening test for cathinones [23], presenting however many cross-reaction issues, both with amphetamines and methamphetamines [21,24].

Several electrochemical sensors have been recently used as screening methods for NPS in seized drugs [25–31], showing numerous advantageous such as low-cost, fast analysis, and potential for portability, namely for the determination of synthetic cathinones, such as ethylone, mephedrone, and 4-methyl-N-ethyl-cathinone (4-MEC) [27,28]. The great majority of the electrochemical sensors reported in the last years are based on screen-printed electrodes (SPEs) due to its versatility, simplicity and cost-effectiveness [32,33]. Moreover, SPEs allow the development of portable and miniaturized systems, enabling the analysis of small volumes of samples, in the microliter range [34]. In addition, adsorptive stripping differential pulse voltammetry (AdSDPV) can be used as detection method to improve the sensitivity of the electroanalytical techniques in different electrodes, as shown in recent works on the determination of stimulants drugs [35–37].

To the best of authors' knowledge this is the first report of the electrochemical behavior of MDPV. An inexpensive and easy-to-handle electrochemical sensor for MDPV is used in this work based on carbon graphite SPE (SPE-Gr). The proposed method uses the AdSDPV technique for the rapid and sensitive detection of MDPV, therefore being a proof-of-concept for the construction of a portable device intended to be applied as a screening test to seized samples, representing a potential major advance in the field of forensic drug analysis.

2. Experimental

2.1. Chemicals and samples

All solutions were prepared with deionized water with resistivity not less than 18.2 MΩ cm (at 25 °C) obtained using the Milli-Q system (Millipore, USA). The analytical standard of MDPV was provided by UNODC in a powder form and was solubilized in LC-MS grade methanol to obtain a 1.0×10^{-2} mol L^{-1} stock solution, which was diluted in a supporting electrolyte for electrochemical measurements. The electrochemical behavior of MDPV was studied in Britton-Robinson (BR) buffer solution, prepared using a mix of boric, phosphoric and acetic acids in different pH values (from 2 to 12), all with 10% (v/v) methanol. Sodium hydroxide was used to adjust the pH. Acetate buffer solution (0.1 mol L^{-1}) in pH 5.0 with 10% methanol was also evaluated as a supporting electrolyte for MDPV detection at a glassy carbon electrode (GCE). All reagents were of analytical grade and were purchased from Sigma-Aldrich (Lancashire, United Kingdom). Reference material donated by UNODC consisted of white crystals, containing 43.1% (w/w) of MDPV and 56.9% of excipients. A 111.5 mg aliquot of the material was weighted, diluted in 2 mL of methanol and sonicated for 10 min. After homogenization, it was diluted in a 0.1 mol L^{-1} BR buffer solution (pH 6.0) and analyzed through AdSDPV technique at SPE-Gr.

The composition of seized samples, namely crystals containing N-ethylpentylone and tablets containing MDMA, was previously confirmed by liquid chromatography quadrupole time-of-flight mass spectrometry (LC-Q-TOF-MS) analysis. Samples were obtained following an extraction step performed in the Institute of Criminology of the police department of the Brazilian Federal District and Minas Gerais State, in Brazil. First, an amount of 100 mg of each sample was crushed, homogenized, diluted in 1 mL of methanol and sonicated for 10 min. The extracted solution was then diluted in methanol (for LC-Q-TOF-MS analysis) or in the supporting electrolyte (for AdSDPV analysis).

2.2. Instrumental and apparatus

A μAutolab type III potentiostat (Metrohm Autolab BV, Utrecht, the Netherlands) controlled by GPES software 4.9 was used to perform all voltammetric experiments. A pure nitrogen gas was bubbled in all the studied solutions for 5 min to remove oxygen. Initial studies of the electrochemical behavior of MDPV were performed using a three-electrode electrochemical cell with a glassy carbon working electrode (Metrohm, diameter of 3 mm), and platinum and Ag/AgCl (in saturated KCl solution) wires were used as auxiliary and reference electrodes, respectively. MDPV determination studies were performed using commercial SPEs from Metrohm DropSens (Oviedo, Spain), with a 4 mm diameter carbon graphite (SPE-Gr, model DRP-110) working electrode, a carbon auxiliary electrode and a silver pseudo-reference electrode.

A 1290 Infinity Ultra High-Performance Liquid Chromatography System coupled with a 6540 Quadrupole Time of Flight Mass Spectrometer (Agilent Technologies, Santa Clara, CA, USA) was used for LC-Q-TOF-MS analysis. Dual Agilent Jet Stream Electrospray Ionization (Dual AJS ESI) was the interface used to transfer the analytes coming out of the LC equipment to the MS. Compounds were detected and reported from accurate mass scan data using Agilent MassHunter Qualitative Analysis version B 06.00 and Personal Compound Database and Library version B 02.00 (PCDL) software, while quantitative analysis was performed by Agilent MassHunter Quantitative Software version B 07.01.

2.3. Electrochemical measurements

Prior to each measurement, SPE-Gr were electrochemically conditioned using a 0.1 mol L^{-1} BR buffer solution (pH 6.0) for 10 scans between −1.2 to +1.6 V by cyclic voltammetry (CV) at a scan rate of 100 mV s^{-1}. Electrochemical measurements on SPE-Gr were performed by drop-casting 100 µL of a solution containing the electrolyte and the analyte, covering all the electrodes. Initial electrochemical studies were performed through CV at a scan rate of 50 mV s^{-1}, using a 1.0 mM MDPV solution in BR buffer supporting electrolyte with different pH values, from 2 to 12. MDPV determination studies were accomplished using AdSDPV under optimized parameters (80 mV amplitude, and 10 mV step potential). Voltammograms obtained by AdSDPV were subjected to a background-subtraction using a polynomial fit with Origin software (OriginPro 2016, Northampton, MA). This analysis was performed according to the following steps: (I) 5 to 10 data points were selected, either before and after the current peak of the voltammogram; (II) a polynomial fit (order 3) was carried out to these data points; (III) all data in the original voltammogram were subtracted using the polynomial fit; (IV) the current peak was obtained using the peak analyzer (Origin software).

Limits of detection and quantification (LOD and LOQ, respectively) were calculated according to IUPAC recommendations [38]. In order to study the influence of potential interferences in the determination of MDPV in seized samples, caffeine (CAF), paracetamol (PAR) and glucose (GLU), the most commonly reported adulterants of 'bath salts' [39,40], were also tested using the proposed method. Interference studies were also performed for the MDMA and other synthetic cathinones such as methylone (also known as bk-MDMA) and mephedrone (also known as 4-MMC), which were previously found in seized samples of tablets or bath salts [41]. Accuracy of the proposed method was determined through quantification of MDPV in a reference material of known MDPV concentration, donated by UNODC.

3. Results and discussion

First, the electrochemical behavior of MDPV is investigated in Section 3.1. A GCE is used to evaluate the oxidation process of this substance as a function of pH, supporting electrolyte, and the possible mass transport control of the electrochemical reaction. In this section, the number of electrons and protons involved in the first oxidation process of MDPV is also calculated, and an oxidation mechanism is proposed. In Section 3.2, the quantification of MDPV at SPE-Gr is performed and the pH and supporting electrolyte conditions are optimized for application to MDPV sensing in seized samples. In Section 3.3, the results of the selective and fast detection of this analyte using a simple SPE-Gr are presented, in which all analytical parameters are determined. The study of potential interferents for MDPV detection in seized samples is also presented in Section 3.3. Finally, Section 3.4 presents the results of the analysis of a reference sample provided by UNODC.

3.1. Electrochemical behavior of MDPV at GCE

The solution phase electrochemical behavior of MDPV was performed at the pH range of 2 to 12 using 0.1 mol L^{-1} BR buffer solution at GCE by CV (Fig. 2). As shown in Fig. 2, depending on the pH value, the MDPV electrochemical behavior at GCE presents up to three irreversible oxidation processes. However, at a pH lower than 3.0, no electrochemical process with defined peaks is observed (not shown).

The influence of pH in MDPV oxidation processes was also evaluated through AdSDPV (Figure S1 of Supplementary Information (SI)). The linear regressions between the anodic peak potential (E_{pa}) and the pH were obtained for the first (E_{pa1}) and second (E_{pa2}) oxidation signals, as shown in Figure S1B of SI, obtaining the following equations: E_{pa1} = 1.22 (± 0.02) − 0.0584 (± 0.004) pH and E_{pa2} = 1.55 (± 0.02) − 0.0309 (± 0.003) pH. The slope obtained for the first oxidation process is very close to the theoretical value of 0.0592 V/pH, indicating that the same number of electrons and protons is involved in this process. Differently, the slope of the second oxidation process is roughly half the theoretical value, 0.0296 V/pH, suggesting the involvement of a number of electrons that is double the number of protons. A third oxidation process of MDPV at GCE is identified between the first and second oxidation peaks, which is more easily noticed in basic medium, as shown by CV in Fig. 2 and by AdSDPV in Figure S1A of SI. However, a slight 'shoulder' for this third oxidation process of MDPV can be observed in pH values higher than 5.0 by CV (Fig. 2). This last oxidation process of MDPV can be related with its reported pKa (7.31) [42], since the pH-distribution shows that this molecule is starting to be deprotonated at a pH around 5.0. Thereby, another oxidation process probably occurs when MDPV is deprotonated, which was also reported for the related substance MDMA [43].

Although the third oxidation process of MDPV appears to be pH-dependent, like the further processes, the immediacy of the first process hinders the study of the relation between E_{pa3} and the pH. Furthermore, the correlation of E_{pa1} with the pH was recalculated for the pH range between 3.0 and 5.0, where only the first oxidation signal is observed. In these conditions, a new linear regression for E_{pa1} *vs.* pH is obtained (r^2 = 0.998) with a slope of 0.04 V/pH, thus being not helpful in determining if the number of electrons and protons involved in this first oxidation process of MDPV is the same.

Since at pH 5.0 well-defined oxidation peaks were observed, further studies were performed at this pH. Additionally, the analysis of MDPV in different supporting electrolytes at pH 5.0 was investigated. The MDPV detection at GCE in acetate buffer solution showed higher sensitivity (Figure S2 of SI), being selected for following studies. Fig. 3 shows the electrochemical behavior of MDPV at the surface of GCE in 0.1 mol L^{-1} acetate buffer solution (pH 5.0), where three oxidation processes can be identified at +0.8, +1.0, and +1.3 V (*vs* Ag/AgCl).

The mass transport control of the electrochemical reaction occurring at the first MDPV oxidation process was evaluated through CV at different scan rates (Figure S3 of SI) using 0.1 mol L^{-1} acetate buffer solution pH 5.0 as the supporting electrolyte. This study shows that the anodic peak currents are linearly proportional to the square root of the scan rates (inset of Figure S3 of SI), showing a linear regression coefficient (r^2) of 0.996 for I_{pa} (µA) = −0.2 (± 0.6) + 50.5 (± 1.3) $v^{1/2}$ (V s^{-1}), indicating that this electrochemical process of MDPV is diffusion-controlled at the GCE. Furthermore, the number of electrons involved in this oxidation process, at +0.8 V (*vs* (Ag/AgCl), was calculated (1.8) and estimated to be 2.0 using the diffusion coefficient of ethylone (1.01×10^{-5} cm^2 s^{-1}) [25], which is molecularly similar to MDPV.

According to the electrochemical studies of this work, and the previously reported studies of similar molecules such as ethylone [27] and MDMA [43], we herein propose an electrochemical mechanism for each of the three identified oxidation processes of MDPV at the GCE (Scheme 1).

The proposed mechanism suggests that in the first step (I) the oxidation process of MDPV at 0.8 V (P1) corresponds to the oxidation of the aromatic nucleus of the molecule, which leads to the loss of one electron and the formation of a radical cation. In step II, the molecule generated in the first oxidation process (I) reacts with a dimerization of the initial radical cation. In the next steps, the molecule previously oxidized in the first step loses one proton (III) and one electron (IV), both on the same aromatic nucleus. The oxidation of the dimerized molecule formed in step

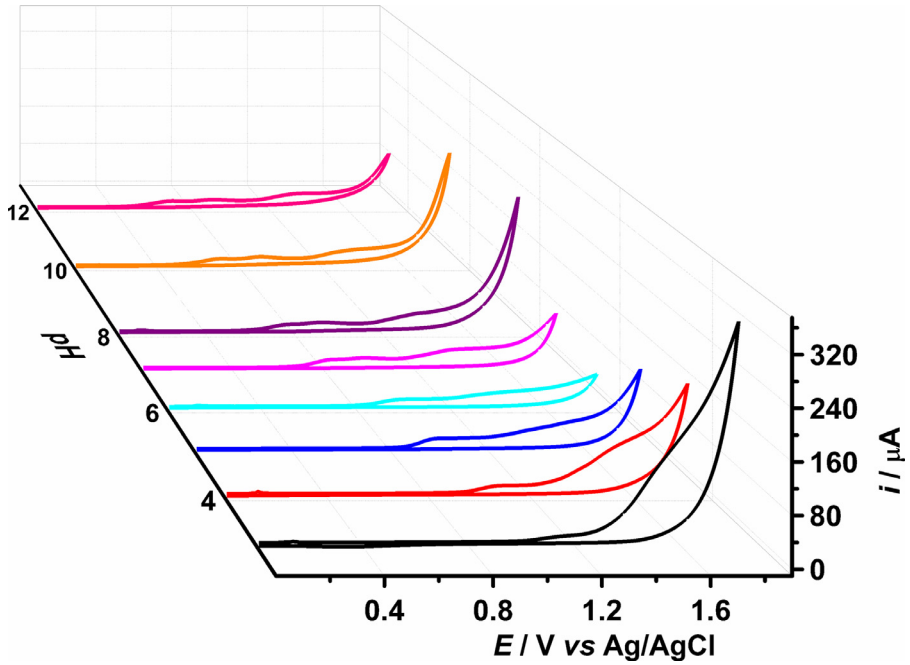


Fig. 2. Voltammograms of 1.0 × 10^{-3} mol L^{-1} MDPV in 0.1 mol L^{-1} BR buffer solutions at GCE of pH 3.0 to 12.0. All potential scans were started at 0.0 V with a scan rate of 50 mV s^{-1}.

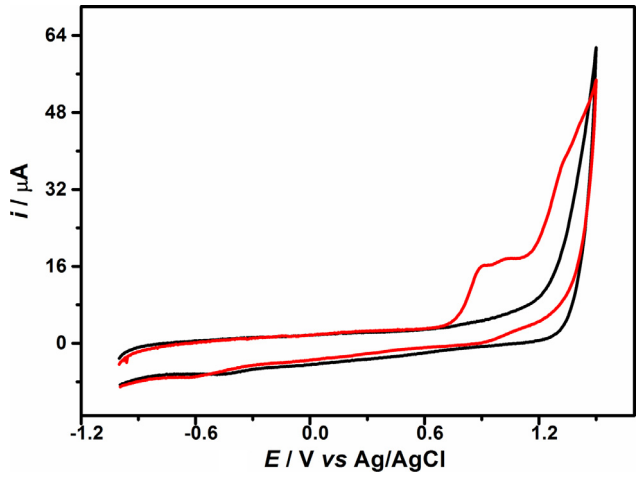


Fig. 3. Voltammograms in 0.1 mol L^{-1} acetate buffer solution pH 5.0 at GCE before (black-line) and after addition of 1.0 mM MDPV (red-line). All potential scans were started at −1.0 V with a scan rate of 50 mV s^{-1}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

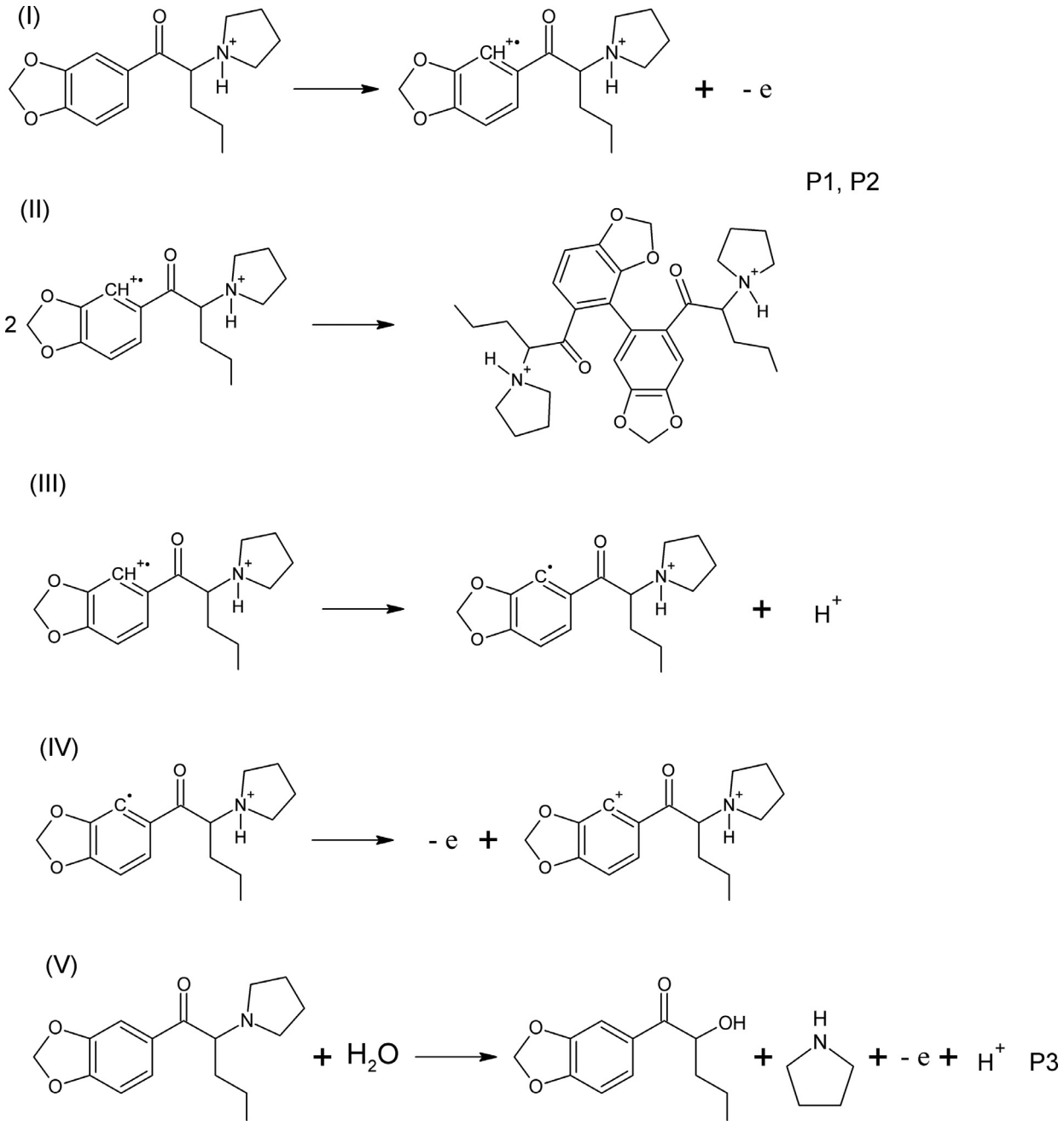
II is related to the second electrochemical process observed at 1.3 V (P2), which occurs with the same steps (I, III and IV) of the first MDPV oxidation. It is worth mentioning that, although MDPV molecule is protonated (Scheme 1), the steps I-IV for P1 and P2 also occur when this molecule is totally deprotonated, as shown in the voltammograms obtained at pH higher than 10.0 (Fig. 2 and Figure S1 of SI). The step V in the proposed mechanism corresponds to the oxidation of the carbon attached to the pyrrolidine ring (P3), with a hydroxylation of this carbon and the pyrrolidine formation, similarly to what was suggested for the third oxidation process of MDMA [43]. This MDPV oxidation process also occurs with the loss of one electron and one proton. As shown for MDMA oxidation [43], the oxidation process (P3) of MDPV at 1.0 V occurs between P1 and P2, when the amine group of this molecule starts to be deprotonated, which was also confirmed in this work.

Although GCE enabled a suitable electrochemical response for MDPV detection, simpler sensors should be used for application in forensics analysis, being the use of SPEs highly convenient and allowing the development of portable electrochemical sensors to be used with microliter-range volume of samples. Thus, and bearing in mind the initial studies of MDPV at the surface of GCE, a carbon graphite-SPE (SPE-Gr) was selected to perform following experiments, due to the lower-cost associated to its application in routine analyses.

3.2. Electrochemical behavior of MDPV at SPE-Gr

The electrochemical behavior of MDPV was studied at the surface of a SPE-Gr in BR buffer solutions in different pH values (from 2.0 to 12.0). As observed at the GCE, the oxidation processes of MDPV at the SPE-Gr showed to be pH-dependent (Figure S4 of SI). The pH 6.0 was selected since better sensitivity and peak profile were observed. Another buffer solution with the same pH (0.1 mol L^{-1} phosphate solution pH 6.0) was also evaluated for the electroanalysis of MDPV (Figure S5 of SI). For this study an external reference electrode (Ag/AgCl, KCl sat.) was used, avoiding a possible shift of oxidation potential peaks of MDPV caused by the pseudo-reference of the different SPEs. As can be seen in Figure S5 of SI, the BR buffer presented better sensitivity than phosphate buffer and was therefore chosen for further MDPV studies.

As shown in Fig. 4, the electrochemical behavior of MDPV at SPE-Gr is similar to the one previously observed at GCE, with three irreversible oxidation processes taking place at +0.6, +0.8 and +1.0 V (*vs.* Ag). Here, however, the mass-transport for the MDPV oxidation process is controlled by adsorption, as suggested by the scan rate study (Figure S6 of SI). The peak currents are linearly proportional to the scan rates (inset of Figure S6 of SI), with a linear regression coefficient (r^2) of 0.997 for *Ipa* (μA) = 28.0 (± 2.6) + 600.0 (± 14.0) v (V s^{-1}). Other analytes with similar profiles (irreversible oxidation process and mass-transport controlled by adsorption) were previously analyzed on carbon working electrodes [36,44-46], including SPEs [35,37].



Scheme 1. Proposed mechanism of the electrochemical oxidation process (P1-P3) of MDPV at the surface of a GCE.

3.3. MDPV determination by AdsDPV using SPE-Gr

In order to obtain the best conditions for detection and quantification of MDPV by voltammetry, the AdSDPV technique was selected and its parameters were optimized considering current intensity and peak half-width parameters. The best conditions were found using an amplitude of 80 mV, a step potential of 10 mV, and a modulation time of 0.05 s. In addition, and since the mass-transport of MDPV electro-oxidation reaction at the SPE-Gr was found to be controlled by adsorption, the effect of pre-accumulation time was evaluated. This was performed by AdSDPV, immediately and following 2 to 10 min the addition of 100 µL of 0.1 mM MDPV in BR 0.1 M pH 6 buffer at the SPE-Gr (Figure S6 of SI). As it can be observed, the effect of accumulation time of MDPV at SPE-Gr surface did not increase significantly the oxidation current of the analyte. However, in order to improve the reproducibility of the electrochemical response, a 1-minute pre-accumulation time was chosen for following analyses. Under optimized conditions, repeatability and reproducibility studies were performed running five AdSDPV consecutive measurements of a standard solution of MDPV in three different SPE-Gr (Fig. 5).

Using the peak currents of the first oxidation process of MDPV, presented in Fig. 5 (A – C), relative standard deviations (RSD) of 1.4, 1.5, and 1.6% for each of the SPE-Gr were obtained. The obtained peak currents for all measurements are present in Fig. 5(D), confirming the great reproducibility (inter-electrode) of the SPE-Gr for the average electrochemical response of MDPV oxidation, with a RSD of 1.5% ($N = 3$). Furthermore, this indicates the possibility of

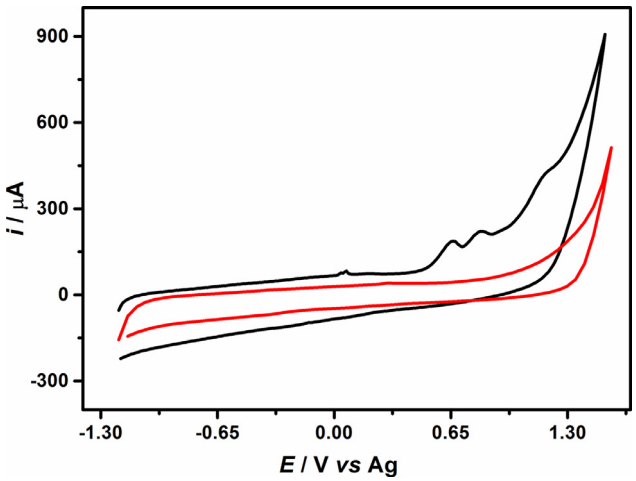


Fig. 4. Voltammograms in 0.1 mol L^{-1} BR buffer pH 6.0 at SPE-Gr (red-line) and after addition of 1.0 × 10^{-3} mol L^{-1} MDPV (black-line). All potential scans were started at −1.2 V with a scan rate of 50 mV s^{-1}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

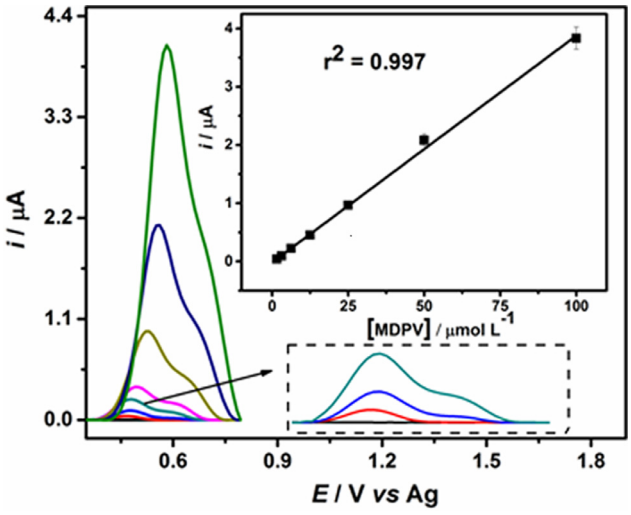


Fig. 6. Voltammograms of 1.6 to 100.0 µmol L^{-1} MDPV solutions in 0.1 M BR buffer, pH 6.0, obtained by AdSDPV at SPE-Gr. Experimental conditions: accumulation time of 1.0 min, amplitude of 80 mV, step potential of 10 mV, and modulation time of 0.05 s. Inlay: linear regression plot and a zoom-in of the lowest measurable signals, corresponding to concentrations from 1.6 to 6.3 µM. Measurements were performed in triplicate.

reusing SPE-Gr following MDPV detection, which is highly convenient for in-field sensing and lowers the cost associated with each determination, thus encouraging its application in forensic analysis.

MDPV linear range determination was evaluated for the proposed method using MDPV solutions ranging from 0.2 to 100 µmol L^{-1} (Fig. 6). A linear relationship between MDPV concentration and its first oxidation peak current (*ca.* +0.6 V *vs.* Ag) was found between 1.6 and 100.00 µmol L^{-1} (inset of Fig. 6), with $r^2 = 0.997$ for the following linear equation: I_{pa1} (µA) = −0.01 (± 0.04) + 0.039 (± 0.001) (µAµmol L^{-1}) [MDPV]. LOD and LOQ obtained by linear regression were of 0.48 and 1.6 µmol L^{-1}, respectively.

It is worth mentioning that although previously reported methods had better sensibility (Table 1), the developed sensor exhibited quite good accuracy and is suitably sensitive for MDPV detection in seized samples. Indeed, the intake dosage of this drug is around 5 to 30 mg [47,48] and the seized sample size containing MDPV is around 100–500 mg [41], indicating a concentration range for this analyte between 1 and 30% (w/w). These MDPV dosages in seized samples are thought to be diluted in a volume of 1 to

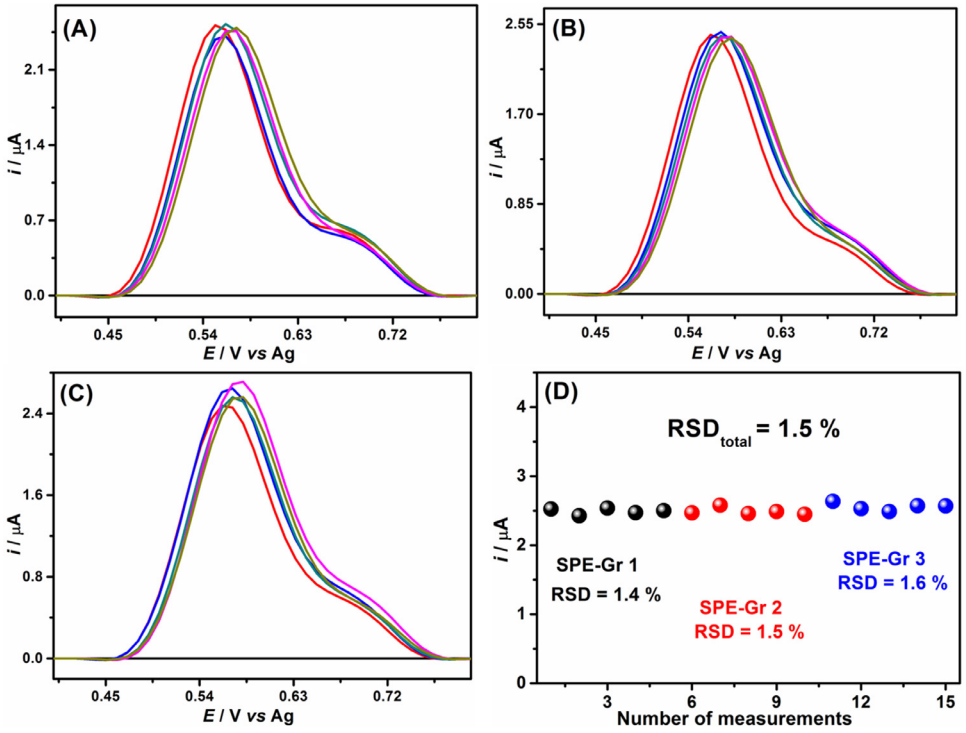


Fig. 5. Voltammograms obtained by AdSDPV of 5 measurements of a 60 mol L^{-1} MDPV solution in 0.1 mol L^{-1} BR buffer pH 6.0 in three different SPE-Gr showed in (A), (B) and (C). Experimental conditions: accumulation time of 1.0 min, amplitude of 80 mV, step potential of 10 mV, and modulation time of 0.05 s. (D) Plot of peak currents *vs.* number of measurements performed in three different SPE-Gr.

Table 1
Analytical methodologies for MDPV.

Method	Extraction	LOD / pg mL^{-1}	LOQ / pg mL^{-1}	Matrix	Reference
SPE-Gr-AdSDPV	none	480	1600	Seized samples	this work
GC–MS	–	–	–	samples purchased online	[8]
LC-MS	SPE[1]	0.5	1.0	human hair	[18]
LC-Q-TOF-MS	SPE	–	–	human blood, urine, liver, vitrous and stomach fluid	[19]
LC-MS/MS	LLE[2]	0.5	1.0	dried urine, plasma and oral fluid	[20]
LC-MS/MS	SPE	25	500	urine	[21]
GC–MS, GC–MS/MS, GC-IR	–	–	–	standard	[22]

[1] SPE: Solid-phase extraction.
[2] LLE: Liquid-Liquid Extraction.

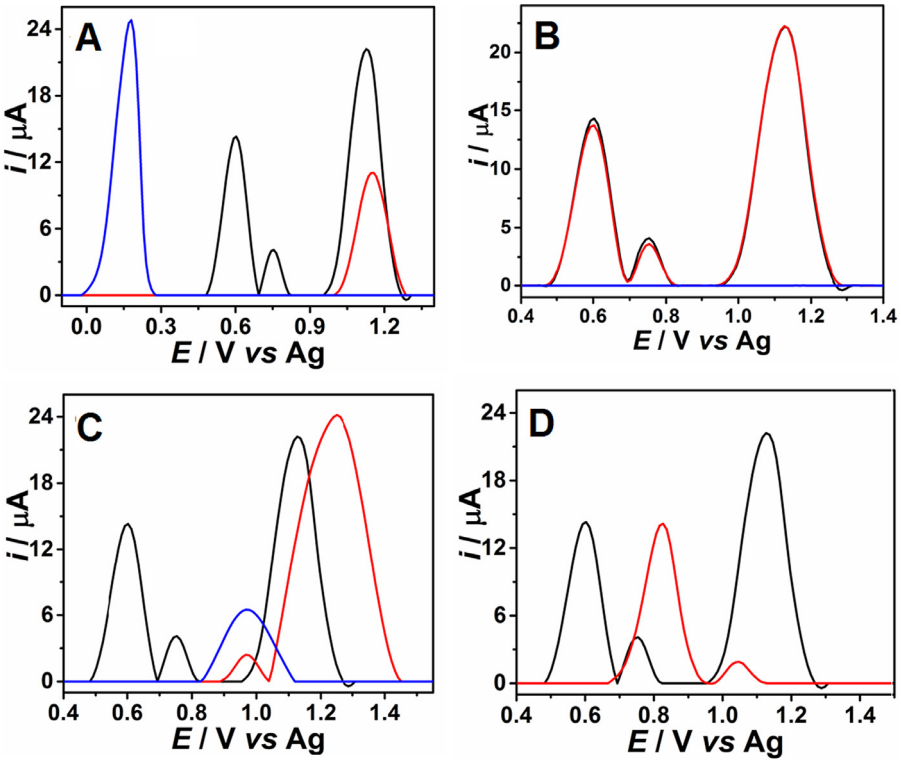


Fig. 7. Voltammograms obtained by AdSDPV at SPE-Gr in 0.1 mol L^{-1} BR buffer, pH 6.0, of standard solutions of MDPV (black-lines) and interferents (A): CAF (red-line) and PAR (blue-line); (B): GLU (blue-line) and MPDV with GLU (red-line); (C): bk-MDMA (red-line) and 4-MMC (blue-line); (D) MDMA (red-line). Experimental conditions: accumulation time of 1.0 min, amplitude of 80 mV, step potential of 10 mV, and modulation time of 0.05 s. The concentration for MDPV and all investigated interferents was 1.0 × 10^{-3} mol L^{-1}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

10 mL of methanol, similarly to what is reported for other NPS seized samples [25,26]. Although these samples need to be further diluted (at least 10 times) in a supporting electrolyte, the final concentration of MDPV is still being sufficiently high (around 100 µmol L^{-1}) for an adequate detection and quantification of MDPV using the proposed method. Additionally, for the first time, an electrochemical method is presented, being an encouraging and powerful alternative for MDPV screening in real samples.

Several adulterants are usually added to illicit substances, either to dilute, mimic or even to enhance their effects, being caffeine (CAF), paracetamol (PAR) and glucose (GLU) the most commonly compounds found in 'bath salts' or in tablets containing synthetic cathinones [39-41]. Thus, in order to evaluate the interference of these compounds, their electrochemical behavior was studied using the proposed method. Fig. 7A shows the voltammograms of CAF (red-line) and PAR (blue-line), both at a concentration of 1.0 × 10^{-3} mol L^{-1}, using the previously optimized conditions for MDPV detection by AdSDPV at SPE-Gr. MDPV previously identified oxidation processes are also shown (black-line). It can be observed that both PAR and CAF exhibit oxidation processes at SPE-Gr, with anodic peak potentials of +0.1 and +1.1 V (*vs.* Ag), respectively. Notwithstanding, such processes are not expected to interfere with the MDPV analysis since they do not overlap with the first oxidation process of MDPV. In addition, while the presence of PAR (+0.1 V) can be easily detected, the presence of CAF can only be noticed if the intensity of the first oxidation peak of MDPV (+0.6 V) is compared to the third oxidation peak (+1.1 V). As can be seen in Fig. 7B, GLU did not present electrochemical activity (blue-line) in the potential range of MDPV detection, indicating that it does not interfere with the screening of this cathinone. It can also be observed that the electrochemical response of MDPV (black-line) remained almost constant after addition of GLU (red-line) in the same concentration to the supporting electrolyte.

Additionally, the interference of other illicit substances, such as the similar cathinones mephedrone (4-MMC) and methylone (bk-MDMA) (Fig. 7C), and the well-known amphetamine MDMA (Fig. 7D) was also evaluated. The blend of MDPV with other cathinones or with MDMA in seized samples is frequent, as can be confirmed in DrugsData.org [48]. As shown in Figs. 7C and 7D, both investigated cathinones and MDMA showed electrochemical

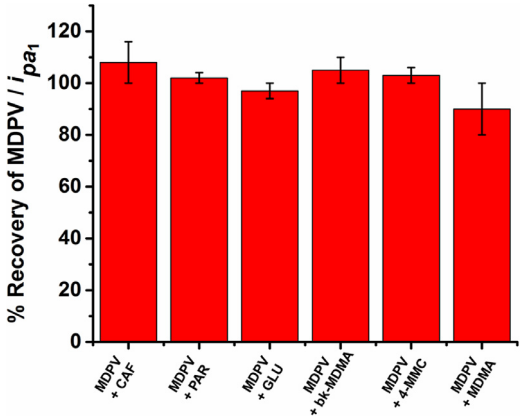


Fig. 8. Recovery results obtained for the first oxidation process of MDPV in solutions simultaneously containing each of the potential interferents (CAF, PAR, GLU, bk-MDMA, 4-MMC and MDMA). Experimental conditions: accumulation time of 1.0-minute, amplitude of 80 mV, step potential of 10 mV, and modulation time of 0.05 s. All measurements were performed in triplicate and standard deviations (SD) are presented in error bars.

activity at the SPE-Gr. However, the selective detection of MDPV is still being possible using the first oxidation process, which indicates that the proposed method can be used for electrochemical screening of this drug in seized samples containing bk-MDMA, 4-MMC or MDMA. An interference study was also performed for MDPV detection in the presence of all investigated interferents (Fig. 8), confirming that no significant differences were observed in the electrochemical response for the first oxidation process of MDPV at the SPE-Gr.

3.4. Comparison with reference sample and recovery study

The accuracy of the proposed method was evaluated through MDPV quantification in a reference sample donated by UNDOC. The identification of MDPV in this sample was performed using the AdSDPV technique at SPE-Gr (Figure S7 of SI), where an electrochemical behavior similar to the one observed for MDPV standard solution was found. Using the proposed electrochemical method, the average concentration value ($N = 3$) obtained for MDPV was 44.0 ± 2.1%(w/w), revealing quite good agreement to the reference sample informed concentration (43.1%, w/w). Statistical test (paired *t*-test) was applied to validate the obtained results, with the calculated value for paired *t*-test being lower than the tabulated critical value, indicating that with a confidence level of 95% there are no significant differences between the labeled and found values of MDPV in the reference sample.

Moreover, recovery studies were performed in real seized samples containing another cathinone (N-ethylpentylone) in bath salts or MDMA in tablets, both drugs previously confirmed by LC-MS. The blend of MDPV with other cathinones or MDMA in these samples has been found according to the information provided by DrugsData.org [48]. As can be seen in Figure S9 of SI, using the first oxidation process of MDPV, the proposed method can selectively detect this substance in seized samples containing N-ethylpentylone (Figure S9A of SI) in bath salts or MDMA in tablets (Fig. S9B of SI). Recovery values of MDPV in these samples ($N = 3$) were of 103 ± 5% and 95 ± 6%, respectively in the presence of N-ethylpentylone and MDMA, indicating that the proposed method can be successfully applied for MDPV screening in real samples containing a mixture of other cathinones in forensic samples.

4. Conclusions

In this work, the electrochemical detection of the synthetic cathinone MDPV is reported for the first time. Its electroanalysis at the surface of GCE and SPE-Gr resulted in the identification of three irreversible oxidation processes. At a SPE-Gr, MDPV presented an adsorption oxidation process, and the AdSDPV technique was efficiently applied for the simple, selective and sensitive detection of the analyte. SPE-Gr provided good reproducibility and the possibility of being reused for MDPV determination. The proposed method demonstrates a simple, fast and cost-effective alternative to the identification and determination of MDPV in seized samples, allowing its application as screening method in forensic analysis.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Camila D. Lima: Investigation, Methodology, Writing - original draft. **Rosa A.S. Couto:** Visualization, Writing - original draft. **Luciano C. Arantes:** Conceptualization, Visualization, Validation, Writing - review & editing, Resources. **Pablo A. Marinho:** Conceptualization, Validation, Resources, Writing - review & editing. **Dilton M. Pimentel:** Investigation, Methodology. **M. Beatriz Quinaz:** Visualization, Writing - review & editing. **Rodrigo A.B. da Silva:** Visualization, Writing - review & editing. **Eduardo M. Richter:** Visualization, Resources, Writing - review & editing. **Sandro L. Barbosa:** Conceptualization, Visualization, Writing - review & editing. **Wallans T.P. dos Santos:** Conceptualization, Visualization, Supervision, Project administration, Resources, Funding acquisition, Writing - review & editing.

Acknowledgements

W.T.P dos Santos wishes to thank CNPq (Grant No. 424432/2018–8) and FAPEMIG (Grant APQ-03637–16) for financial support. RASC wishes to acknowledge FCT for her PhD fellowship (PD/BD/127797/2016) from the PhD Programme in Medicines and Pharmaceutical Innovation (i3DU). This work was supported in part by UID/QUI/50006/2019 and UID/MULTI/04378/2019 with funding from FCT/MCTES through national funds.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.electacta.2020.136728.

References

[1] R.A.S. Couto, L.M. Gonçalves, F. Carvalho, J.A. Rodrigues, C.M.P. Rodrigues, M.B. Quinaz, The analytical challenge in the determination of cathinones, key–players in the worldwide phenomenon of novel psychoactive substances, Crit. Rev. Anal. Chem. 48 (2018) 372.
[2] United Nations Office on Drugs and Crime (UNODC), Global synthetic drugs. Market analysis of synthetic drugs: amphetamine-type stimulants, New Psychoactive Substances, United Nations, Austria, 2017.
[3] United Nations Office on Drugs and Crime (UNODC), Stimulants World Drug Report 2019, United Nations, Austria, 2019.
[4] United Nations Office on Drugs and Crime (UNODC), Analysis of Markets: Opiates, Cocaine, Cannabis, Synthetic Drugs, United Nations, Austria, 2018.
[5] United Nations Office on Drugs and Crime (UNODC), Current NPS Threats, II, United Nations, Austria, 2020 January.
[6] European Monitoring Centre for Drugs and Drug Addiction and Europol, EU Drug Markets Report 2019, Publications Office of the European Union, Luxembourg, 2019.
[7] L. Karila, G. Lafaye, A. Scocard, O. Cottencin, A. Benyamina, MDPV and α-PVP use in humans: the twisted sisters, Neuropharmacol. 15 (2018) 65.
[8] J. Ramsey, P.I. Dargan, M. Smyllie, S. Davies, J. Button, D.W. Holt, D.M. Wood, Buying 'Legal' recreational drugs does not mean that you are not breaking the law, Q.J. Med. 10 (2010) 777.
[9] K. Miotto, J. Strebel, A.K. Cho, C. Wang, Clinical and pharmacological aspects of bath salt use: a review of the literature and case reports, Drug Alcohol Depend. 132 (2013) 1.

[10] Drug Enforcement Administration, Final Rule, Establishment of drug codes for 26 substances, Fed. Regist. 78 (3) (2013) 664.
[11] United Nations Commission on Narcotic Drugs. Scheduling decisions. https://www.unodc.org/unodc/en/commissions/CND/Mandate_Functions/Mandate-and-Functions_Scheduling.html [Accessed 10 Apr 2020].
[12] Agência Nacional de Vigilância Sanitária (ANVISA), Lista de Substâncias Sujeitas a Controle Especial no Brasil, http://portal.anvisa.gov.br/lista-de-substancias-sujeitas-a-controle-especial [Accessed 11 Apr 2020].
[13] J.C. Yohannan, J. Joseph, S. Bozenko, The Characterization of 3, 4-methylenedioxypyrovalerone (MDPV), Microgram J. 7 (2010) 12.
[14] C.L. German, A.E. Fleckenstein, G.R. Hanson, Bath Salts and synthetic cathinones: an emerging designer drug phenomenon, Life Sci. 97 (2014) 2.
[15] A.M. Leffler, P.B. Smith, A.D. Armas, F.L. Dorman, The analytical investigation of synthetic street drugs containing cathinone analogs, Forensic Sci. Int. 234 (2014) 50.
[16] S. Anizan, K. Ellefsen, M. Concheiro, M. Suzuki, K.C. Rice, M.H. Baumann, M.A. Huestis, 3, 4-methylenedioxypyrovalerone (MDPV) and metabolites quantification in human and rat plasma by liquid chromatography-high resolution mass spectrometry, Anal. Chim. Acta 827 (2014) 54.
[17] B. Mathias, B.S. Forrester, Synthetic cathinone exposures reported to texas poison centers, Am. J. Drug Alcohol Abuse 38 (2012) 609.
[18] F. Freni, S. Bianco, C. Vignali, A. Groppi, M. Moreti, A.M.M. Osculati, L. Morini, A Multi-Analyte LC-MS/MS method for screening and quantification of 16 synthetic cathinones in hair: application to post-mortem cases, Forensic Sci. Int. 298 (2019) 115.
[19] L. Glicksberg, R. Winecker, C. Miller, S. Kerrigan, Postmortem distribution and redistribution of synthetic cathinones, Forensic Toxicol. 36 (2018) 291.
[20] J.C. Alvarez, I. Etting, E. Abe, A. Villa, N. Fabresse, Identification and Quantification of 4-methylethcathinone (4-MEC) and 3,4-methylenedioxypyrovalerone (MDPV) in Hair by LC-MS/MS bater chronic administration, Forensic Sci. Int. 270 (2017) 39.
[21] A. De Castro, E. Lendoiro, H. Fernández-Vega, S. Steinmeyer, M. López-Rivadulla, A. Cruz, Liquid chromatography tadem mass spectrometry determination of selected synthetic cathinones and Tow Piperazines in oral fluid. cross reactivity study with an on-site immunoassay device, J. Chromatogr. A 1374 (2014) 93.
[22] Y. Abiedalla, J. Deruiter, R. Clark, GC–MS, GC-MS/MS and GC-IR Differentiation of Carboyl Modified Analogues of MDPV, Forensic Chem. 3 (2017) 58.
[23] United Nations Office on Drugs and Crime (UNODC), Métodos Recomendados Para La Identificación Y El Análisis De Las Catinonas Sintéticas Em Los Materiales Incautados, United Nations, New York, 2016.
[24] M. Nieddu, L. Burrai, C. Trignano, G. Boatto, Evaluation of commercial multi–drug oral fluid devices to identify 39 new amphetamine-designer drugs, Legal Med. 16 (2014) 106.
[25] G.A. Souza, L.C. Arantes, T.J. Guedes, A.C. De Oliveira, P.A. Marinho, R.A.A. Muñoz, W.T.P. Dos Santos, Voltammetric signatures of 2,5-Dimethoxy-N-(2-Methoxybenzyl) phenethylamines on boron-doped diamond electrodes: detection in blotting paper samples, Electrochem. Commun. 82 (2017) 121.
[26] G.A. Souza, D.M. Pimentel, A.B. Lima, T.J. Guedes, L.C. Arantes, A.C. De Oliveira, R.M.F. Sousa, R.A.A. Muñoz, W.T.P. Dos Santos, Electrochemical sensing of nbomes and other new psychoactive substances in blotting paper by square-wave voltammetry on a boron-doped diamond electrode, Anal. Methods 10 (2018) 2411.
[27] G.L. Scheel, F.M. De Oliveira, L.L.G. De Oliveira, R.A. Medeiros, C.C. Nascentes, C.R.T. Tarley, Feasibility study of ethylone determination in seized samples using boron-doped diamond electrode associated with solid phase extraction, Sensor Actuat. B-Chem. 259 (2018) 1113.
[28] J.P. Smith, J.P. Metters, O.I.G. Khreit, O.B. Sutcliffe, C.E. Banks, Forensic electrochemistry applied to the sensing of new psychoactive substances: electroanalytical sensing of synthetic cathinones and analytical validation in the quantification of seized street samples, Anal. Chem. 86 (2014) 9985.
[29] A.F.B. de Andrade, J. Gonzalez-Rodriguez, Electroanalytical identification of 25I-NBOH and 2C-I via differential pulse voltammetry: a rapid and sensitive screening method to avoid misidentification, Analyst 144 (2019) 2972.
[30] A.F.B. de Andrade, S.K. Mamo, J. Gonzalez-Rodriguez, Rapid screening method for new psychoactive substances of forensic interest: electrochemistry and analytical determination of phenethylamines derivatives (NBOMe) via cyclic and differential pulse voltammetry, Anal. Chem. 89 (2017) 1452.
[31] E.N. Oiye, J.M.T. Katayama, M.F.M. Ribeiro, M.F. de Oliveira, Electrochemical analysis of 25H-NBOMe by square wave voltammetry, Forensic Chem. 5 (2017) 90.
[32] M. Li, Y. Li, D. Li, Y. Long, Recent developments and applications of screen-printed electrodes in environmental assays-A review, Anal. Chim. Acta 734 (2012) 31.
[33] H.M. Mohamed, Screen printed disposable electrodes: Pharmaceuticals applications and recent developments, Trends in Anal. Chem. 82 (2016) 1.
[34] R.A.S. Couto, J.L.F.C. Lima, M.B. Quinaz, Recent developments, characteristics and potential applications of screen-printed electrodes in pharmaceutical and biological analysis, Talanta 146 (2016) 801.
[35] W.T.P. Dos Santos, R.G. Compton, Simple method to detect the stimulant modafinil in authentic saliva using a carbon-nanotube screen-printed electrode with adsorptive stripping voltammetry, Sensor Actuat. B-Chem. 285 (2019) 137.
[36] W.T.P. Dos Santos, H.M.A. Amin, R.G. Compton, A nano-carbon electrode optimized for adsorptive stripping voltammetry. Application to detection of the stimulant selegiline in Authentic Saliva, Sensor Actuat. B-Chem. 279 (2019) 433.
[37] A.B. Lima, R.G. Compton, W.T.P. Dos Santos, Simple and sensitive determination of sibutramine in slimming tea beverages using a carbon screen-printed electrode with adsorptive stripping voltammetry, Electroanalysis 31 (2019) 975.
[38] J. Mocak, A.M. Bond, S. Mitchell, G. Scollary, A statistical overview of standard (IUPAC and ACS) and new procedures for determining the limits of detection and quantification: application to voltammetric and stripping techniques, Pure Appl. Chem. 69 (1997) 297.
[39] C.L. German, A.E. Fleckenstein, G.R. Hanson, Bath salts and synthetic cathinones: an emerging designer drug phenomenon, Life Sci. 97 (2014) 2.
[40] L.T.A. Alcântara, Adulterantes encontrados em drogas ilícitas: uma abordagem forense, Acta de Ciências e Saúde 5 (2016) 1.
[41] DrugsData.org (formely EcstasyData): Lab Test Results for Ecstasy/Molly and other Recreational Drugs, (n.d.). https://www.ecstasydata.org/ (accessed May 24, 2020).
[42] M. Swain Chemicalize.org, J. Chem. Inf. Model. 52 (2012) 613.
[43] 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.
[44] J. Saichanapan, K. Promsuwan, Warakorn Limbut, Adsorption and determination of sibutramine in illegal slimming product using porous graphene ink–modified electrode, Talanta 212 (2020) 120788.
[45] M.R. Montoya, E.Morales I.Giraldez, R.E. Brito, J.M.R. Mellado, Electrochemical oxidation of isothiazolinone biocides and their interaction with cysteine, Electrochim. Acta 337 (2020) 135770.
[46] X. Chen, T. Ren, M. Ma, Z. Wang, Guoqing Zhan, C. Li, Voltammetric sensing of bisphenol A based on a single-walled carbonnanotubes/poly{3-butyl-1-[3-(N-pyrrolyl)propyl] imidazolium ionicliquid} composite film modified electrode, Electrochim. Acta 111 (2013) 49.
[47] M. Coppola, R. Mondola, 3, 4-Methylenedioxypyrovalerone (MDPV): chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online, Toxicol. Lett. 5 (2012) 2.
[48] L.D. Simmler, T.A. Buser, M. Donzeli, Y. Schramm, L.H. Dieu, J. Huwyler, S. Chaboz, M.C. Hoener, M.E. Liechti, Phamarcological characterization of designer cathinones in vitro, Br. J. Pharmacol. 168 (2013) 458.