Electrochemical Devices For Forensic Chemical Sensing

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This chapter covers the range of electrochemical approaches for a variety of chemical sensing utilised within forensic analysis. Electrochemical based sensors are powerful analytical tools which can be exploited by the forensic community and they have found widespread applications within the fields of illicit drug detection, toxicological analysis, alcohol detection and explosives analysis. This chapter presents an overview of these applications of electrochemical sensing and an assessment of current technological advancements as well as future areas of research. Within the forensic community the need for versatile, portable, selective, sensitive and robust methodologies has made electrochemical sensors an attractive alternative to more traditional analytical technologies. Herein, we will highlight the distinctive prospects electrochemistry offers to the field of forensic chemical analysis as well as showcasing the most significant advancements to date.

1 Introduction

The versatility of electrochemical sensing methods lends itself well to a wide range of applications across a diverse range of fields.[1-4] Electrochemical sensors are particularly amenable for forensic analysis, the portability, sensitivity and minimal sample preparation required makes them ideally suited for crime scene and evidential analysis particularly as a screening tool during the initial phases of an investigation.[5] With their continued development leading to increases in specificity and their ability to facilitate direct detection within complex sample matrices including biological fluids without pre-treatment or extraction greatly expands their potential applications within the forensic environment. Flexibility in electrode material and surface functionalisation allows sensors to be easily fabricated for specific analyte detection thereby improving specificities towards the target analyte but also allowing for versatility in their applications dependent on the surface modification. Whilst the increased use of screen-printed electrodes (SPE) can offer a mechanism for reducing the risk of potential contamination as a result of their disposability, they can easily undergo surface modification for targeted detection. The incorporation of different species for surface modification has never been simpler or more attainable, with facilities allowing fabrication of electrodes in-house. Portable potentiostats (now widely available) in combination with disposable SPE and minimal sample preparation facilitates on-site and point-of-care analysis, a key goal for future forensic analysis. By enabling the rapid identification of substances, the police and forensic investigators are able to make informed decisive investigative decisions, whilst also minimising any potential for cross contamination or evidence destruction during transportation between crime scenes and forensic laboratories where full characterisation and analysis is performed.

Electrochemical methods are unlikely to entirely replace the traditional gold

standard analytical techniques currently employed within forensic analysis. This is partly due to the complex and diverse range of sample matrices, often requiring the employment of a range of techniques for sample analysis and the legal requirements for presentation within courts. However, they do offer a viable portable technique, whose employment at crime scenes would ultimately only improve forensic investigations. In recent years the application of electrochemical analysis within forensic science, commonly termed "Forensic Electrochemistry" has been observed in a number of areas; including the detection of drugs[6-9], poisons[10, 11], explosives[12-14] and gun shoot residue.[15-17] Whilst these may be considered more obvious applications forensic electrochemistry, others applications such as fingerprint detection[18] and alcohol sensing have also been utilised.[19, 20]

2 Toxicology and Drugs

2.1 Drug and Poison Detection

The abuse of illicit substances still remains an important global problem, emphasised further by the continually evolving nature of the global drug market, which has seen the increased presence of novel psychoactive substances (NPS).[21, 22] Although many of the traditional drug analysis methods, such as high performance liquid chromatography mass spectrometry (HPLC-MS) and gas chromatography mass spectrometry (GC-MS) are still considered the gold standard analytical techniques in forensic analysis, there is a growing need for rapid, sensitive and inexpensive detection systems for in-field analysis of both illicit substances and poisons in clinical and law enforcement environments.[23] This is further emphasised when you consider that the well-established techniques used for on-site screening methods, primarily consisting of the colorimetric presumptive tests whose colour changes indicate the presence of a specific drug class, are often inadequate for NPS whilst their poor selectivity hinders their reliability across all drug classes.[23] Electrochemical sensors can combat these issues, and present an opportunity to address the current gap in forensic practices for rapid and crude identification of illicit and poisonous substances.

Electrochemical sensors have already demonstrated their suitability for forensic substance identification with their detection capabilities of a range of illicit and poisonous substances across a diverse range of sample matrices. These include the more common recreational drugs such as cocaine[7, 24], amphetamine type stimulants[6, 25] and NPS[8, 26, 27] but also include more unusual species such as atropine.[4, 10, 28] Atropa belladonna, Datura and Mandrake all share the deadly tropane alkaloids atropine and scopolamine. Atropine and scopolamine behave as anticholinergic hallucinogens, as a result of their antagonists' actions toward the acetylcholine receptors. These actions make these tropane alkaloids ideally suited as poisons whilst their hallucinogenic effects make them appealing as recreational drugs. In comparison to well know naturally occurring recreational drugs, such as cannabis, atropine and scopolamine producing species remain largely unregulated in many countries. Whilst the purchase of pharmaceutics containing the alkaloids can often be performed without a medical prescription further increasing their appeal.[29]

The use of atropine as a poison is not a recent. In fact, one of the more interesting and well-known cases of atropine poisoning occurred in the UK 1994, when Dr Paul Agutter, a biology professor at Edinburgh Napier University, attempted to murder his wife, spiking her gin and tonic with the alkaloid. Agutter subsequently attempted

to cover his tracks, lacing multiple bottles of tonic, before returning the poisoned bottles to the supermarket shelf, resulting in a mass panic when a number of people in the Edinburgh area fell ill.[30, 31] This case led Ramdani *et al.*[10] to investigate the use of electrochemical sensors for the detection of atropine in spiked drink samples. Fabricated in-house via the printing of carbon paste onto a flexible polyester substrate, Ramdani *et al.*[10] constructed a graphite SPE sensor for the detection of atropine. A small volume (typically within the µL range) of a liquid sample to the electrode surface to complete the electrochemical cell, as shown in Figure 1. Using this sensor platform, Ramdani *et al.*[10] achieved detection limits of 18.4 µM in diet Coca-cola™ replicating potential real life circumstances. Utilising only cyclic voltammetry and a portable system Ramdani *et al.*[10] where able to detect the alkaloid at a forensically relevant range.[28, 32] Considering the concentrations of 0.35 to 1 mM[10] encountered in the Agutter case and that none of Agutters victims received a fatal dose, it becomes apparent that the higher concentrations required for effective poisoning could thus be easily detected utilising this basic sensor design.

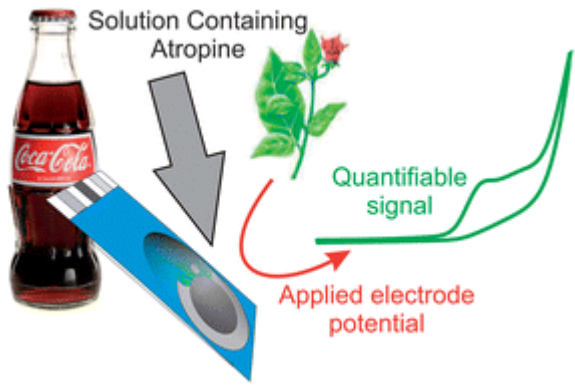


Figure 1: Schematic diagram of the general electrochemical sensor processes which occur when detecting atropine within Coca-Cola™ (Reproduced from Ramdani et al.[10] with permission from The Royal Society of Chemistry)

Ramdani *et al.*[10] provided a strong proof of concept for the detection of atropine within commercial drinks, however much work is still required to assess the viability of such a detection technique for application to wider range of sample matrices, including alcoholic beverages, often spiked in drug-facilitated sexual assaults. As noted within the work of Ramdani *et al.*[10] other species present within drink formulations can interfere or inhibit detection, impacting upon sensor specificity.[10] In the case of Ramdani *et al.*[10] quinine, a component of tonic water, experiences a similar electrochemical mechanism to atropine as a result of oxidation occurring at the tertiary amine group present within heterocyclic nitrogen ring systems in both alkaloid species. As depicted in Figure 2, the oxidation potentials of both atropine and quinine occur over the same potential range of 0.8 to 1.2 V (vs SCE).[10] Thus, in the Agutter case the use of the electrochemical sensor of Ramdani *et al.*[10] would not have been identified the presence of the poison within the spiked samples.

Specificity between species of similar chemical structure becomes a serious limitation when applying direct electrochemical detection methods to real life scenarios. Increasing specificity is however not an insurmountable limitation,

alternative electrochemical techniques such as electrochemiluminescence, (ECL), can be considered. ECL continues to develop as an effective electroanalytical tool ever since its introduction.[33]

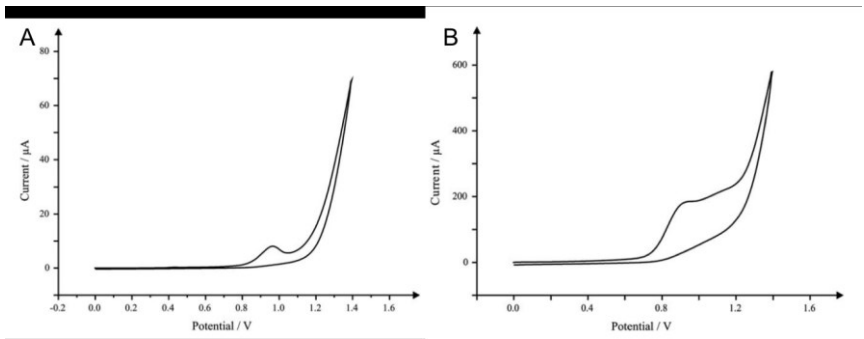
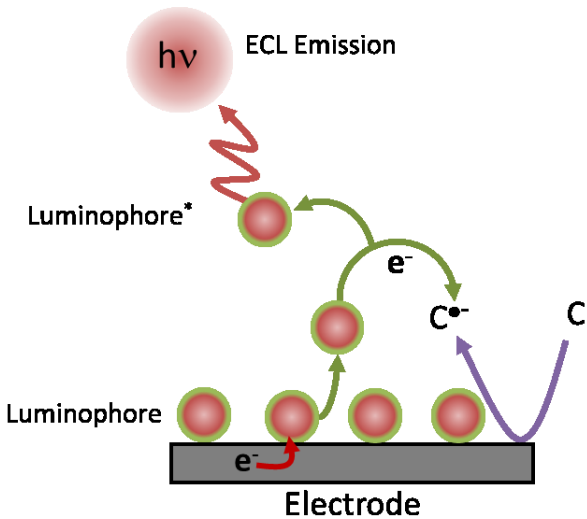


Figure 2: Typical cyclic voltammetric responses recorded at screen printed graphite electrochemical sensing platform vs SCE of (A) tonic water in the absence of atropine buffered to pH 10, scan rate 50 mV s^{-1} (B) 1 mM atropine in pH 10 buffer, scan rate 100 mV s^{-1}. (Reproduced from Ramdani et al.[10] with permission from The Royal Society of Chemistry)

Unlike chemiluminescence, ECL does not require an external light source thus benefiting from simplified instrumentation. This combination of electrochemistry and chemiluminescence affords many potential benefits.[1] These include the fact that some reactants can be electrochemically generated and regenerated at the electrode surface, often resulting in many photons produced per measurement cycle and thus enhanced sensitives. Since the often unstable chemiluminescence reagents or intermediates are generated in situ, this provides another advantage over traditional chemiluminescence. The electrochemical generation of reactants at the electrode surface also means that it is possible to generate species that may not take part in chemiluminescent reactions.[34, 35] As the reactants are electrochemically generated as illustrated in Schematic 1, it allows greater control over the position of emission which can be beneficial for sensitivity, selectivity, the detection of multiple analytes as well as for imaging analysis. Control over the time at which these reactions occur is offered, improving reproducibility and often simplifying operation. Since both current and light signals are obtained simultaneously, investigations into the electrochemical reactions as well as the ECL detection can be monitored.[6, 9] In addition, the use of mixed metal systems, exploitation of pH, the use of multi-electrode arrays continues to improve and provide the specificity required within forensic analysis. Alternatively, the application of separation strategies prior to detection can also be considered. It is worth noting that it is unlikely that any electrochemical screening methods would not be followed by confirmatory analysis. Thus, any interferent effects would be identified during these subsequent testing procedures.

Agutter may have chosen atropine as a result of its poor detection within bodily fluids, however since his murder attempt in 1994 a number of electrochemical methods have since demonstrated the ability to successfully detect the poison within complex matrices including urine[28,37-39] and human serum.[37, 38] The ability to electrochemically detect atropine indicates that scopolamine, a closely related tropane alkaloid, could be successfully detected employing the same methodologies. Much like that observed between quinine and atropine, the two tropane alkaloids

will oxidise within the same potential range as a result of their electrochemical behaviour arising from the tertiary amine group present within their tropane ring functionality. The use of scopolamine for drug-facilitated robberies and sexual assaults has been reported since the 1950's with a high number of cases observed within South America.[29] The effects of scopolamine leads the consumer to become submissive and obedient due to the reduction of declarative memory.[29] Criminals use this side effect to their advantage persuading victims to perform tasks or willingly surrender their valuables, without any recollection of what has occurred once the drug been excreted from their system.[29, 40] Victims can be dosed through inhalation, ingestion for example via drink spiking or even topical adsorption with one case detailing the presence of scopolamine found within moisturizing creams.[40] Whilst reports of the electrochemical detection of scopolamine are scarce with no direct detection methods reported, Yuan *et al.*[11] and Gao *et al.*[41] both demonstrated the successful detection of scopolamine from Datura samples using capillary electrophoretic separation prior to ECL detection with $[Ru(bpy)_3]^{2+}$ and unmodified platinum disk working electrodes.[11, 41] Yuan *et al.*[11] and Gao *et al.*[41] successful detection of scopolamine and atropine utilising the same electrochemical detection method, thus confirms that their similarity in chemical structure and electrochemical behaviour would facilitate the direct detection of scopolamine through the methods already reported for atropine.



Schematic 1: Schematic representation of the electrochemical processes occurring to produce ECL from a co-reactant system undergoing a reductive-oxidation pathway. Adapted with permission from Stewart *et al.*[36] Copyright 2018 American Chemical Society

Arsenic is an extremely toxic metalloid particularly when present in its inorganic form. Less toxic organic forms of arsenic also exist and are often found in many food products including fish, selfish and meat.[42] Thus, the consumption of arsenic consumptions in not uncommon and occurs global wide. However, it is only when large amounts of the highly toxic inorganic forms are consumed that poisoning occurs.[42] Arsenic poisoning often occurs from the consumption of contaminated ground water where the toxic forms of arsenic, arsenate (As(V)) and arsenite

(As(III)) are naturally found.[42] Although deliberate arsenic poisonings were previously common the restrictions in place surrounding its purchase have reduced its availability and thus cases which involve the toxic compound.[43] The detection of As(III) is however becoming increasingly more important with the World Health Organisation (WHO) reporting in 2018 that over 140 million people across 50 countries consume arsenic contaminated water with concentrations above their threshold value of 10 ppb.[42] With As(III) being more challenging to remove from water and more toxic than As(V) it is important that sensitive techniques are available to be able to accurately determine the arsenic quantities within drinking water or any potential poisoning cases. Recently a new electrochemical system utilising ECL has been reported by Liang *et al.*[44] offering an extremely sensitive system toward As(III) with a limit of detection reported down to 0.0007 ppt.[44] The novel system developed offers a two pronged approach for the detection of As(III). The system utilises bio-recognition through the employment of the Ars-3 aptamer. Whilst employing a dual luminophore system in the form of the traditional $[Ru(bpy)_3]^{2+}$ and graphitic carbon nitride nanosheets functionalised with AuNPs (Au-g-C_3N_4 NS).[44] Use of the dual luminophore system facilitates ratiometric ECL, where here the $[Ru(bpy)_3]^{2+}$ acts as an internal standard eliminating the chance of false positive or negative results.[44] When present As(III) in combination with $[Ru(bpy)_3]^{2+}$ quenches the ECL signal produced by the Au-g-C_3N_4 NS, whilst the $[Ru(bpy)_3]^{2+}$ also generates a secondary signal. Their detection mechanism involves the modification of their electrode with the Ars-3 aptamer and the Au-g-C_3N_4 NS, which produces a strong emission signal at 460 nm.[44] Incorporation of poly-diallyldimethylammonium (PDDA) which binds to the Ars-3 aptamer prevents accumulation of the $[Ru(bpy)_3]^{2+}$ on to the single stranded Ars-3 aptamer, thus a minimum background signal for $[Ru(bpy)_3]^{2+}$ is observed. When As(III) is present it is captured by the Ars-3 aptamer facilitating the electrochemical generation of As(0) which quenches the ECL produced by the Au-g-C_3N_4 NS at 460 nm, thus a reduction of ECL intensity is observed. Simultaneously the capture of the As(III) by the Ars-3 aptamer results in a conformational changes, which results in a reduction of the adsorption of PDDA. Due to this $[Ru(bpy)_3]^{2+}$ can then begin to accumulate at the single stranded Ars-3 aptamer resulting in the increase of an ECL signal at 620 nm.[44] Thus the two pronged approach detects the presence of As(III) through simultaneous quenching of the ECL signal at 460 nm and increase of a signal at 620 nm. Liang *et al.*[44] demonstrated how their dual luminophore ratiometric ECL system offered significantly enhanced sensitivity, whilst also offering good accuracy and specificity toward As(III).[44] The use of the ratiometric ECL systems therefore may offer enhanced sensitivities over the traditionally used single luminophore systems. The system described by Liang *et al.*[44] demonstrates a strong proof-of-concept for this and it is thus likely that future work will see a greater employment of such systems.

The rapid detection of poisons such as atropine and scopolamine or drug species such as the commonly used “date rape” drug Rohypnol™ is vital due to rapid excretion of these species, making detection after 24 hours a significant challenge. This is where forensic electrochemistry can strongly challenge the more traditional analytical techniques. The portability of the instrumentation, particularly when paired with the use of SPE, which require only micro-litre sample volumes facilitate the development of point-of-care or in-field analysis for almost instantons’ results. The lack of or minimal sample preparation required, with some samples, such as

spiked drinks, able to act as their own electrolyte due to the preservatives and natural buffers present further enhance the applicability and ease of use of these techniques for on-site analysis.[45] Electrochemical sensing can therefore provide vital information in the initial stages of investigations. Whilst rapid in-field testing allows for analysis to be performed during the 'golden hour' window, a time where potential contamination or destruction of evidence is at a minimum.

The best approach for the detection of species involved in drug-facilitated crimes or sexual assaults would offer the opportunity for a two-tiered approach. Firstly where samples are taken directly from the suspected crime scene which might include the victims drink, and the second where samples are taken directly from the victim, such as urine or blood within a hospital setting. Various species have been successfully detected electrochemically within complex matrices. As previously discussed atropine has been directly electrochemically detected in serum, urine and Diet Coca-Cola™. Smith *et al.*[46] used screen printed graphite electrodes and cyclic voltammetry for the successful detection of Rohypnol™ in Coca-Cola™ and WKD™, with no sample preparation required.[46] However to date no current literature reports on the direct sensing of Rohypnol in any biological matrices without the application of separation techniques such as HPLC prior to electrochemical detection.[47] Thus more work on the direct sensing of such species is required if developed sensors are to be considered as truly portable and field appropriate techniques.

The ability to apply the same methodologies to species with similar electrochemical and structural properties allows for the application of those already developed to a wider range of species with ease. Cocaine is among the highest abused illicit substances and the greatest of the tropane alkaloid species. Possessing the same tropane ring responsible for the electrochemical behaviour within atropine and scopolamine, the electrochemical detection likely follows the same pathway. The literature available on the electrochemical detection of cocaine is extensive compared with the lesser known tropane alkaloids, with greater consideration of interference effects observed.[7,24,48-51] Specificity is particularly important for sensing of illicit substances where adulterants, to mimic or enhance the effects or cuttings agents to dilute the samples are included. Almost 90% of cocaine street samples are adulterated or diluted, often these adulterants or diluents lead to false positive or negatives when the traditional presumptive tests are used.[52] However, these interference effects also impact their electrochemical detection. Although there are advantages to being able to apply the same methodologies for species with similar chemical structures this also results in undesirable interference effects due to species with similar redox potentials. Often, modified working electrodes are used to avoid or overcome these interference effects. Asturais-Arribas *et al*.[24] employed carbon nanotubes, immobilised on a carbon SPE in combination with square wave voltammetry (SWV). They observed that the use of carbon nanotubes allowed for a greater separation between overlapping peaks of cocaine and some of its common adulterants; codeine, paracetamol and caffeine. The greater separation between the peaks of the analyte and those of the adulterants, allowed for the employment of ordinary least squares regression to construct the calibration curves and allow for the quantification of street samples. Asturais-Arribas *et al*.[24] quantitatively identify cocaine within adulterated street samples, across a concentration range of 10 to 155 μM.[24] Oliveira *et al*.[48, 49] described the use of carbon paste[48], glassy carbon[49] and platinum electrodes[49] modified with a uranyl Schiff base for the determination of

cocaine in the presence of common adulterants lidocaine and procaine without any interference issues.[48, 49] Further specificity has been coined through the use of bio-based sensors, where highly selective species such as single-stranded aptamers or antibodies are used.[50, 51, 53] The general principle of aptamer-based sensors is depicted in Figure 3, where the aptamer will selectivity bind to cocaine generating a signal but will not bind with any adulterants of similar structure. Queslati *et al.*[51] recently describe their development of a highly selective and portable aptamer-based sensor for the detection of cocaine in serum samples. Using their system they were able to achieve a detection limit down to 1.39 pM in neat serum, demonstrating remarkable sensitivity and specificity.[51]

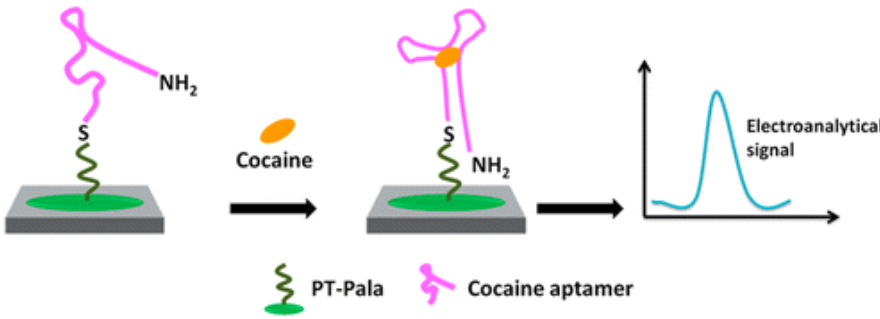


Figure 3: Schematic representing how a cocaine aptamer allows for cocaine detection. Reprinted with permission from Bozokalfa et al.[47] Copyright 2018 American Chemical Society.

Jong *et al.*[7] took the portability of electrochemical sensors to a new level, developing the electrochemical fingerprint for on-site screening. By imbedding the three-electrode set up into the fingertip of a standard glove and using a gelatine gel B hydrogel as the electrolyte Jong *et al.*[7] developed a fingertip based electrochemical sensor. The sample is then collected by wiping the electrode containing tip over the surface containing the suspicious powder. To complete the cell the sample and the gel fingers are connected and square-wave voltammetry performed, Figure 4 outlines the measurement protocol. Using their system Jong *et al.*[7] were able to improve upon the detection limit of presumptive tests and the accredited GC-MS methodology with detection down to 2 µM for pure cocaine samples.[7] Their portable sensor also displayed promise for the analysis of street samples in both solution and powdered forms, with cocaine peaks readily identifiable amongst adulterants without the requirement of surface modification.[7] Their system highlights the flexibility and portability achievable with electrochemical techniques, and demonstrates how an simple unconventional system can improve upon the validated 'gold standard' methodology. With no sample preparation required the potential incorporation of such techniques into crime scene analysis would be simple, offer lower cost analysis with less expensive instrumentation and lower reagent consumption, whilst improving upon current techniques with better sensitivity and specificity than presumptive tests already demonstrated.

As previously discussed electrochemical sensors have been applied for the detection of a variety of illicit substances. One area of current interest is the detection of NPS or 'legal highs'. Despite the maturity of forensic drug detection, NPS with their

diverse origin, often unknown or poorly understood effects, structural similarities and often short lifespan within the drug market poses a significant challenge to forensic practitioners.[22] With over 110 countries reporting the presence of at least one NPS and over 800 substances reported to the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory up to December 2017, there is high demand for detection methods able to successfully identify these types of substances.[54] Electrochemical sensing of 'legal highs' has been observed since 2014, when Smith *et al.*[55] described how of a range of synthetic cathinone's could be irreversibly oxidised at a potential of +1.0 V (vs SCE) on SPE graphite, glassy carbon and boron doped diamond electrodes. With the SPE sensor offering the highest anodic current and lowest overpotential, there was an obvious advantaged driving their use over and above the portability aspect. The sensor designed by Smith *et al.*[55] although able to successfully detect synthetic cathinone's, caffeine and benzocaine individually, lacked the specificity required for identification of the individual species within a mixed matrix, as would be found within street samples.[55] From this early work it was quite clear that forensic electrochemistry offered a viable alternative detection method for NPS. However, much work was still required to improve specificity, widen compatible sample matrices and expanded the types of NPS which could be successfully detected.

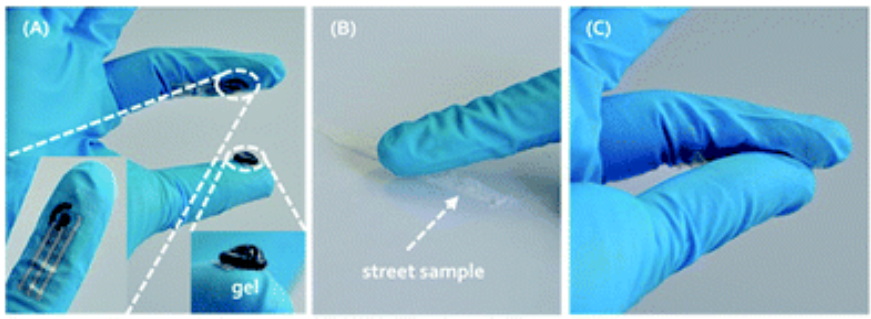


Figure 4: Schematic of the measuring protocol for suspicious powder samples using the wearing fingertip device. (A) the three-screen printed electrode set is imbedded into the index finger of the nitrile glove and the conductive hydrogel immobilised onto the thumb of the same nitrile glove. (B) sampling procedure via wiping the fingertip containing the electrode set up over the suspected powder, directly collecting onto the electrode surface. (C) completion of the electrochemical cell by joining the electrode surface to the conductive hydrogel electrolyte. (Reproduced from Jong et al.[7] with permission from The Royal Society of Chemistry)

Despite the electroactivity of synthetic cathinone's and the initial promise demonstrated by the sensor of Smith *et al.*[55] further development of electrochemical sensors for the detection of synthetic cathinone's is somewhat scarce. The subsequent year the same authors proposed a further electrochemical sensor design for the detection of mephedrone (4-MMC) and 4′-methyl-*N*-ethylcathinone (4-MEC).[56] Mephedrone became one of the most popular NPS and widely known synthetic cathinone's, whose similar structures to the phenylamine class of psychoactives results in pharmacological effects similar to amphetamines and cocaine. The novel sensor design saw the employment of a one pence coin (post 1992 mint) as the working electrode, alongside a platinum wire counter and saturated calomel electrode (SCE) reference. The design of the working electrode is detailed in Figure 5 and was fabricated such that the geometry of the working electrode area was always consistent but facilitated the switching of the coin post

measurement, creating a disposable system.[56] The copper oxide within the coin resulted in one oxidation peak occurring at approximately -0.01 V (vs SCE) and two reduction peaks at -0.4 and -0.6 V (vs SCE).[56] The authors proposed that mephedrone could be detected indirectly through the reduction in the oxidation peak, occurring as mephedrone adheres to and blocks the working electrode surface hindering the electroactivity. A decrease in oxidation peak intensity with an increase in mephedrone concentration was observed with a R^2 value of 0.97, and a detection limit of 0.56 µg mL^{-1}.[56] However, their indirect detection method lacks any specificity, as demonstrated through their analysis of 4-MEC which had the same effect upon the oxidation peak of the copper oxide species.[56] Detection through a decrease in oxidation peak intensity due to the adsorption of species onto the electrode surface is an unselective process and would result no matter the species present. Although their sensor was novel and inexpensive to produce, it would be unsuited for implementation into forensic analysis, where it is vital to minimise the possibility of false positives and species specificity or at minimum drug class is required.

Nevertheless, electrochemical techniques have since been applied to an array of different NPS including synthetic cocaine[25], phenethylamines[27], piperazines[57] and synthetic cannabinoids[26]. Synthetic cocaine or "synthacaine" like many legal highs is comprised of a mixture of substances with a lack of consensus across different countries and vendors of which specific compounds are present.[25] In the UK synthacaine primarily contains a mixture of central nervous system stimulants, with methiopropamine (MPA) predominantly detected. The increased presence of MPA within the UK lead to its classification as a Schedule 1 Class B drug. Cumba *et al.*[25] investigated a range of different techniques for the analysis of synthacaine street samples, known to contain MPA and 2-aminondane (2-AI). As is the case with many NPS, they discovered the traditional presumptive tests, although valid on pure samples of the individual components, when applied to the real-life mixtures gave unreliable results. Raman spectroscopy although able to reliably detect 2-AI, was unsuited for the detection of MPA as a result of the significant fluorescence background preventing acquisition of a useable spectra.[25] Proposing a viable on-site detection method, Cumba *et al.*[25] applied linear sweep voltammetry together with SPE to address the limitations of the presumptive and Raman spectroscopic analysis. Utilising a graphite SPE, direct oxidation of MPA was observed with an irreversible oxidation peak +0.94 V (vs Ag/AgCl).[25] However, 2-AI did not display any electrochemical behaviour across the scanned potential range of 0.2 to 1.6 V. As with Raman spectroscopy the ability to identify only one of the two components was not a viable technique. By employing an indirect detection method using *N*,*N*′-(1,4-phenylene)dibenzenesulfonamide as a mediator, which chemically reacts with the MPA and 2-Al to form species which can be subsequently electrochemically reduced, allowed for the detection of both MPA and 2-Al. The species produced underwent reduction on the graphite SPE at -0.16 V (2-Al) and -0.36 V (MPA).[25] Using their indirect system Cumba *et al.*[25] were able to successfully analyse the mixed MPA and 2-Al samples with detection limits of 0.49 µM and 0.07 µM respectively.[25] Application of their methodology to street samples display good correlation against the validated HPLC method, with concentrations for MPA within ±0.35% and ±0.78% for 2-Al.[25] Cumba *et al.*[25] hence demonstrated the strength of electrochemical methods, over traditional systems for NPS analysis.

This was more recently further confirmed by Razavipanah *et al.*[8] whose

electrochemical sensor achieved detection limits down to 0.8 nM for mephedrone, only bettered by LC-MS-MS at 0.3 nM.[8] Although likely that electrochemical methods would be primarily employed as screening tools their comparison to validated HPLC and LC-MS-MS methods demonstrates the possibility for the employment of such methodologies for quantitative analysis, utilising portable instrumentation with less reagent consumption and hence lower operating costs.

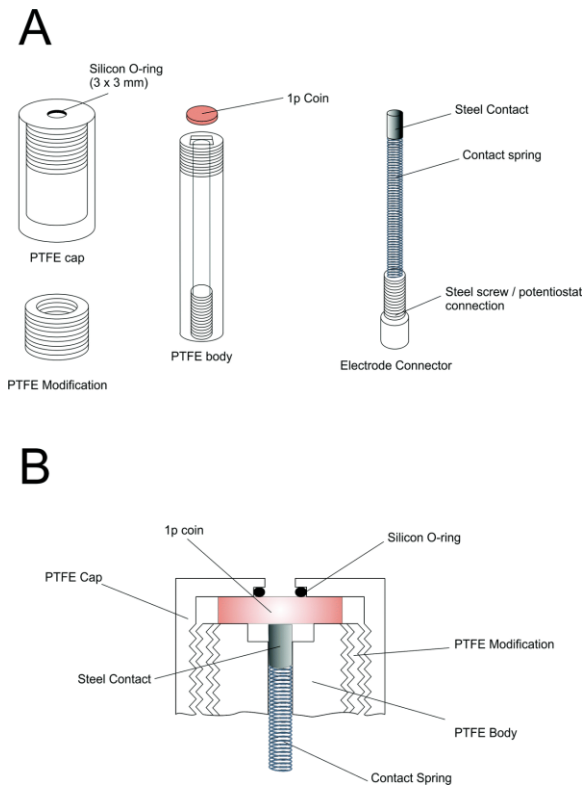


Figure 5: (A) Schematic diagram of the 1 pence coin working electrode construction, with the PTFE housing which holds the coin in place for analysis accurately defining the electrode area. (B) cross section of the assembled electrode which is then inserted into solution for analysis. Reproduced from Tan et al.[53] with permission from the Royal Society of Chemistry

More recently the electrochemical detection of NPS has progressed past only the analysis of raw drug products and expanded into biological fluid analysis, addressing the need for point-of-care devices. Razavipanah *et al.*[8] described the detection of the synthetic cathinone, mephedrone in urine and serum samples, using an electrochemically imprinted sensor. The electrochemical sensor combined a nanocomposite of gold nanoparticles and functionalised multi-walled carbon nanotubes with a sol-gel molecular imprinted polymer and polytyramine. The film formed was then electrochemically deposited onto a glassy carbon electrode and the template from the polymer matrix removed prior to analysis. Razavipanah *et al.*[8] sensor development lead to a highly sensitive electrode which could successfully detect mephedrone down to 3 nM in both urine and serum samples, with no interferant effects for the complex matrices.[8] Although the concentrations achievable

are well within an forensically relevant range and show promise for sensors of this kind, more research onto the impact of other drug species or metabolites likely to found in bio-fluid samples would need to be performed to properly assess the suitability of the sensor for real world applications.

Up to June 2018 179 synthetic cannabinoids were detected in Europe, and as such they represent the largest group of substances currently monitored by the EU early warning system.[58] Common functional groups found within synthetic cannabinoids are the indole or indazoles. This functionality makes synthetic cannabinoids ideal for electrochemical detection, as a result of the electroactivity of these groups. Thus electrochemical sensors could offer a viable detection method which tackles the limitations surrounding sensitivity of the colorimetric methods currently used.[26] In contrast to the highly specific immunoassay methods, which fail upon structural alterations of compounds, electrochemical sensors are still valid if the electroactive functionality is maintained, despite changes to the peripheral structure. Electrochemical techniques can be easily adjusted to facilitate the detection of the new structures within a drug class. This intrinsic advantage arises as a result of electrode material flexibility, possibility to employ indirect and alternative detection techniques, such as ECL. Dronova *et al.*[26] revealed that a number of synthetic cannabinoids could be irreversibly oxidised on unmodified boron-doped diamond, glassy carbon and platinum electrodes across a potential range of +0.7 to +2.7 V, with glassy carbon showing the lowest sensitivity and boron-doped diamond the most, whilst platinum electrodes facilitated oxidation at the lowest overpotentials.[26] To prove the applicability of their system for detection within real life biological samples, analysis was performed within an artificial saliva matrix, replicating sample conditions which could be encounter during road side testing. Application of anodic pre-treatment of the boron-doped diamond electrode facilitated for the lowest detection limits in the nM range at the least positive potentials. Although detection could still be observed using the platinum electrode.[26] Further to their proof-of-concept in bio-fluids, Dronova *et al.*[26] also describe detection within the herbal material which synthetic cannabinoids are typically sprayed onto. Despite interference from this sample matrix previously observed within colorimetric testing, Dronova *et al.*[26] demonstrated no interference was present within the electrochemical analysis. Therefore Dronova *et al.*[26] were able to demonstrate the potential of their standard cell setup sensor for the two-tiered approach which would be required for forensic applications. However, again the specificity between different indole and indazole species, with their similar oxidation potentials prevented the identification of multiple synthetic cannabinoids present within the one sample matrix.

Electrochemical sensors have thus far demonstrated the ability to detect a wide range of species across diverse and complex matrices. The availability of portable potentiostats, SPE and micro-litre sampling volumes with minimal sample preparation offer unprecedented portability for in-field and point-of-care devices. Whilst their specificity can often hinder their application for detection of structurally similar compounds further development of different strategies to improve specificity, in particular the increased use of bio-sensors, will inevitability reduce the limitations this might impose. What is more comparing electrochemical methods to the current colorimetric test widely used, which only offer class identification, electrochemical methods offer improved sensitivity, reliability and ease of use.

3 Alcohol Sensing

Alcohol is the most abused drug worldwide. The ability to accurately detect and quantify alcohol (ethanol) from biological samples has many important applications, from work place testing to policing, where it is vital to establish an accurate blood alcohol concentration when analysing a biological or breath sample at a suspected incident of drink-driving. Blood alcohol concentration (BAC) can be determined via blood, urine and breath samples and transdermal testing. Breath analysis is typically the most common sampling method employed at the initial scene or roadside. Through the use of Henry's Law it is assumed that the ethanol concentration in the exhaled alveolar air is directly proportional to the ethanol concentration in blood.[59] Whilst as a non-invasive technique; breathalyser testing can be easily performed in public places, whilst offering rapid low cost and accurate determination of BAC.

Electrochemical detection of alcohol in exhaled air is the most widespread and reliable use of an electrochemical device within the forensic environment. The fuel cell-based breath alcohol sensor dates back to 1935 when Tom Parry invented the "Alcolmeter", whilst today the majority of commercial breathalysers still employ the fuel cell system.[59] The fuel cell sensor operates on the principle of catalytic electro-oxidation of ethanol, which generates protons, electrons and by-products such as CO_2, CH_3CHO and CH_3COOH. The electrons generated pass through the external circuit to the counter electrode within the cathode compartment, whilst the protons are transported through an exchange membrane. Within the cathode compartment water forms upon reaction with atmospheric oxygen. The resulting current between the anodic and cathodic compartments is directly related to the number of ethanol molecules present, allowing for calculation of ethanol concentration. Although commercial fuel cell systems have been employed for over three decades there remains a number of disadvantages intrinsic to their design, including high manufacturing cost linked to the employment of platinum catalysts, limited durability due to degradation and poisoning of the catalyst reducing the electroactive area available and specificity issues.[59] Despite these inherent disadvantages, little research and development to improve upon the fuel cell system has occurred over the years.

One area of increased interest for the electrochemical sensing of alcohol is the development of transdermal sensing systems. Here alcohol is detected in the sweat of the wearer, allowing for real time monitoring. In 2016 Kim *et al.*[20] described their wearable tattoo-based epidermal electrochemical sensor design, depicted in Figure 6. Their sensor comprised of cathodic and anodic Ag/AgCl iontophoretic electrode compartments with amperometric (working, counter and reference) electrodes located in the sensor's anode compartment. The working and counter electrodes were formed from a Prussian Blue conductive carbon ink, with the prior additionally modified with the alcohol-oxidase enzyme. The complete circuitry for the sensor was printed on a flexible substrate and paired with a flexible circuit board, forming a wearable sensor offering maximum comfort. Results obtained from sensor application were relayed to a laptop via Bluetooth connectivity, offering a truly portable transdermal sensor system. The sensor operates principally via two mechanisms the induction of sweat through iontophoresis, via application of pilocarpine across the skins surface and the ampermometric biosensing of ethanol as a result of the presence of the alcohol-oxidase enzyme. Kim *et al.*[20] demonstrated a proof-of-concept for the development of a wearable transdermal sensor testing their

design *in-vitro* and of more interest on human subjects. Testing different subjects, they demonstrated how their sensor could confidently identify if the subject had consumed alcohol as a result of the decrease in the amperometric current in the presence of ethanol and their data showed good agreement of BAC between the breathalyser and transdermal results. To establish their model, measurements were collected on each test subject prior to and following alcohol consumption. Good correlation between subsequent measurements prior to consumption was observed, giving a consistent baseline however correlation between subsequent measurements post consumption was not reported.[20] Variation in the measurements between subjects was observed, despite each consuming the same amount of alcohol. However, this variability is not unique or unexpected. Similar variation was also observed within the BAC calculated from the breathalyser samples collected alongside the transdermal measurements and can be accounted for due to variations in metabolism rate and body weight between the subjects.[20] Kim *et al.*[20] demonstrated how their developed sensor could be applied to determine a wearer's BAC from the ethanol concentration within their sweat.

Further work is required to validate their system on a wider subject pool and investigate the prospect of device personalisation to account for differences in sweat composition and skin permeability. The device developed by Kim *et al.*[20] could offers the potential for a low-cost single use real time monitoring sensor for non-invasive determination of BAC. The use of the screen-printed technology offers a low-cost solution to the high manufacturing cost of the breathalyser fuel cell system which employs expensive platinum catalysts. The connectivity of the sensor offers a potential range of applications and the opportunity for continuous monitoring where required. While unlikely to be utilised by law enforcement for roadside testing, they highlight the ability of electrochemical sensors for portable sensing within a forensic context.

Cinti *et al*.[60] described the development of a paper based electrochemical biosensor for the detection of ethanol. Unlike Kim *et al.*[20], Cinti *et al.*[60] do not focus on the detection of alcohol in human samples but on the direct estimation of ethanol concentration within an alcoholic drink. This represents an important area of analysis within the food industry where labelling must be accurate. The ability to determine ethanol concentration of an alcoholic drink with ease can have forensic applications such as the identification of counterfeit alcohol or for drink spiking incidents. The sensor designed by Cinti *et al.*[60] is a low-cost paper-based device utilising common 80 g m^{-2} paper and wax and screen printing facilities. Similar to Kim *et al*. the alcohol oxidase enzyme is employed to incorporate a bio-recognition element, producing H_2O_2 as the by-product. Ethanol concentrations can then be determined indirectly through monitoring the production of H_2O_2 through chronoamperometric measurements.[60] Cinti *et al.*[60] achieved sensitive detection of ethanol down to 0.6 mM through the use of graphite SPE modified with nanocomposites of carbon black and Prussian Blue on an 80 g m^{-2} paper support. Their modification of the working electrode with the alcohol oxidase enzyme facilitated detection down to 0.52 mM and showed a stability of three weeks on storage at 4 ºC after casting of the enzyme.[57] The use of a biosensor allows for increased specificity, as previously discussed when aptasensors were employed for drug detection.[50,51] Cinti *et al.*[60] demonstrated the increased specificity offered via bio-sensors through their interference study with acetic acid, ascorbic acid, methanol and glucose chosen due to their presence in commercial beer. No inference effects

were observed for all species bar methanol which produced a response, although smaller than that of ethanol. This is however not unexpected, since the alcohol oxidase enzyme catalyses the breakdown of all primary alcohols and is not specific to ethanol.[60] Cinti *et al.*[60] validated their developed sensor for real life applications using commercial beers. Their sensor showed good precision and accuracy with all ethanol concentrations calculated matching those stated by the manufacturer. The sensor developed demonstrated how a low-cost sensor could offer rapid identification, with an analysis time of 40 seconds and quantification of ethanol in real life samples.[60] The use of a paper-based support and single use sensor offers a low-cost and disposable sensor ideal for field applications. The three-week stability post manufacturer would further facilitate its infield application allowing for the sensor to be produced within a laboratory environment, stored and then transported to a scene with ease.

Electrochemical detection of alcohol dates back to the 1935, with the fuel cell system offering one of the most reliable and common applications of electrochemical sensors in a commercial and forensic environment. Despite the wide employment of the fuel cell breathalyser system often the use of forensic electrochemistry for alcohol detection is overlooked or not considering, whilst little research and development has been performed to improve upon the system and address its limitations include significant manufacturing cost. Development in recent years for alcohol detection using portable and low-cost sensors has demonstrated the possibility to enhance the current detection systems. Wearable sensors offer a non-invasive collection and would facilitate real time monitoring. These paper-based devices offer robust, easily fabricated sensors at a minimum manufacturing cost. Further development into the robustness of these systems would be required in order to assess whether they would be a suitable alternative to the fuel cell system, however the recent developments do highlight the promise of these alternative electrochemical systems offer.

3 Explosives Detection

The detection and identification of trace explosives following detonation is a crucial first step in any incident involving suspected explosive devices. At scenes where explosives are suspected it is vital that assessments and identification of any substances are made as quickly possible. Often however identification is hindered by time consuming procedures, particularly when only trace levels of material remain. Traditionally evidence collected from the scene is transported back to a forensic laboratory for analysis introducing a significant time delay between identification of a suspected substance and identity confirmation. The ability to offer rapid detection at scene would offer a considerable time advantage and allow investigators to take immediate action which could be vital for public safety. Recent developments in instrumentation have facilitated the employment of portable instrumentation at scenes involving explosives. Typically, these include portable Raman and infrared (IR) spectrometers and gas chromatograms. However, although they offer portability they come at both high operational and purchase costs and often required a level of expertise to operate and interpret results. In contrast electrochemical devices offer a significantly smaller footprint, are relatively simple to operate and as previously discussed offer low cost detection systems with single use disposable electrodes ensuring the possibility of cross-contamination is almost eradicated. Whilst still

offering the sensitive and selective detection offered by the spectroscopic and chromatographic techniques.[13]

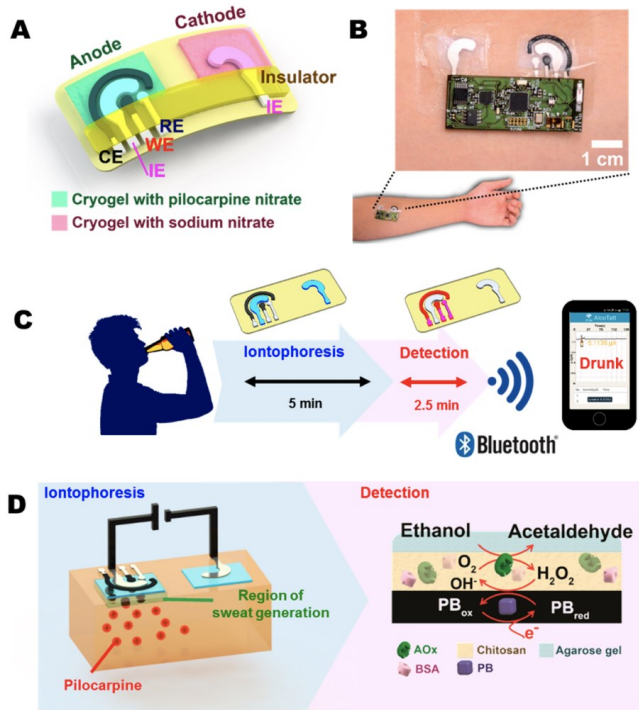


Figure 6: Tattoo-based transdermal alcohol sensors developed by Kim et al.[20] (A) Schematic of sensor containing the iontophoretic electrodes (IE, anode and cathode) and the amperometric electrodes (working WE, counter CE and reference RE) (B) Photograph of the sensor applied to skin (C) Schematic of the wireless operation of the sensor, with the highlighted zones depicted those active during the iontophoresis and aperometric detection. (D) Schematic of the principle of operation of the iontophoretic system(left) and the amperometric sensing of alcohol at the working electrode (right). Reprinted with permission from Kim et al.[20] Copyright 2018 American Chemical Society.

Nitroaromatic and nitroamine compounds such as 2,4,6-trinitrotoluene (TNT) lend themselves well to electrochemical detection due the presence of the easily reducible nitro groups within their structures.[13] The presence of these easily reducible groups facilitates the detection of TNT on bare conventional glassy carbon electrodes at low over-potentials. With the three ntiro-groups resulting in three distinct peaks observed under CV analysis.[13] TNT detection of bare glassy carbon electrodes has been reported for almost a decade, with Toh *et al.*[61] reporting the detection of TNT below 5 ppm in 2012.[61] Since then developments in surface modifications have further improved the sensitivity of detection systems. In 2018 Saglam et al.[62] described how the use of an energetic polymer film template of poly-carbazole-aniline functionalised with gold nanoparticles resulted in a highly sensitive sensor with detection limits for TNT down to 25 µg L^{-1} utilising square wave voltammetry.[62] The specificity offered by the molecular imprinting of the nitro

energetic memory film was demonstrate by the lack of interferences observed when paracetamol-caffeine, acetylsalicylic acid, aspartame and d-glucose where present.[62] Although both these systems show good sensitivity and specificity the use of conventional glassy carbon electrodes limits there portability, with conventional set up typically requiring a lab based systems in addition to increased risk of cross contamination as a result of the reusable electrodes. Although typically TNT and nitro-aromatic substances are detected due to the direct reduction of the electron deficient nitro groups, Xi *et al.*[63] described an alternative indirect system, which they proposed is beneficial for ultra-trace level detection or for the detection of reductive trinitramine explosives.[63] Xi *et al.*[63] system involves an indirect detection method which relies upon the the ability of TNT to substantially prevent the redox of polyanaline (PANI), resulting in a reduction in the anodic current of the oxidation peaks. To achieve this glassy carbon electrodes were modified with a mixture of gold nano particles (AuNP) and carbon nanotubes (CNT), followed by electropolymerisation of aniline.[63] The number of layers of polyaniline deposited was accurately controlled by the number of cycles performed during the depositioning process with maximum sensitivity observed at an optimum of 30 layers. On addition of TNT to their electrode system Xi *et al*.[63] observed a reduction in the anodic peak current at a potential of +0.65 V.[63] Their system displayed a linear correlation between the concentration of TNT added and the percentage of decrease in the current observed, over a concentration range of 4 to 40 ppt and a second linear relationship was observed over a concentration range of 40 to 200 ppt.[63] However above 200 ppt little decrease in the anodic current was observed, as shown by Figure 7 suggesting at higher concentrations the thin films become saturated and poor diffusion of the TNT to the AuNP/CNT is observed. Thus the system although beneficial for ultra-trace levels of nitro-aromatic explosives would not be suited for analysis of high concentrations. The sensitivity of their developed sensor was exceptionally greater than the surface modifications previously reported and that of bare glassy carbon surfaces, with an analysis detection limit of 4 ppt (18 pm) shown and a calculated limit of detection of 1.1 ppt and limit of quantification of 3.7 ppt.[63]

Traditionally glassy carbon electrodes have been the electrode of choice for explosive detection. However, investigation into the use of SPE has increased in recent years.[13] Cetó *et al*.[64] described the use of a carbon SPE for the detection of a mixture of explosives utilising CV. Using SPE with an unmodified carbon working and counter and silver pseudo-reference electrodes measurements of HMX, PETN, RDX, TNT, Tetryl, C-3, Comp. B, Pentolite, Semtex and Tetrytol at conentrations of 50 μg mL^{-1} were collected with samples prepared in a mixture of acetonitrile (ACN) and PBS to ensure enough conductivity was present.[64] Individual measurements of each of the explosives were collected and used as the basis to build a chemometric model allowing for identification of the individual substances within a mixed standard despite overlapping peaks. Using a bare carbon SPE electrochemical signatures of all the nitro-containing explosives were successfully obtained. The chemometric model was then able to identify the explosive substances present within mixed standards, due the electrochemical fingerprint produced. Thus the employment of chemometrics alongside electrochemical analysis facilitated tentative identification of the nitro-aromatic explosives present within a mixture. The strategy of Cetó *et al.*[64] therefore provides an initially proof-of-concept toward the development of field portable systems suitable for the analysis of mixed standards,

which would facilitate the rapid identification of different explosive materials.

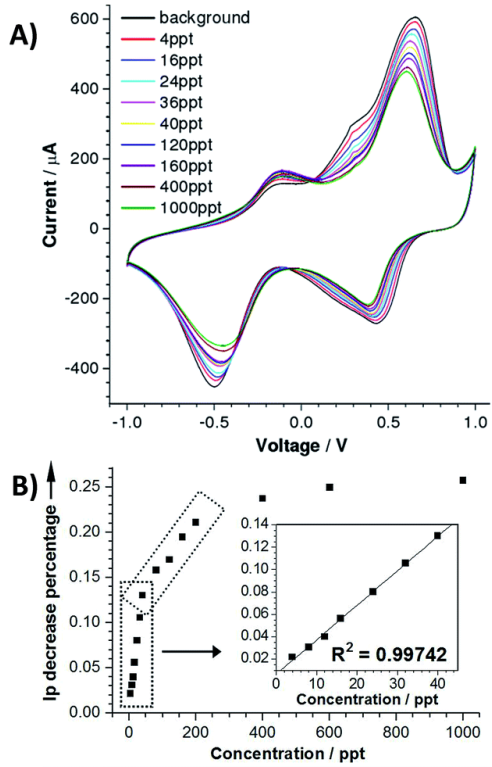


Figure 7: A) CVs obtained from the PANI/AuNPs/CNTs electrodes on addition of increasing concentrations of TNT, hightlighting the decrease in anodic peak current at +0.65 V with a 0.5 M NaCl electrolyte and can rate of 500 mV s^{-1}. B) Calibration plot of andoic current percentage decrease against TNT concentration. Reproduced from Xi et al.[63] with permission from the Royal Society of Chemistry.

4 Conclusions and Future Research

This chapter describes the versatility of electrochemical approaches to tackle a vast array of challenges faced by forensic science. However, despite the wide ranging applications and its numerous advantages over traditional techniques, electrochemical sensors still struggle to be implemented within the forensic environment. Many fields could benefit greatly from the exploitation of electrochemical sensors including areas such as screening for drugs and illicit substances as well as metabolites within toxicological analysis. Significant research and work is required to showcase the ability of electrochemical sensors to be considered as effective screening tools. Particular emphasis is needed to develop high-through puts analysis of multiple evident types from street drug samples to toxicological samples to illustrate the many benefits electrochemical sensors can offer the forensic investigator. The growing field of NPS means that research should be expanded to encompass NPS metabolites to allow for effective laboratory and in-field analysis. This would great expand the potential areas where electrochemical sensors could be applied to address the current gaps in forensic requirements.

However, as this chapter has shown, there has been a rapid process in all areas of electrochemical sensors highlighting this dynamic research environment and clearly demonstrating the potential of this field as an analytical tool.

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