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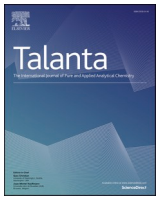

Towards the development of a portable device based on modified-voltammetric sensors for the detection of illicit drugs and seized samples

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ABSTRACT

Illicit drugs are a global burden, not only for society, but also for the various control authorities for which its rapid on-site detection remains a challenge. In this context, the potential of a voltammetric electronic tongue (ET) for the analysis of different drugs is evaluated herein. Concretely, the discrimination and identification of cocaine, heroin, 3,4-Methylenedioxymethamphetamine (MDMA), methamphetamine and ketamine in self-prepared and real samples were attempted. For its analysis, an array of three carbon-based screen-printed electrodes (SPE) was prepared, and their responses towards the different drugs and some of the more common cutting agents and adulterants were assessed by means of square wave voltammetry (SWV). To this aim, a tiny amount (*ca.* 3 mg) of the drug powder was added to the electrochemical cell containing phosphate buffer (pH 12), shaken, and measured directly without any other pre-treatment than its dilution. Next, to identify their characteristic fingerprint, obtained voltammograms were submitted to linear discriminant analysis (LDA), which allowed to correctly identify the different drugs regardless of the presence of the different cutting agents and other possible interfering compounds, or their concentration. Satisfactory results were obtained both for the synthetic and the "street" seized samples, with a classification rate of 100 % for the external test subset of the latter (n = 10).

1. Introduction

Over the last years, illicit drugs have become a worldwide burden for the society, but also for the different control agencies which have to deal with their consequences [1,2]. However, the rapid on-site detection of illicit drugs remains a challenge. The low accuracy of color tests, or the high cost of spectroscopic or spectrometric instruments, are significant limitations of currently used on-site methods for the detection of illicit drugs and their precursors. Besides, color tests are devoted to a certain substance, meaning that a different test must be employed for each of the drugs that are suspected, while in turn those are only available for certain drugs.

As an alternative, point-of-care (PoC) immunoassay-based testing methods are reported in the literature as a more powerful approach due to its ease of use, rapid turn-around time and the ability to screen multiple drug classes [3,4]. Normally, those tests provide only a positive or negative reading if the drug concentration is above an arbitrarily set limit of detection (LOD). However, those methods are also expensive and, as happens with the color tests, may have limited sensitivity and specificity due to the cross-reactivity of the capture antibody with structurally similar interfering compounds, producing false-positive results [3,5,6]. Furthermore, immunoassays for selected drug classes, *e.g.*, opiates and benzodiazepines, are also subject to clinically important false negatives [5].

Lastly, there is also the use of chromatographic methods, especially when coupled with mass spectrometry (MS) detection, being gas chromatography (GC-MS) or liquid chromatography–tandem mass spectrometry (LC-MS-MS) the most common ones. Regrettably, those are

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costly (both from the equipment and reagents side), time-consuming and might require a sample pre-treatment step and/or controlled laboratory facilities, causing additional delays until the result is obtained. Consequently, MS-based methods are clearly not suitable for on-site analysis, but are commonly employed as confirmatory analysis. Indeed, the common trend is to run those analyses upon having obtained a positive result with one of the currently available screening methods. Over the last years, portable MS-based instruments have emerged to overcome some of those limitations [7,8]. However, despite those becoming more readily available, their cost, analysis time and servicing fees are drawbacks that make them potentially less viable. Therefore, to improve decentralized drug testing and drug checking, the development of compact sensors that are sufficiently sensitive and selective, inexpensive, and amenable for mass production is required.

In this direction, electrochemical sensors can provide an interesting alternative for the detection of illicit drugs and their precursors due to the inherent electrochemical behavior of most of them [9–12]. Electrochemical sensors offer fast and accurate information in a cost-effective manner, while their high sensitivity, wide linear range, minimal power requirement, potential for miniaturization and portability, low-cost instrumentation and ease of operation, are among their advantages; all this makes them suitable for the development of compact and user-friendly hand-held devices for on-site analysis [13]. However, due to the structural similarities between many drugs, especially regarding the redox groups of those, similar electrochemical fingerprints might be obtained. Unfortunately, this behavior also occurs for cutting agents, adulterants that are commonly used in street samples, thus creating false positives if not properly accounted for. Moreover, certain electroactive adulterants might suppress or modify the specific electrochemical fingerprint of each illicit drug, thus creating false negatives.

When the analysis of the target illicit drugs is hindered by adulterants [14], alternative strategies must be applied to avoid this analytical flaw. One of the most promising strategies to overcome such shortcomings is the use of electronic tongues (ETs) [15]. The performance of electrochemical sensors can be enhanced by including electrode surface modifiers to enrich its signal, but more importantly by considering the features originated from different electrodes in combination with statistical data analysis (the ET approach) [16–19]. Thus, through the combination of the inherent advantages of electrochemical strategies with the use of chemometric methods, the highly accurate selective detection of trace levels of illicit drugs and precursors might be possible.

In this context, some initial reports pointed out the potential of ETs in this field [15,20]. However, these studies focused on a single drug, employed only stock solutions of the pure drugs, and/or cutting agents and did not consider their mixtures. More importantly, the analysis of real samples was not tackled; the latter being much more challenging given the higher complexity of the matrix in terms of compounds present, but also given a varying concentration of the different compounds.

Based on the aforementioned, herein we evaluate the combination of an array of carbon-based screen-printed electrodes (SPEs) for the generation of distinct electrochemical fingerprints for the most common drugs and cutting agents, with linear discriminant analysis (LDA) as the pattern recognition method for the identification of each of the drugs. To evaluate the potential of the approach, a series of experiments with increasing degree of complexity were planned, in which we ensured that factors such as the concentration or the presence of different cutting agents would not demote the proper assay of the different drugs. Overall, the following approach aims to offer accurate and redundant sensor technology as an alternative for screening methods in on-site drug analysis.

2. Experimental

2.1. Reagents and materials

All chemicals used were analytical reagent grade and were used as received. Cocaine, 3,4-Methylenedioxymethamphetamine (MDMA), methamphetamine, α-pyrrolidinovalerophenone (PVP), paracetamol, benzocaine, caffeine, lactose, procaine, quinine and starch were purchased from Cayman Chemicals (Ann Arbor, MI, USA). Potassium hydrogen phosphate, potassium phosphate and potassium chloride were purchased from Merck (Darmstadt, Germany).

All solutions were prepared using deionized (DI) water from a Milli-Q system (Millipore, Billerica, MA, USA). Phosphate buffer saline (PBS 0.1 M) at pH 12 containing 100 mM KCl as supporting electrolyte was employed for the preparation of the different samples as well as for the measurements. Stock solutions of the different drugs and cutting agents were freshly prepared daily.

2.2. Samples under study

For the initial studies, 500 μM individual stock solutions of the different drugs and cutting agents were prepared in PBS. Concretely, 4 different drugs (cocaine, MDMA, methamphetamine and PVP) and 7 cutting agents (paracetamol, benzocaine, caffeine, lactose, procaine, quinine and starch) were initially considered.

Next, equimolar mixtures of the different drugs with the different cutting agents were also prepared to evaluate the potential of the proposed approach for the discrimination of real "cut" samples. Thus, a total of 28 mixtures (4 drugs x 7 cutting agents) were prepared in replicate ($n = 6$).

Finally, a total of 35 samples corresponding to seized drugs by *Mossos d'Esquadra* police were also analyzed. Those included 7 unrelated samples (with different origin, purity, composition, etc.) for each of the five different drugs considered: cocaine, heroin, MDMA, methamphetamine and ketamine. For its analysis, a tiny amount of the drug powder (*ca.* 3 mg) was added to the electrochemical cell containing PBS (*ca.* 6 mL), shaken and measured directly without any other pre-treatment than its dilution.

2.3. Voltammetric measurements

Square wave voltammetry (SWV) was used to obtain the voltammetric fingerprints of the different drugs in graphite-, multi-walled carbon nanotubes- (MWCNTs) and graphene- (GPH) modified working electrodes (DropSens; Oviedo, Spain). Each SPE had a 3 mm working electrode, a carbon counter electrode and a pseudo-silver reference electrode. The measurements were performed employing a Palmsens MultiEmStat4 potentiostat (PalmSens, Houten, The Netherlands) controlled using the MultiTrace software, by scanning in the potential window between 0 and +1.6 V with a step potential of 5 mV, an amplitude of 25 mV and a frequency of 10 Hz. Upon completion of the measurements, the electrodes were discarded, employing a new array for each of the samples.

2.4. Data processing

All data analysis was done in MATLAB R2020b (MathWorks, Natick, MA, USA) employing its Statistics toolbox. Firstly, recorded voltammograms were baseline corrected, which removed the non-faradaic current (mainly capacitive contribution) from different sensors and facilitated the identification of the different peaks [21]. Next, the individual responses obtained with the different electrodes were concatenated and compressed employing fast Fourier transform (FFT), which besides reducing the risk of over-fitting, provides further advantages during the modelling stage [22,23]. Finally, the obtained coefficients were submitted to principal component analysis (PCA) for preliminary analysis of the data and to LDA for the actual classification of the samples [24,25].

PCA was used to assess initial patterns in the data, while the actual classification of the samples was achieved by means of LDA. The former was preferred for the initial exploratory analysis given as an

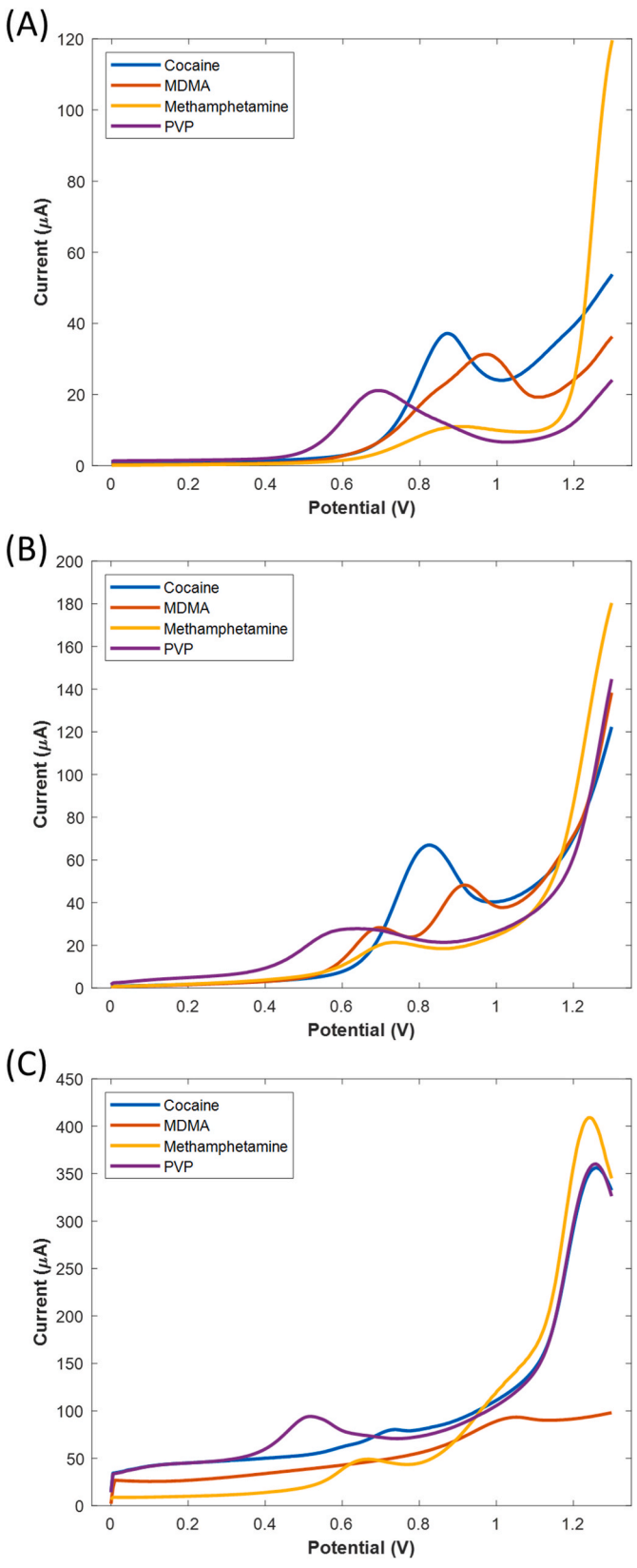

Fig. 1. Voltammetric fingerprints obtained for 500 μM solutions of the different drugs considered in this study with: (a) graphite, (b) MWCNTs and (c) GPH screen printed electrodes.

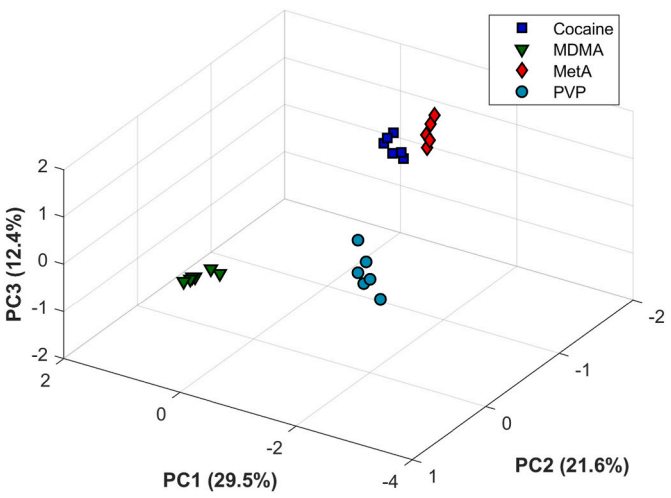

Fig. 2. 3D score plot obtained from the PCA of the voltammetric responses of different drugs at different concentrations: (dark blue ■) cocaine, (green ▼) MDMA, (red ◆) methamphetamine and (light blue ●) PVP.

unsupervised method, any clustering that may arose is only due to the samples (dis)similarities, without considering any prior expected relationship between them [26,27]. Next, upon confirmation of the suitability of the sensor array, the use of a supervised method that allowed the actual classification of the samples was required; in this case, LDA. Briefly, the main difference is that the LDA model is built seeking the parameters that best predict the desired output; and afterwards, its performance is evaluated employing the remaining cases not used in the training step.

3. Results and discussion

3.1. Voltammetric responses of pure drugs

The first step was the evaluation of the voltammetric fingerprints of the different drugs with the considered sensor array (graphite, MWCNTs and GPH-based electrodes). The aim was to confirm that the different drugs show an electroactive response for each of the electrodes, but more importantly, that the responses between the distinct electrodes are also different so that complimentary information can be obtained from their combination.

An extract of the responses obtained for four different drugs (cocaine, MDMA, methamphetamine and PVP) are shown in Fig. 1. As can be seen, most drugs present a single oxidation peak. In the case of cocaine, the observed peak at *ca.* 0.8 V (0.85 V for graphite, 0.80 V for MWCNTs and 0.77 V for GPH) is associated to the oxidation of the tertiary amine to a secondary amine, with the loss of an aldehyde [28]. The proposed mechanism involves the transfer of an electron from the amino–nitrogen, followed by a rapid proton loss to form a neutral radical, which then loses an electron and is hydrolyzed (Fig. S1 in Supplementary data). For MDMA, the voltammogram shows two oxidation peaks at 0.7–0.8 V and 0.9–1 V (again, varying depending on the sensor). The first peak is attributed to the removal of one electron from the aromatic ring, while the second peak is attributed to the oxidation of the secondary amine present in MDMA (Fig. S2) [29]. Similarly, in the case of methamphetamine, the oxidation peak observed at 0.6–0.9 V (0.9 V for graphite, 0.7V for MWCNTs and 0.65 V for GPH) has been attributed to the oxidation of the secondary amine in its aliphatic part (Fig. S3) [30]. Finally, PVP also shows a single peak at *ca.* 0.6 V (0.65 V for graphite, 0.6 V for MWCNTs and 0.55 V for GPH) corresponding to the oxidation of the tertiary amine (Fig. S4) [31].

To facilitate the interpretation of the above fingerprints and assess whether those are different enough to allow the discrimination of the

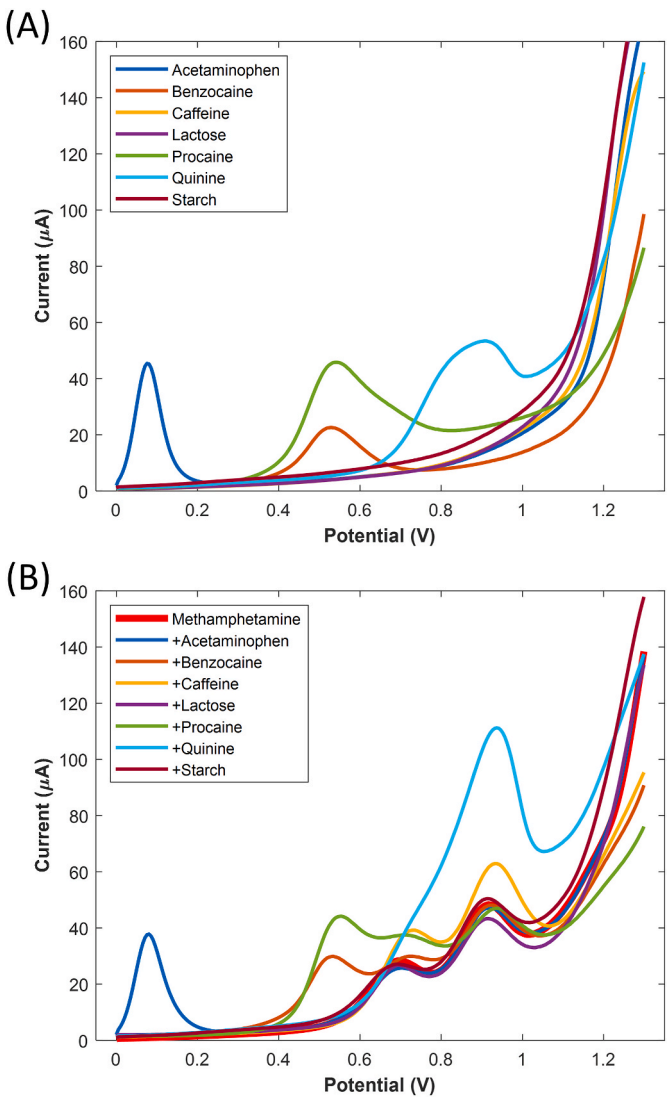

Fig. 3. Voltammetric fingerprints obtained with the MWCNTs screen printed electrode for (A) the different cutting agents considered in this study, and (B) the different cutting agents mixed with MDMA in equimolar proportions (500 μM of each).

different drugs, PCA was used. PCA is an unsupervised pattern recognition method which allows the projection of the information carried by the original variables onto a smaller number of underlying ("latent") variables called principal components (PCs) with new coordinates called scores, obtained after data transformation [22]. Then by plotting the PCs, one can view interrelationships between different variables, and thus detect and interpret sample patterns, groupings, similarities, or differences.

In this manner, the voltammetric responses obtained from replicate measurements of the different drugs with the three-sensor array were combined and analyzed by PCA. The obtained scores plot is shown in Fig. 2, where a clear clustering for each of the drugs can be observed, confirming that different fingerprints are obtained. Moreover, the effect of the concentration on the voltammetric fingerprints was also evaluated to ensure that those could be identified in a real scenario where the concentration may be unknown; a situation that can be overcome during the processing of the data with FFT as previously demonstrated [15,32]. Significantly, even when varying the concentration of those (data not shown), the algorithm is still able to correctly identify each substance, as will be further evidenced in the analysis of the real samples (Section 3.3).

Nevertheless, despite the potential shown above, it must be reckoned that "in the streets," drugs are rarely found in such high purity, but "cut" (mixed) with different substances (known as "cutting agents"). The use of those substances is aimed to "dilute" the drug with a less expensive substance than the drug itself, while at the same time some of them might even enhance its effects. Thus, to achieve the correct identification of different drugs in real samples, the next step was the analysis of some common cutting agents and their mixtures with different drugs to ensure that even in such case, the latter could be correctly discriminated and categorized.

3.2. Analysis of drug mixtures

Under the same conditions as reported above, the responses of different common cutting agents were also evaluated. Firstly, to assess if they are electroactive, and secondly, to obtain their voltammetric profile and to evaluate if they could potentially interfere in the discrimination of the different drugs. Concretely, the following cutting agents were considered: paracetamol, benzocaine, caffeine, lactose, procaine, quinine, and starch. Those were chosen taking into account the most common agents reported in previous research articles [33–36], the information provided by specialized drug control agencies and the information found on websites of specialized observers such as "Energy control" (where information is constantly updated based on the analysis performed on street samples [37]).

An extract of the responses obtained for those is shown in Fig. 3A. As can be seen, some of them are barely (or not even) electroactive (*e.g.*, starch), others show non-overlapping peaks and consequently represent a minor interference (*e.g.*, paracetamol), while some of them could result in a higher interference due to the position of the oxidation peaks (*e.g.*, caffeine and benzocaine). Nevertheless, all of them present a characteristic electrochemical fingerprint, whose discrimination could again be easily achieved (data not shown).

However, it must be reckoned that the aim is not the discrimination of any possible cutting agent, but the identification of the drugs themselves. Besides, despite the promising results obtained for the pure samples, it cannot be neglected that the analysis of mixtures of the compounds may distort the previous fingerprints, an already reported problem. Consequently, the next step was the analysis of equimolar mixtures of those. Again, an extract of the voltammetric responses obtained are shown in Fig. 3B. As could be expected, the overall fingerprint is different, but in all cases the peak corresponding to the drug can still be observed. Apart from the new peaks that appear at different potentials than the actual drugs, and that are attributed to the respective cutting agents, there is also a significant effect on the observed peak of the drug by making it shift to either higher or lower potentials as well as increasing or decreasing its current (Table S1) [38].

Consequently, to facilitate the identification of the drugs when "cut" (mixed), the analysis of the data with the aid of a pattern recognition method turns much more advantageous. Moreover, in this case, given the aim is to discriminate the presence of the drugs (regardless of these being mixed with a cutting agent or not), a supervised method such as LDA was chosen instead of PCA. The reasoning behind is that now we want to infer a function that allows the discrimination of samples into a priori defined classes rather than based only on its variance, as the latter would not allow us to group jointly in a unique cluster the mixtures of each drug with the different cutting agents. In other words, the aim is to find the characteristic fingerprint of each drug within the whole voltammetric response, while discarding the non-relevant parts (*e.g.*, presence of cutting agents).

To this aim, a set of 234 samples was prepared consisting of 6 replicate samples each of the pure drugs (4 drugs x 6), binary mixtures of each of the drugs with the different cutting agents (4 drugs x 7 cutting agents x 6) and replicates of the pure cutting agents (7 cutting agents x 6). The set of samples was divided into two subsets (train and test) in the ratio 2:1, and those were classified into 5 different groups: one for each

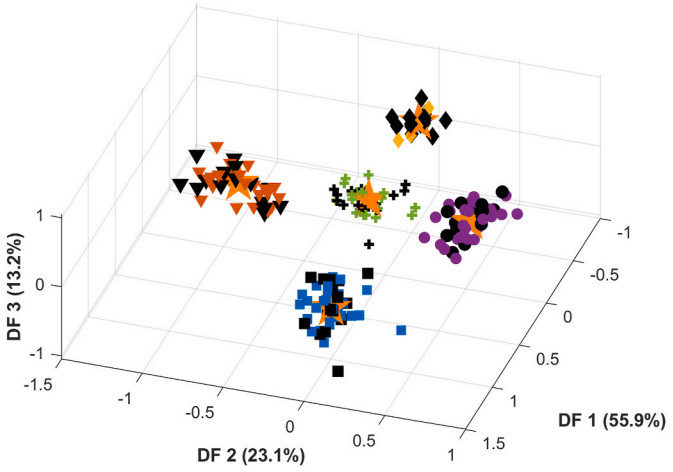

Fig. 4. 3D score plot obtained from the LDA of the voltammetric data for stock samples containing: (dark blue ■) cocaine, (red ▼) MDMA, (yellow ◆) methamphetamine, (purple ●) PVP and (green +) cutting agents. Colored filled symbols correspond to the training subset, whereas black ones to the testing subset. The centroid for each of the classes is also plotted (★).

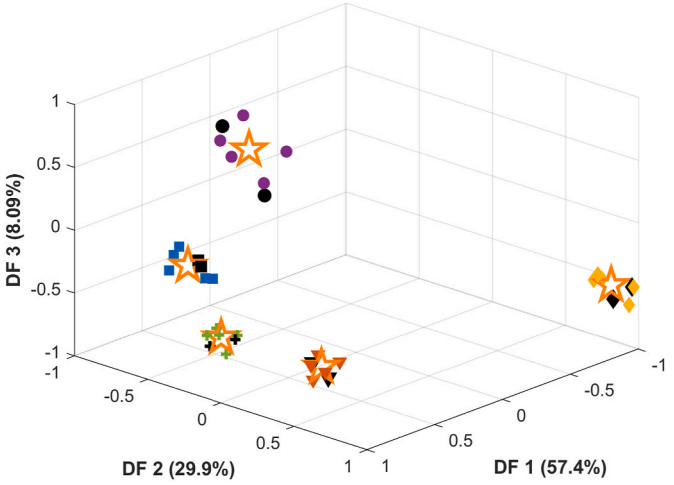

Fig. 5. 3D score plot obtained from the LDA of the voltammetric data for seized drugs: (dark blue ■) cocaine, (red ▼) MDMA, (yellow ◆) heroin, (purple ●) methamphetamine and (green +) ketamine. Colored filled symbols correspond to the training subset, whereas black ones to the testing subset. The centroid for each of the classes is also plotted (★).

of the drugs (mixed or not with the cutting agents) and one for the cutting agents. The obtained scores plot is shown in Fig. 4, with recognizable clusters obtained for each of the drugs.

Despite it is true that a higher dispersion within clusters was observed in this case, it should be reminded that clusters do not correspond to a unique compound, but each of the clusters comprises also binary mixtures. For example, the cocaine cluster groups together the samples that only contain cocaine with those that contain mixtures of cocaine with paracetamol, cocaine with benzocaine, etc. That is, each drug cluster is formed by what could be considered 8 subgroups. Similarly, the cutting agent cluster groups jointly the 7 different compounds included for this study. Lastly, it should also be noted that the actual model is comprised of four discriminant functions (DFs) which are all considered for the classification. Thus, the 3D plot shown in Fig. 4 only provides a visualization of a specific rotation of the first three DFs, as it is not possible to provide a higher dimensionality plot. Consequently, the actual model provides even better discrimination than that visually observed in the plot.

In this context, to numerically assess the performance of the LDA model, the confusion matrix for the test subset was built (Table S2), achieving a percentage of classification success for the testing subset (samples not intervening in the building of the identification model) of 100 %. At this stage, to evaluate the importance of the array in comparison to the usage of a single electrode, analogous models were built employing the exact same preprocessing, modelling, and data division, so that the only difference was the inputs to the model. The classification rate diminished from 100 % to *ca.* 80 % if only employing one of the sensors. This decrease was mainly motivated to a higher dispersion observed around the clusters centroids, as it has to be taken into account that the developed model is grouping into the same class samples that contain different compounds; *i.e.,* the drug and those that contain the drug plus any of the cutting agents (the latter slightly modifying the voltammetric response towards the former) plus all the cutting agents into the "negative" cluster (no drug present). Therefore, the use of an array of sensors assists in improving the detection as a more robust model can be generated through the combination of the different and complementary voltammetric signals.

3.3. Analysis of seized drugs

Upon confirmation of the potential of the ET to not only discriminate between the different pure drugs, but also to achieve the correct discrimination and identification of those when mixed with the more common cutting agents, the next step was to assess its applicability for the discrimination of seized drugs. That is, the analysis of actual drug samples confiscated by the police with different degrees of purity and mixed with different cutting agents.

The main challenge herein deals in the higher complexity of the samples as, on the one side, the number of components present in the sample will be higher, and on the other side, not only the concentration of the drugs will be varying, but also the ratio of the different components present in the sample.

To this aim, a set of 35 samples comprising five of the more common drugs were analyzed with a three-sensor array as earlier. Concretely, cocaine, MDMA, heroin, methamphetamine and ketamine samples were considered (7 for each type of drug). Although PVP was considered previously to prove that also synthetic cathinones could be detected, this was not considered in this case due to the low spread of this specific drug in Spain, and consequently, the small number of representative samples available.

Drug samples were analyzed directly, without weighing the sample nor performing any sample pre-treatment, by simply adding a small amount of the drug powder to the measuring cell. As before, for building the classification model, the set of samples were split into two subsets (in the ratio 5:2 between train and test) to ensure a more unbiased evaluation of its performance. The obtained scores plot is shown in Fig. 5, where a clear discrimination can be seen for most of the drugs. Besides, it must be reminded that this plot just provides a representation of the first three DFs, while the actual model is composed of four DFs.

In this context, to evaluate its performance, the confusion matrix was also built (Table S3), achieving a percentage of classification success for the testing subset of 100 %. The efficiency of the classifier can also be evaluated in terms of sensitivity (*i.e.* the percentage of objects of each class identified by the classifier model) and to its specificity (*i.e.* the percentage of objects from different classes correctly rejected by the classifier model) [18]. Average values for the classes considered, for the two metrics, were 100 % in both cases.

Lastly, despite already taking the precaution of using a separate validation subset of data (the test subset), a permutation test or "target shuffling process" was conducted to demonstrate that neither the high dimensionality of the data nor the use of LDA resulted in over-fitted modelling. Such test allows the identification of incorrectly perceived cause-and-effect relationships in modelling (sometimes referred to as "chance correlation") by taking as null hypothesis that samples labels

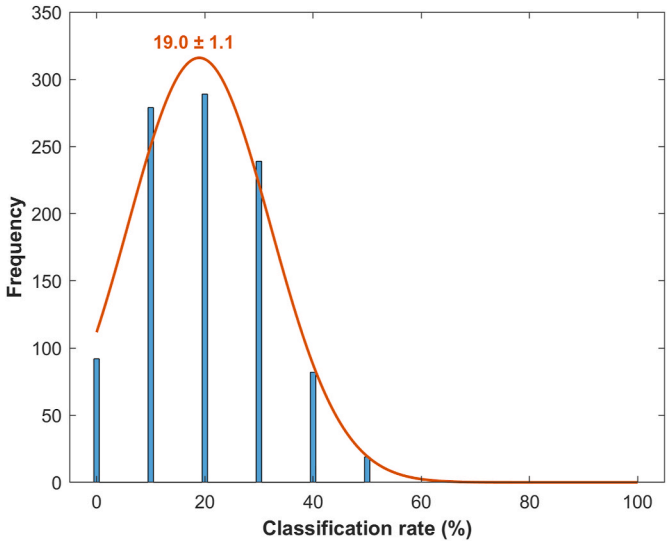

Fig. 6. Histogram summarizing the success of the shuffled models (1000 iterations) plus their fitting to a 3 parameter Gaussian curve.

are exchangeable. Briefly, this test involves repeated and random reordering of the responses variables (Y), followed by the building of a new model upon shuffling of the data labels. In other words, a new model is built upon assignment of an "incorrect" y-value to each sample corresponding to the one from another sample. This process is repeated with random reassignment to ensure that the statistics calculated are significant (up to 1000 times in our case). For each of the permutations, the classification success was calculated and compared to the actual model with the proper labels. The histogram summarizing the values of the different models for the seized drug samples is shown in Fig. 6, from which the significance of the obtained results is evident ($P < 10^{-9}$). Moreover, it can be seen how the fitted Gaussian is centered at 20 %, which corresponds to the probability of a sample being correctly classified by chance, given the number of classes considered (*i.e.*, 1/5).

As a recap, Table S4 of the supporting information presents a brief summary of the main features of the proposed approach in comparison to current alternatives already cited in the introduction, while further details can also be found in *e.g.,* Ref. [39].

4. Conclusions

The application of an ET for the discrimination and identification of different drugs has been reported. Concretely, the performance of the ET for the identification of cocaine, heroin, MDMA, methamphetamine and ketamine were assessed in both self-prepared and real samples.

The presented results demonstrate that the combination of an array of carbon-based screen-printed electrodes (SPEs) with machine learning such as LDA represents a promising approach for decentralized drug testing or drug checking. On the one side, the use of different SPEs has been proven to be sufficient for the generation of distinct electrochemical fingerprints for the most common drugs and cutting agents. On the other side, the use of chemometric tools allowed the recognition of the characteristic fingerprints for each of the drugs, which allowed to correctly conduct its identification regardless of the presence of possible interfering compounds or its concentration.

Overall, the proposed approach represents an appealing and promising tool for the analysis of drugs, allowing the field detection to be performed rapidly, reliably, and inexpensively, and should thus facilitate decentralized security screening applications. That being said, extensive validation with a much larger set of samples might be required prior to its actual application as could be expected. In this context, future efforts with this approach may involve the detection of other types of illicit substances such as cathinones, thereby obtaining a system capable of detecting all types of drugs. More importantly, it paves the way for the development of similar applications in other security scenarios.

CRediT authorship contribution statement

Xavier Cetó: Writing – original draft, Software, Methodology, Conceptualization. **Florina Maria Truta:** Methodology, Investigation. **Ana-Maria Dragan:** Methodology, Investigation. **Elena Rodríguez-Franch:** Investigation. **Mihaela Tertis:** Visualization, Methodology, Investigation. **Ángela Sánchez-Pereña:** Validation, Methodology, Investigation, Resources. **Sara Comellas-Tena:** Validation, Investigation, Resources. **Cecilia Cristea:** Methodology, Funding acquisition, Writing – review & editing. **Manel del Valle:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2024.127055.

Data availability

Data will be made available on request.

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