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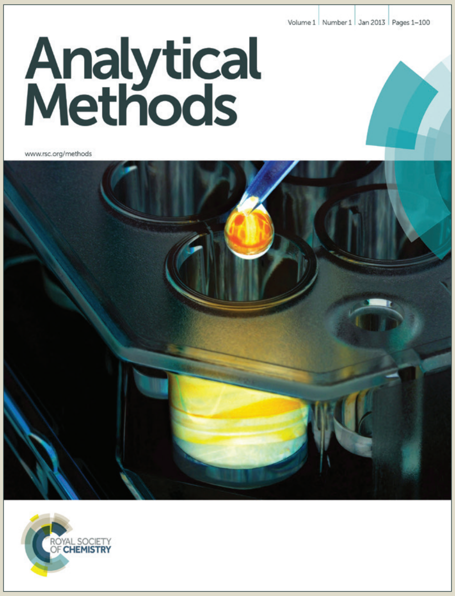

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Regal Electrochemistry: Sensing of the Synthetic Cathinone Class of New Psychoactive Substances (NPSs)

Fang Tan, Jamie P. Smith, Oliver B. Sutcliffe and Craig E. Banks*

Faculty of Science and Engineering, School of Science and the Environment, Division of Chemistry and Environmental Science, Manchester Metropolitan University, Chester Street, Manchester M1 5GD, UK

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*To whom correspondence should be addressed.

Email: c.banks@mmu.ac.uk; Tel: +44 (0)161-247-1196; Fax: +44 (0)161-247-6831; Website: www.craigbanksresearch.com

Abstract

In this paper the concept of ‘Regal Electrochemistry’ is expanded towards the electrochemical sensing of Novel Psychoactive Substances (NPSs) namely synthetic cathinone derivatives where British coinage is used as the electrochemical sensor. In this proof-of-concept approach, the electrochemical sensing of mephedrone (4-MMC) and 4’-methyl-*N*-ethylcathinone (4-MEC) is shown to be possible using a British 1 pence coin for the first time. This novel electrochemical protocol is validated towards the detection of cathinone derivatives in a seized street sample that has been independently analysed via high performance liquid chromatography demonstrating its potential use as a novel electrochemical sensor for NPSs.

Keywords: New Psychoactive Substances; Legal highs; Electrochemistry; Regal Electrochemistry; 1p sensor

Introduction

Synthetic cathinones are a class of New Psychoactive Substance (NPS; newly abused substances that may, or may not, be controlled by national drug legislations in light of their recent discoveries) that are derived from cathinone, an organic stimulant found in Khat (*Catha edulis*) and are both similar in structure and pharmacological effect as the phenethylamine class of psychoactives (*e.g.* amphetamine and methamphetamine).[1, 2] Despite being controlled by drug legislation internationally (*e.g.* Misuse of Drugs Act 1971 in the United Kingdom) synthetic cathinone-derivatives are still prevalent in many NPS products marketed as 'legal highs'[2-6] and are sold at head shops and on the internet. For example, mephedrone (4-MMC) has been found in products labelled 'legal highs' in the UK after it was made a controlled substance in 2010[5] and its use has been linked to several deaths worldwide;[7, 8] therefore development of rapid, economical methods for their detection and quantification is still timely.

A range of chromatographic techniques including High Performance Liquid Chromatography (HPLC) and Gas Chromatography-Mass Spectrometry (GC-MS) have been applied to the detection of synthetic cathinones by many groups,[4, 5, 8-27] however electrochemistry is advantageous as an analytical tool being sensitive, selective as well as low cost and having the potential to be scaled down to a portable device.[28-34] Previous work [2, 34] has reported novel electroanalytical sensing protocols developed towards the electrochemical oxidation[34] and reduction of synthetic cathinones, mephedrone and 4'-methyl-*N*-ethylcathinone (4-MEC) using disposable carbon based screen-printed sensors which was successfully applied to their quantification in seized street samples; the protocol was also validated by independently performed HPLC.[2]

In this communication, electrochemical sensors based upon a British 1 pence coin are utilised to successfully detect 4-MMC and 4-MEC for the first time. This novel electrochemical sensing platform based upon British coinage offers an economical approach to the sensing of NPSs 4-MMC and 4-MEC (see Scheme 1) using a 1 pence coin, where the benefits of a sensor costing 1 pence (each side of the coin is useable) are unmistakeable. This new electrochemical approach is explored in ideal solutions and validated towards a seized street sample that has been independently analysed using HPLC.

Experimental

All chemicals used were of analytical grade and used as received without any further purification from Sigma-Aldrich (Gillingham, UK). All solutions were prepared with deionised water of resistively no-less than 18.2 Ω cm. All solutions (unless stated otherwise) were vigorously degassed with nitrogen to remove oxygen prior to analysis. The synthetic cathinone hydrochloride (or hydrobromide) salts, were prepared at the University of Strathclyde prior to the legislative change on 16th April 2010 using the methods reported in previous work.[34] A street sample was obtained via internet vendors.

Voltammetric measurements were carried out using a Palmsens (Palm Instruments BV, The Netherlands) potentiostat/galvanostat and controlled by PSTrace version 4.4 . A 1 pence British coin was used as the working electrode along with a platinum wire counter electrode and a Saturated Calomel Electrode (SCE) reference (Radiometer, Copenhagen, Denmark) completing the conventional three electrode electrochemical system. The 1 pence coin has a different composition depending on the time it was minted; between its inception in1971 and September 1992 minted coins comprised of bronze (97% copper, 2.5 zinc, 0.5% tin) however post 1992 they have been copper-plated steel. The study herein used coins minted post 1992 in light of the scarcity of coins minted pre-1992. The working electrodes, 1 pence coins, were placed in to a polytetrafluoroethylene (PTFE) ‘housing’ unit which comprised of a PTFE cap (with 3.0 mm diameter bore hole leaving a working electrode area of 7.1 mm) and PTFE body allowing easy electrical wiring of the coin; see Figure 1 for a schematic representation of the bespoke electrochemical cell. This cell is required to ensure that a reproducible geometric electrode area is obtained. Prior to analysis the 1 pence coin was sonicated in methanol to provide thorough surface cleaning for 2 mins. A new 1 pence coin was utilised for each experiment with each side utilised. Scanning electron microscope (SEM) images and surface element analysis were obtained with a Zeiss Supra 40vp model equipped with an energy-dispersive X-ray microanalysis package (GenesisEdax).

Results and Discussion

The cyclic voltammetric behaviour of 4-MMC using the 1 pence coin (1p-sensor) in aqueous buffer solutions was first explored. Figure 2A depicts the voltammetric response obtained in a solution of pH 8.5 acetate buffer using a 1p-sensor in the absence and presence of 4-MMC. Inspection of the resultant cyclic voltammograms reveals two reduction peaks observed at approximately – 0.4 V and - 0.6 V respectively in order of potential cycling and a single oxidation peak at −0.01 V, all of which are in agreement with the literature regarding the electrochemical behaviour of copper oxide.[35] Note: the oxidation peak at – 0.01 V is visible in the absence of 4-MMC and is seen to decrease in intensity upon its addition, this can be attributed to the 4-MMC adhering to the surface of the electrode and obstructing its electroactivity; as such the sensing of 4-MMC is an indirect approach.

The electroanalytical method was explored through additions of 4-MMC into a pH 8.5 acetate buffer using the 1p-sensor; pH 8.5 was chosen since this maintains copper in the form of an oxide (CuO or Cu_2O) which appears useful to provide an indirect sensing platform and is also a pH that ensures that the degradation of the NPSs, which occurs at alkaline pH is not significant. As is represented in Figure 3, the oxidation peak observed at approximately -0.01 V decreases in magnitude upon the addition of 4-MMC. The corresponding calibration plot (Figure 3 Inset) demonstrates the linear response observed ($I/\mu A = 0.1 \times 10^{-3}$ A [$\mu g\ mL^{-1}$]+ 4 $\times 10^{-5}$ A, $R^2 = 0.97$, N=3; *RSD% 21.4*) over the analytical range studied ($1 \times 10^{-3} – 0.1$ µg mL^{-1}). The limit of detection (3σ) for 4-MMC utilising the 1 pence sensor was estimated to correspond to 0.56 µg mL^{-1} which is a large improvement on our earlier work[2] which reported a value of 11.80 µg mL^{-1}. Note that this novel proof-of-concept has a substantial error when the average of three different coins is used. .

Attention was now turned to another novel psychoactive substance (similar to 4-MMC), 4-MEC (also found in seized street samples[2]) wherein the cyclic voltammetric behaviour towards a 1 pence sensor in pH 8.5 acetate buffer is visible in Figure 2B. A similar response to 4-MMC is observed with again a single oxidation peak at – 0.01V and the two reduction peaks at approximately – 0.3 and – 0.6 V with the intensity of the oxidation peak again decreasing proportionally to the increasing concentration of 4-MEC. The resultant calibration plot demonstrated a linear response ($I/\mu A = 0.2 \times 10^{-3}$ A [$\mu g\ mL^{-1}$]+ 6 $\times 10^{-5}$ A, $R^2 = 0.97$, N=3; *RSD% 4.3*) over the studied analytical range ($1 \times 10^{-3} – 0.1$ µg mL^{-1}) with a limit of detection (3σ) equal to 0.50 µg mL^{-1} . Whilst this protocol performs admirably in terms of levels of detection, there are limitations regarding the selectivity between similar compounds. The electrochemical mechanism is an indirect approach where the electrochemistry of copper oxide is inhibited due to the adsorption of the NPSs under investigation. As shown in ESI figures 1 and 2, Scanning Electron Microscopy-Energy Dispersive X-ray microanalysis (SEM-EDX) shows a higher percentage of copper (and therefore CuO) in the 1 pence coins minted post-1992. Since the underlying mechanism is dependent upon the presence of copper oxide, post-1992 are ideal. This is fortunate given the scarcity of coins minted pre-1992 further justifying the use of post-1992, which are in current circulation.

To define the qualities of a 1p-sensor, the analytical protocol was applied to a seized street sample (NRG-2), previously analysed,[34] to determine if the 1p-sensor has merit as a potential sensor for the content of 4-MMC within. Note: Previous analysis[2] of NRG-2 seized street samples via HPLC (see ESI) has shown their contents comprise of adulterants such as caffeine and benzocaine.[2] Seized street sample for analysis in this manuscript was known to contain 11.15 % (w/w) 4-MMC and 87.99 % (w/w) caffeine (see reference 2 for more details). The standard addition method was utilised in an attempt to quantify the amount of 4-MMC in a street sample and was compared to the previously reported values obtained by cyclic voltammetry (with a carbon screen-printed sensor) and HPLC (See ESI for further details).[34] Following analysis, the standard addition plot revealed a reported 4-MMC content of 10.99 % (w/w) which is in excellent agreement with 11.15% (w/w) obtained via HPLC and 11.32% (w/w) reported previously [2] using the carbon based screen-printed sensor and is indicative that an electrochemical sensor using British coinage has analytical merit.

Conclusions

Proof-of-concept has been shown for the detection of NPSs using a 1 pence coin as a novel electrochemical sensor. This novel approach is extremely cost effective with the sensor costing just 1 pence (both sides of the coin can be used), and a PTFE ‘housing’ unit which is readily made using cheap components readily available in university workshops. The proposed protocol has been successfully validated against independently performed HPLC in seized street samples. Future work will expand the concept of using British coinage towards other NPSs or using other coinage such as foreign currency and adaption in HPLC-ECD systems.

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Scheme 1. Chemical structures of A: mephedrone (4-MMC) and B: 4’-methyl-*N*-ethylcathinone (4-MEC)

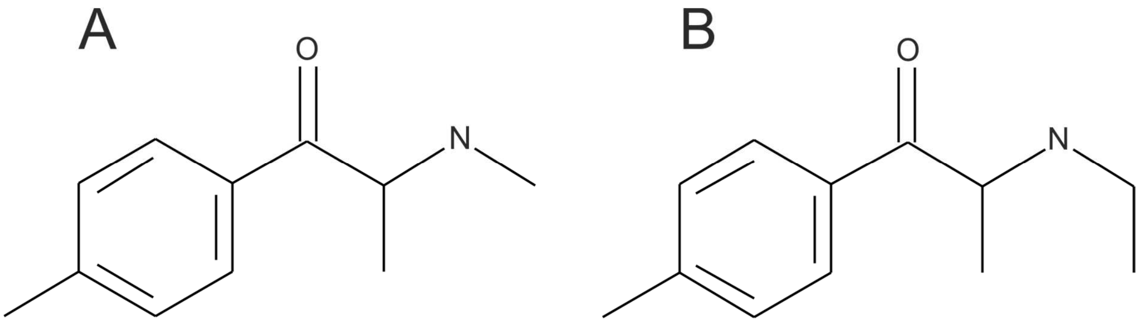


Figure 1 A: Schematic diagram of the Regal Electrochemistry experimental cell PFCE ‘housing’ unit used to hold the 1 pence sensor in place for analysis and accurately defines the working electrode area. B: Cross sectional diagram of assembled PFCE ‘housing’ unit with a retrofitted 1p-sensor in place which is then inserted into the solution under investigation.

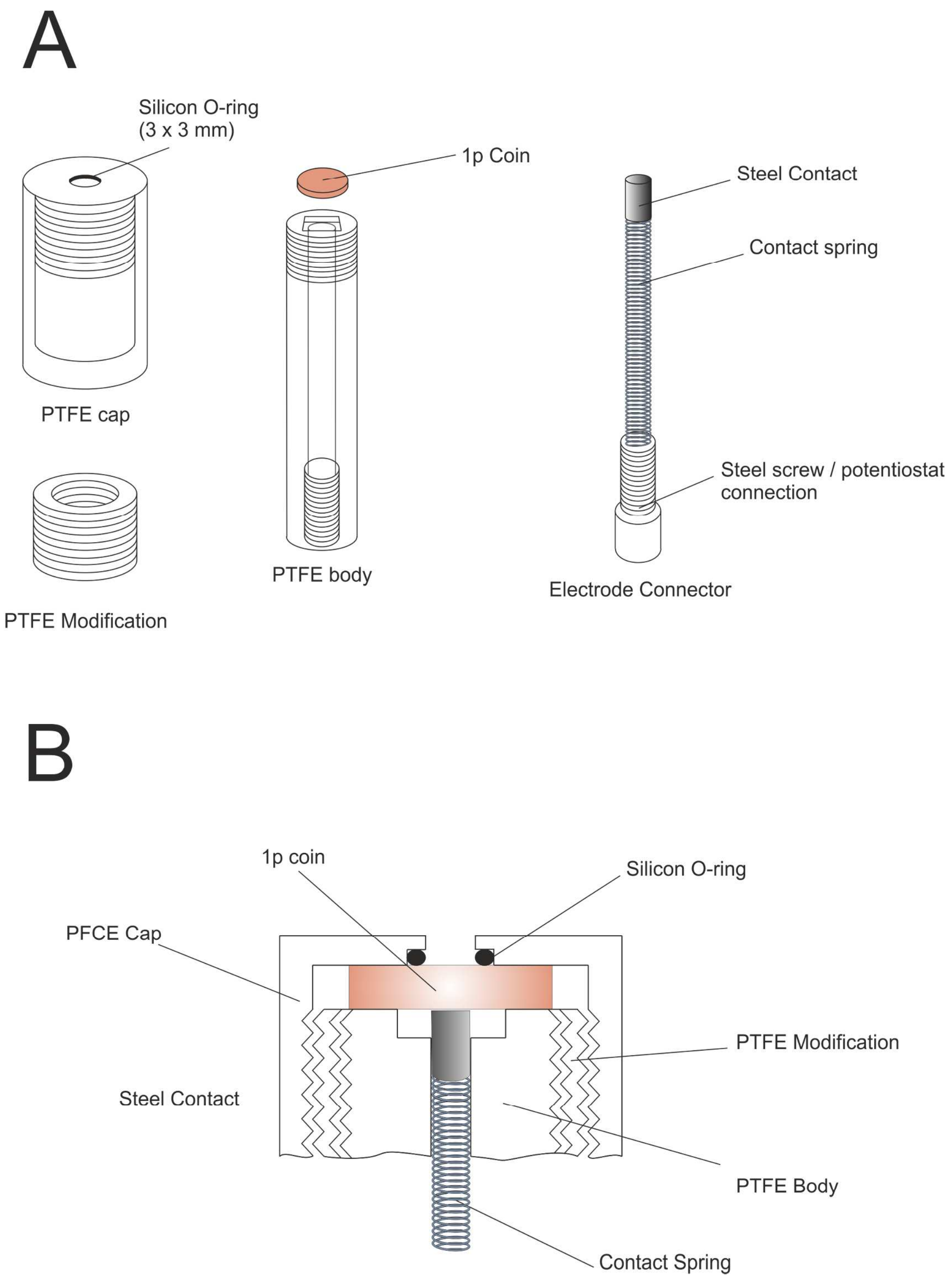


Figure 2. Typical cyclic voltammograms using a 1 pence electrochemical sensor in the absence (black) and presence of 4-MMC (red) and 4-MEC (blue) in pH 8.5 acetate buffer. Scan rate: 50 mVs^{-1} (vs. SCE).

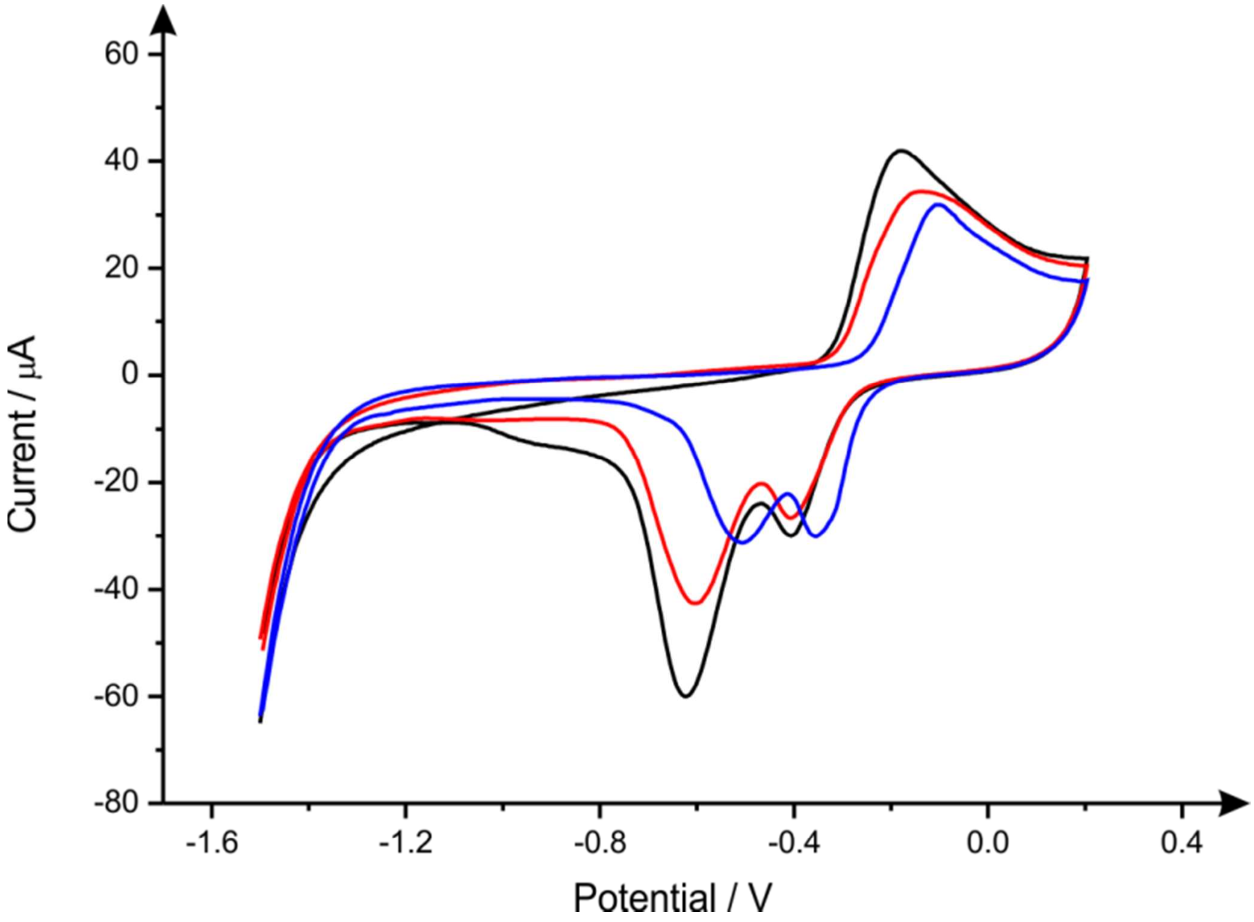
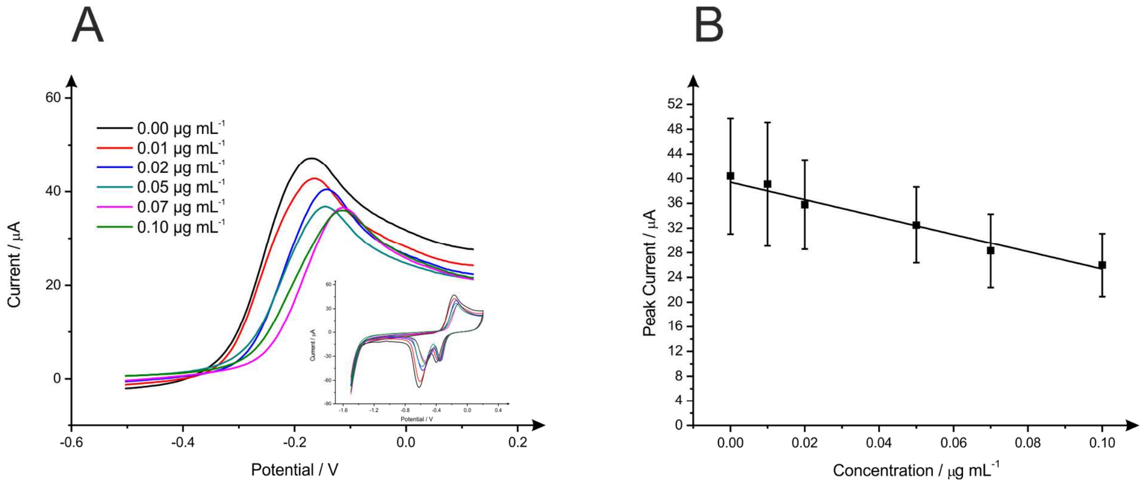


Figure 3. A: Typical voltammetric responses between the range -0.5 and +0.1 V as a result of increasing concentrations of 4-MMC using the 1p-sensor recorded in a pH 8.5 acetate buffer. Scan rate 50 mV s^{-1} (vs. SCE), using the oxidative peak at approximately - 0.1V as the analytical peak. Inset: Typical voltammetric responses as a result of increasing concentrations of 4-MMC B: Typical calibration resulting from the analysis of voltammetric signatures obtained in the form of a plot of peak height (current) against 4-MMC concentration using a 1p-sensor in a pH 8.5 acetate buffer over a linear range of 0.00 – 0.10 µg mL^{-1}. Scan rate: 50 mV s^{-1} (vs. SCE) ($N = 3$ – average and standard deviation is plotted).



Regal Electrochemistry: Discovering new economical electrochemical sensors by utilising a British 2 pence coin; proof-of-concept protocol successfully applied towards the detection of novel psychoactive substances.