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Evaluation of an electrochemical sensor and comparison with spectroscopic approaches as used today in practice for harm reduction in a festival setting—A case study: Analysis of 3,4-methylenedioxymethamphetamine samples

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Abstract

More and more countries and organisations emphasise the value of harm reduction measures in the context of illicit drug use and abuse. One of these measures is drug checking, a preventive action that can represent a quick win by tailored consultation on the risks of substance use upon analytical screening of a submitted sample. Unlike drop-in centres that operate within a fixed setting, enabling drug checking in a harm reduction context at events requires portable, easy to use analytical approaches, operated by personnel with limited knowledge of analytical chemistry. In this case study, four different approaches were compared for the characterisation of 3,4-methylenedioxymethamphetamine samples and this in the way the approaches would be applied today in an event context. The four approaches are mid-infrared (MIR), near-infrared, and Raman spectroscopy, which are today used in drug checking context in Belgium, as well as an electrochemical sensor approach initially developed in the context of law enforcement at ports. The MIR and the electrochemical approach came out best, with the latter allowing for a direct straightforward analysis of the percentage 3,4-methylenedioxymethamphetamine (as base equivalent) in the samples. However, MIR has the advantage that, in a broader drug checking context, it allows to screen for several molecules and so is able to identify unexpected active components or at least the group to which such components belong. The latter is also an important advantage in the context of the growing emergence of new psychotropic substances.

KEYWORDS

ATR–(N)IR, drug checking, electrochemical detection, 3,4-methylenedioxymethamphetamine (MDMA), mobile detection approaches

1 | INTRODUCTION

The European Unions' Drugs Strategy and Action Plan (2021–2025) states the need for a balanced and evidence-based response to the drug phenomenon to tackle the challenges it poses to both public health and security.[1,2] Different initiatives were already undertaken, that is, legislative initiatives[3,4] and initiatives focussed on prevention and harm reduction.[2] The latter is deeply implemented in the European Union drugs strategy and involves a more pragmatic approach in dealing with the issue of drug abuse.[5,6] One initiative in this context is drug checking, a service enabling individuals to have their drugs chemically analysed, providing information on the content of the samples as well as advice and, in some cases, counselling or brief interventions. Service aims vary, ranging from information collection to harm reduction by informing and warning users about the drugs on the market.[7–11]

One context in which drug checking can represent a quick win is cultural events such as the summer festivals. Indeed, several incidents occur each year during the summer festival season due to intoxications caused by the use of psychoactive substances or their combination with other licit and/or illicit substances for enhanced party sentiment.[12] In this setting, drug checking is a strategy with three main objectives: (a) at the level of persons who use drugs, by educating and informing, increasing awareness to avoid short- and long-term adverse reactions, (b) for the event organisers, to reduce the number of incidents due to timely feedback to persons who use drugs or by warning the event public for dangerous products circulating on-site, (c) and at the level of society, to provide a better insight of the products circulating on the illicit market, allowing for future prevention initiatives and possible policy adaptions.[12,13]

These days, most of the analytical work involving illicit drugs is performed in well-equipped and accredited laboratories. However, to perform on-site harm reduction-oriented drug checking at events, easy to move and portable approaches are needed. Indeed, although mobile laboratories exist, these are most of the time used in the context of law enforcement thus not immediately available for preventive analysis. The ideal analytical technique for on-site testing should be easy to use, portable, nondestructive for the samples, and requiring minimal sample handling by the operators. Up to now, drug checking services used a lot of colorimetric tests for some of the most frequently encountered drugs or for detection of specific (groups of) compounds, for example, fentanyl analogues.[5,14] However, this situation is changing, and it can be seen that drug checking services turn to spectroscopic approaches in order to screen for drugs in different matrices. Applications exist for mid-infrared (MIR) and near-infrared (NIR) as well as Raman spectroscopy. Additionally, portable instruments with high resolution exist for all three techniques, which continue to develop and improve.[5,7,13–15] The on-site screening of products using these three techniques is often based on library comparisons. This approach is however not the most optimal to make use of all the benefits of these techniques. As was recently reviewed by our group,[16] the combination of spectroscopic techniques with data processing and chemometric modelling techniques is a powerful tool for the analysis of different kinds of illicit drugs. This processing can go from preprocessing of the spectra using normalisation, derivatives, and so forth to eliminate interference to complex modelling for the full characterisation of samples. Though such applications are for the moment limited to the academic world and only scarcely find their way to routine applications, often in the forensic field. In the context of harm reduction, drug checking, especially at cultural events, is often performed by personnel with a more social background and only limited knowledge about analytical chemistry. This, combined with the fact that portable instruments often allow for only limited processing of spectra, is probably the reason why in a drug checking set-up, spectroscopic techniques are only applied with classical library search.

The recently introduced Narcoreader®[17] approach is based on electrochemistry using an electrochemical sensor. This device was developed for fast and accurate identification of illicit drugs and their major cutting agents in collaboration with border authorities and police services at ports and airports. The device is based on voltammetry, which entails that a change in voltage is applied to a solution of the sample and the resulting current is measured.[17] If an analyte gets oxidised or reduced due to the changing potential, a spike in current is observed. The potential at which this peak in current is observed (i.e., the peak potential) can be related to the analyte and thus be used for sensing purposes.[18] Applications of this approach were already reported for cocaine,[19] 3,4-methylenedioxymethamphetamine (MDMA),[20,21] and heroin.[22] In all these cases, the approach was focussed on identification of the drugs. This is sufficiently useful for applications in law enforcement environment in which a confirmation of the presence of (il)licit psychoactive substances is required for further operating procedures. However, from a harm reduction point of view, identification of the main illicit compounds allows for partial risk assessment only. Next to a person's history of drug use and circumstances related to the event itself, for example, the potentially ingested dose of an MDMA tablet can indicate the risk for intoxication or even lethal overdose.[23] In this context, an application for the Narcoreader® was developed to not only identify MDMA in ecstasy tablets but also perform a quantitative analysis.

We present a case study on MDMA tablets, where the use of the Narcoreader® is evaluated by comparing it with approaches using MIR, NIR, and Raman spectroscopy. MDMA samples were collected during the festival season of the summer of 2022 in Belgium and analysed with validated analytical approaches using gas chromatography–mass spectrometry (GC–MS) for identification and ultraviolet (UV) spectroscopy for quantification. Next, the collected samples were analysed by MIR, NIR, Raman spectroscopy, and the Narcoreader® as if operated on-site by a person with limited knowledge of analytics and limited experience with illicit drug characterisation. This means that the spectroscopic approaches are used as they are used today by drug checking services in Belgium, that is, using a simple library comparison between the recorded spectra and reference spectra of pure MDMA as well as reference samples.

2 | METHODS AND MATERIALS

2.1 | Samples

Seventy-three seized drug samples suspected of containing MDMA were collected at a summer festival in Belgium in 2022. The samples came in the form of intact tablets, parts of tablets, or crystals.

2.2 | Sample preparation

All samples were first weighed and crushed using a pestle and mortar. The resulting powder was then used for further analysis. For the recording of the spectra in MIR, NIR, and Raman spectroscopy, the powder was used as such without any further pretreatment.

For GC–MS, 1 mg/mL solutions of the powdered samples were prepared, by weighing the appropriate amount in a volumetric flask, dissolving it in High Performance Liquid Chromatography (HPLC)-grade methanol (Biosolve, Valkenswaard, the Netherlands), and bringing it to volume with methanol after sonification for 10 min. Prior to injection, the solutions were filtered using a polytetrafluoroethylene (PTFE) syringe filter (PTFE, 13 mm diameter, 0.2 µm pores, Whatman, Sigma-Aldrich, Saint-Louis, VS).

For UV spectroscopy, the solutions prepared for GC–MS were diluted 20 times using HPLC-grade methanol.

For the Narcoreader®, 1 mg/mL solutions of the powdered samples were prepared in Milli-Q water (Milli Q® 7000 system, Merck, New Jersey, USA). The solutions were sonicated for 15 min after which 0.5 mL of the solution was transferred to an Eppendorf® tube, combined with 1 mL of a premade 0.1 M acetate buffer pH 5 (buffer for Narcoreader®, A-sense Lab, University of Antwerp, Antwerp, Belgium) and vortexed.

2.3 | Data acquisition

2.3.1 | Fourier transformed-MIR

MIR analysis was performed on a Nicolet iS10 FT-IR (ThermoFisher Scientific, Waltham, USA) instrument, equipped with a Smart iTR accessory (attenuated total reflectance (ATR)) and a deuterated triglycine sulphate detector. The Smart iTR accessory used a single bounce diamond crystal and was weekly calibrated using a polystyrene film.

The instrument measured the infrared spectrum of the samples in the wavelength range from 4000 to 400 cm^{-1}. The spectral resolution was set at 4 cm^{-1}, and 32 coadded scans were performed. The spectra were treated using the OMNIC Software version 8.3 (Thermo Scientific, Madison, USA) and compared with an in-house library for identification. This library contained the reference spectra of illicit drugs as well as the spectra of samples, confirmed to be positive for MDMA by GC–MS. Between each sample, the crystal was cleaned using a soft tissue soaked with methanol and left to dry at ambient air. A blank measurement (air) was performed between each sample to check the crystal for contamination and carry-over using the absorbance limits for contamination defined by the European Directorate for the Quality of Medicines and HealthCare.[24] Every hour, a background spectrum against air was measured as well.

Standard base line correction and normalisation was applied before library comparison.

2.3.2 | Near-infrared

The NIR spectra were recorded using a Frontier MIR/NIR Spectrometer™ (PerkinElmer™, USA). The spectra were measured in reflectance mode with a spectral resolution of 8 cm^{-1} and a number of coadded scans of 16. The spectra are recorded for the wavelength range of 4000–1000 cm^{-1} and compared with the spectra of references and other confirmed MDMA samples. The powdered samples were transferred into glass vials through which the spectra were measured. The background was recorded between each sample and subtracted automatically.

Standard base line correction and normalisation was applied before library comparison.

2.3.3 | Raman spectroscopy

Raman spectroscopy was performed using a portable Metrohm Instant Raman Analyser DS Raman spectrometer (Metrohm, Laramie, USA). The spectrometer was equipped with Orbital-Raster-Scan technology which consisted of a small aperture with a tightly focussed laser that moves over the sample in order to scan a large area of the samples. This technology improves resolution and sensitivity and avoids the problems that may occur due to sample degradation. The spectrometer used a laser at 785 nm with a laser output power lower or equal to 100 mW. The Raman spectra were recorded through the glass vial, the same as used for the recording of the NIR spectrum, in the range of 400–2300 cm^{-1} at a spectral resolution of 10 cm^{-1}. The recorded spectra were compared with those of references and confirmed MDMA samples.

2.3.4 | Gas chromatography–mass spectrometry

GC–MS screening was performed on an Agilent 8860GC GC system (Agilent Technologies, Santa Clara, California, USA) equipped with an Agilent 7683B Series injector and hyphenated with an Agilent 5973 Network Mass Selective Detector. The machine was operated, and data were treated using Agilent MassHunter Unknowns Analysis software. The chromatographic column was an Agilent J&J VF-5 ms capillary column (40 m × 0.25 mm; 0.25 µm), and the following temperature gradient was applied: The gradient started at 80°C for 2 min, followed by a gradient at a rate of 15°C/min until a temperature of 280°C was reached. This temperature was held for 17 min (total run time 32.3 min). The injection volume was 1 µL, and helium

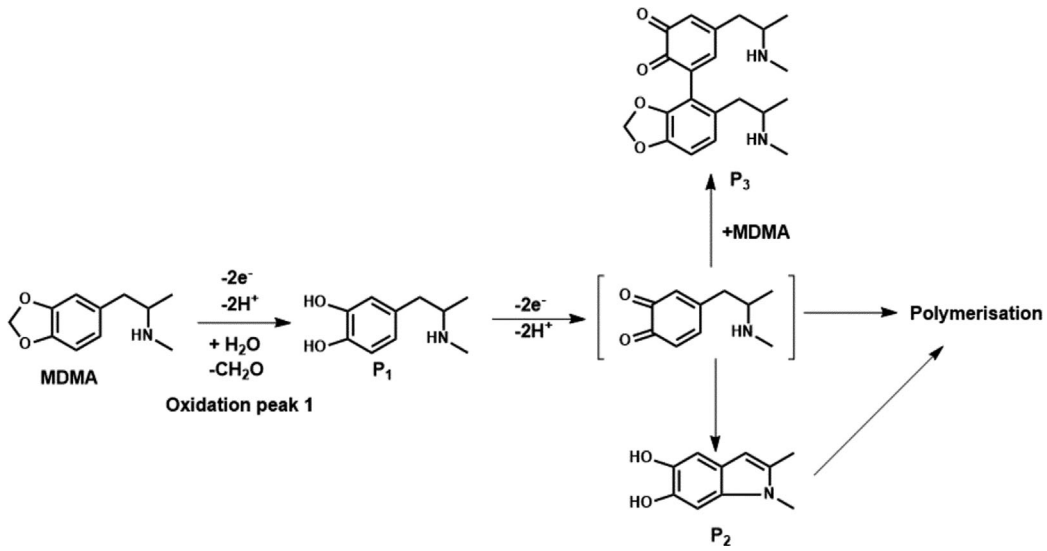

FIGURE 1 Redox reaction of 3,4-methylenedioxymethamphetamine (MDMA) in a 0.1 M acetate buffer of pH 5.

was used as carrier gas at a constant flow rate of 1 mL/min. The injector was used in split mode (ratio 1:10). Temperatures of the injection port, the ion source, the quadrupole, and the interface were 250°C, 230°C, 150°C, and 280°C, respectively. The analysis was performed in full scan mode.

2.3.5 | UV spectrophotometry

Quantification of MDMA in the samples was performed on a Perkin Elmer Lambda 35 UV/visible (Vis) spectrophotometer (Perkin Elmer, Waltham, Massachusetts, USA) using quartz cuvettes (Quartz Suprasil, 10 × 10 mm, Hellma, Müllheim, Germany) and methanol as blank. The UV spectrum was measured in the range of 200 to 350 nm at a rate of 480 nm/min. The wavelength for quantification of MDMA was 286 nm, and the specific extinction coefficient for MDMA.HCl 172.3100 mL/g cm^{-1} was used for the calculation of the percentage MDMA present in the sample.

This procedure was validated using the total error approach, compliant to the ISO17025 standard, and is performed routinely in our laboratory under accreditation. The process consists in a screening by GC–MS. If no interfering compounds can be detected in GC–MS, quantification is performed as described above using UV. In case of, for example, the presence of caffeine, GC-Flame Ionisation Detection (FID) would be applied. Validation under ISO17025 accreditation included parallel analysis of samples with UV and GC-FID.

2.3.6 | Electrochemistry

As mentioned before, electrochemical detection was performed using a Narcoreader® device (A-sense Lab, Antwerp, Belgium) with unmodified screen printed electrodes (SPEs) (PalmSens, Utrecht, the Netherlands). The SPEs contain a graphite working electrode (diameter = 3 mm), a carbon counter electrode, and a silver reference electrode. The Square Wave Voltammetry (SWV) parameters are as follows: potential range of −0.1 to 1.5 V vs Ag/AgCl, frequency of 10 Hz, 25 mV amplitude, and 5 mV step potential. Electrochemical measurements were performed in a pH 5 acetate buffer at 20 mM ionic strength with 100 mM KCl.

The detection of MDMA was based on a redox reaction where the methylenedioxy moiety is oxidised (Figure 1) resulting in a diagnostic peak of current at 1.11 V in the electrochemical profile in pH 5.[25] A typical example of the MDMA electrochemical profile is given in Figure 2. The reaction is externally driven by an applied voltage range generated by the potentiostat at the surface of the single, unmodified SPE.

The surface of the SPE is covered by the sample, which is prepared as described in Section 2.2. Subsequently, a SWV measurement is performed using the parameters described in the previous paragraph. The voltammetric output was then analysed by an algorithm[26] to identify the characteristic signal of MDMA, returning a positive or negative response to the user. The magnitude of the measured current was proportional to the concentration, which allowed the algorithm to estimate the dosage if a sample weight was entered into the software. For each sample, a new SPE is used.

2.3.7 | LOD determination

The limits of detection (LODs) for MDMA were determined by preparing low dosed samples of MDMA starting from the sample consisting of the purest crystal (sample 53; Table 1). The samples were prepared by cutting the powdered crystal with a matrix consisting of excipients often encountered in MDMA tablets. The

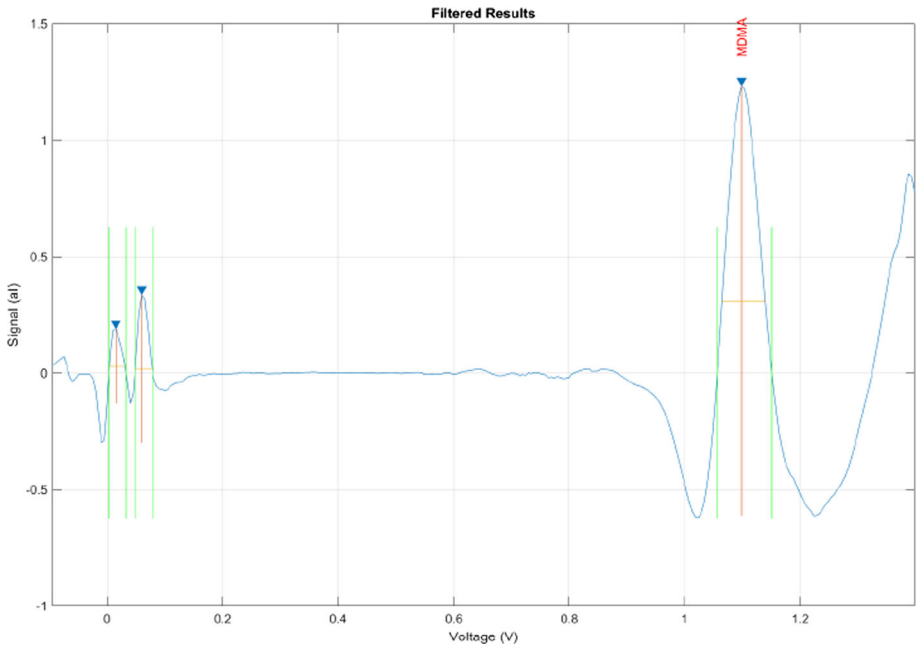

FIGURE 2 Screenshot: Example of a processed methylenedioxymethamphetamine (MDMA) electrochemical profile (first two signals are normal blank signals).

matrix consisted of one third of each lactose, mannitol, and starch. A series of seven concentrations were prepared resulting in samples containing 4%, 2%, 1%, 0.5%, 0.25%, 0.12%, and 0.06% w/w MDMA (as base equivalent).

These samples were analysed with both MIR as the Narcoreader® and the sample with the lowest concentration found positive for MDMA was considered as the LOD.

3 | RESULTS

3.1 | Characterisation of the samples

As discussed above, the 73 samples suspected of containing MDMA were screened using GC–MS, and if positive for MDMA, MDMA was quantified using UV–Vis analysis. Table 1 shows the GC–MS screening and UV–Vis quantification results obtained for the sample set. Out of the 73 samples, 50 contained MDMA as the main active substance, four of which also contained caffeine. The latter could not be quantified due to interference of caffeine with the UV spectrum of MDMA. The percentage MDMA in the samples ranged from 13.4% to 80.3%. For the 23 remaining samples, 11 did not contain any detectable active substance or contained a substance that could not be identified. Four samples contained amphetamine and two trazodone. The last six samples each contained one active substance only: ibuprofen, methylenedioxyamphetamine, nordiazepam, ketamine, 4-chloromethcatinone, and caffeine.

3.2 | Alternative methods

The GC–MS and UV–Vis results were used as reference data for the calculation of the sensitivity, specificity, and precision of the different techniques. Table 2 gives an overview of the true/false positive/negative rates obtained for the different techniques.

3.2.1 | Spectroscopic techniques

Figure 3 represents some examples of the obtained MIR and NIR spectra. The presented spectra are for the MDMA reference, a common high purity sample, a common sample found as false positive during library matching and examples of a true negative sample. Unfortunately, for Raman spectroscopy, the present configuration of the portable device did not allow a correct export of the spectra, so those could not be shown in the figure.

For the spectroscopic techniques, the best results were obtained with MIR. A sensitivity of 100% was seen, meaning that all MDMA-positive samples identified by GC–MS were also considered positive by MIR. When comparing the samples spectra to the reference spectra, a matching factor of at least 80% was used to consider it a positive identification. This matching factor was selected in order to optimise the number of false positives and false negatives in the sample set, based on the GC–MS results. Furthermore, a specificity of 79% and a precision of 91% were obtained. Specificity reflects the probability that a negative sample will be identified as being negative, while precision is the fraction of true positive results compared with all positive results obtained.

Five samples were considered false positives. According to the GC–MS, all these samples tested negative for MDMA, although it was observed that during the analysis with the Narcoreader® device (see further), four of these samples tested positive, albeit containing only traces of MDMA. Here, two possibilities exist: The samples are also false positives for the Narcoreader® device or the GC–MS method could not detect these traces, due to interference of matrix components or the use of a matching factor of 85% for positive identification

TABLE 1 Identification and dosage results of the 73 potential methylenedioxymethamphetamine (MDMA) samples with, respectively, gas chromatography–mass spectrometry and ultraviolet spectroscopy.

Sample number	Substance	Content (%base)	Sample number	Substance	Content (%base)
01	MDMA	19.0	38	Ketamine	77.0
02	MDMA	23.2	39	4-CMC	/
03	MDMA	41.2	40	MDMA	33.9
04	Amphetamine	/	41	MDMA	27.6
05	Negative	/	42	MDMA	22.0
06	Amphetamine	/	43	MDMA	21.0
07	MDMA	79.4	44	Negative	/
08	MDMA	78.8	45	MDMA	28.2
09	MDMA	80.1	46	MDMA	16.2
10	MDMA	79.1	47	MDMA + caffeine	/
11	MDMA	30.1	48	MDMA	76.6
12	MDMA + caffeine	/	49	MDMA + caffeine	/
13	MDMA	45.8	50	MDMA	25.9
14	MDA	/	51	MDMA	30.9
15	Negative	/	52	MDMA	28.2
16	MDMA	31.6	53	MDMA	80.3
17	MDMA	77.9	54	MDMA	15.5
18	Negative	/	55	Negative	/
19	MDMA	27.1	56	MDMA	74.5
20	MDMA	26.1	57	MDMA	27.3
21	MDMA	27	58	MDMA	22.2
22	Negative	/	59	Negative	/
23	Caffeine	/	60	MDMA	27.2
24	MDMA	31.2	61	MDMA	31.7
25	Ibuprofen	/	62	MDMA	35.3
26	Negative	/	63	MDMA	30.6
27	Trazodone	/	64	MDMA	34.9
28	Negative	/	65	MDMA	13.4
29	Amphetamine	/	66	MDMA	26.9
30	Amphetamine	/	67	MDMA + caffeine	/
31	Negative	/	68	MDMA	20.7
32	Nordiazepam	/	69	MDMA	24.5
33	Negative	/	70	MDMA	29.3
34	Trazodone	/	71	MDMA	79.4
35	MDMA	26.9	72	MDMA	29.1
36	MDMA	77.2	73	MDMA	28.0
37	MDMA	18.9			

Abbreviation: 4-CMC, 4-chloromethcatinone.

in GC–MS. It has to be kept in mind that the GC–MS method used for the screening of illicit drugs has been developed with focus on active amounts of the drugs.

Figure 4 shows the recorded MIR spectra for the references as well as the five samples considered as false positives in this study at a threshold of the matching factor of 80%. For the five samples, the figures show some clear similarities with the reference sample, though also clear differences. Because the matching factors for these samples were in the range of 80% to 82%, these misclassifications will probably be due to the threshold of 80%, which was selected as the best compromise between the rates of false positives and negatives.

Because MIR showed very good performance parameters, the LOD was determined using the dilution series as described above. From these experiments, it could be concluded that the LOD must be

TABLE 2 Overview of the true/false positives/negatives rates for mid-infrared (MIR), near-infrared (NIR), Raman spectroscopy, and Narcoreader® compared with gas chromatography–mass spectrometry.

	True positive	True negative	False positive	False negative
MIR	49	19	5	0
NIR	47	2	21	3
Raman	42	1	22	8
Narcoreader	50	16	7	0

Note: The sample set was composed of 50 samples positive and 23 samples negative for 3,4-methylenedioxymethamphetamine.

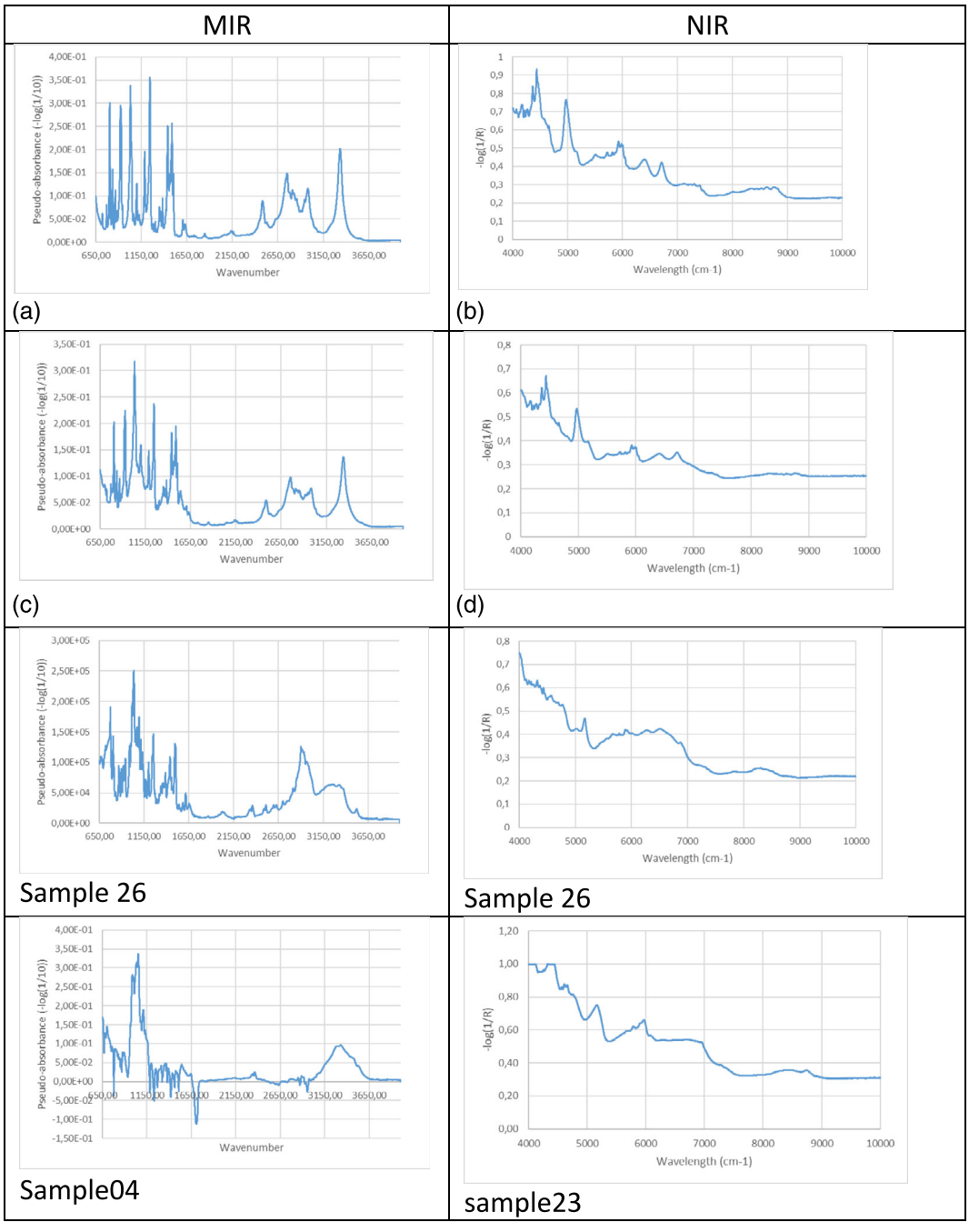

FIGURE 3 Example mid-infrared (MIR) and near-infrared (NIR) spectra for the 3,4-methylenedioxymethamphetamine reference (a, b), a common high purity sample (c, d), sample 26 as example of a false positive sample and sample 04 and sample 23 as example of true negative samples.

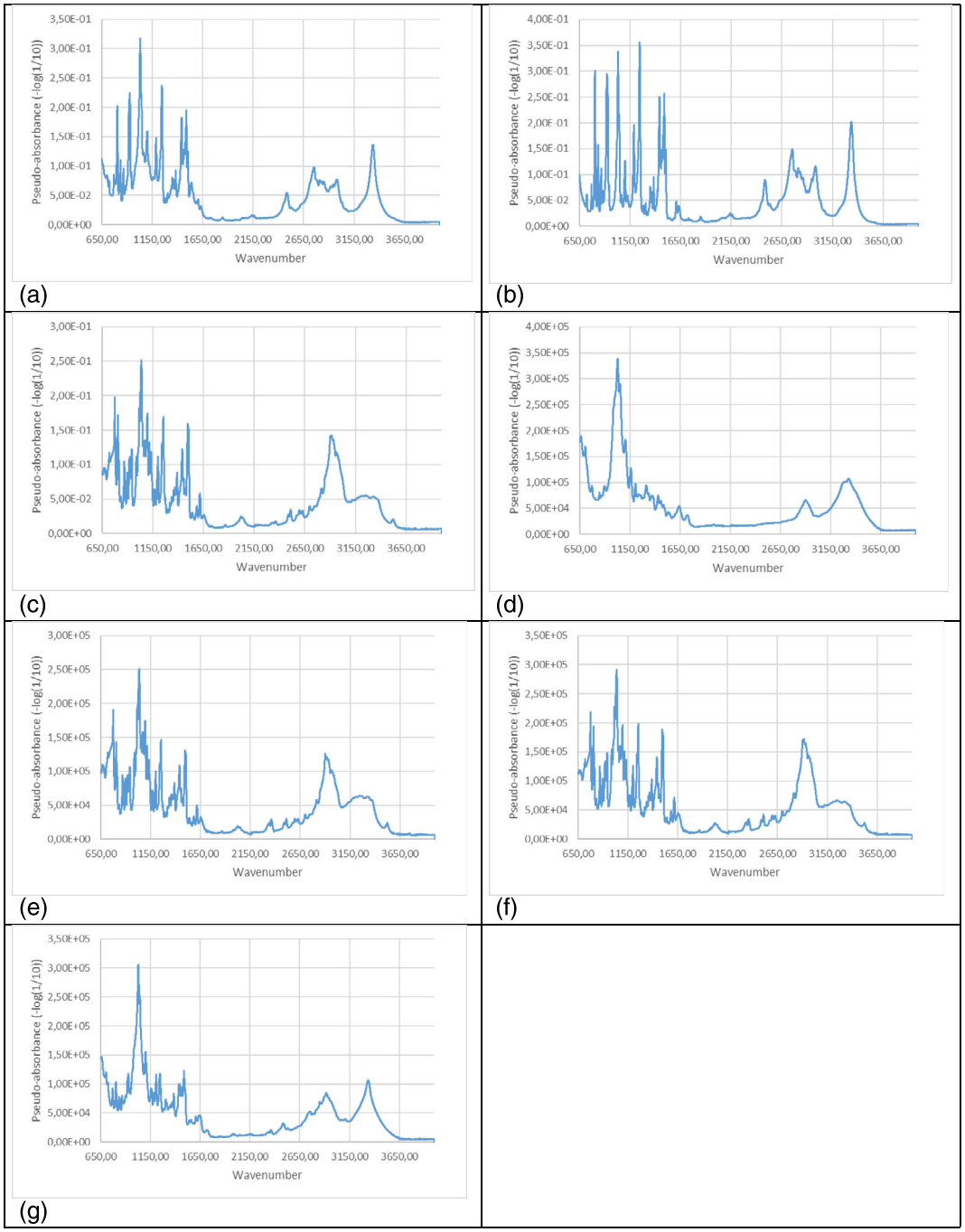

FIGURE 4 Mid-infrared spectra obtained for the reference 3,4-methylenedioxymethamphetamine sample (a), the reference for methylenedioxymethamphetamine (b), and the five false positive samples: sample 15 (c), sample 18 (d), sample 26 (e), sample 28 (f), and sample 59 (g).

higher than 4% because none of the prepared samples tested positive. The lowest dosage from our series of samples which tested positive with MIR was sample 65 (Table 1) containing 13.4% MDMA (as base equivalent). This seems to confirm that the false positive samples, discussed above, are real false positives.

The two other spectroscopic techniques, NIR and Raman, were, within the context and set-up of this study, underperforming. For NIR, a sensitivity was obtained of 94%, though a specificity of only 9% and a precision of 69% were obtained. The latter means that when a sample tests positive, it is correct in 69% of the cases. Similar results were obtained for Raman spectroscopy, that is, a sensitivity, specificity, and precision of 84%, 4%, and 66% were obtained, respectively. Also here, a cut-off matching factor of 80% seemed the best compromise for the rates of false positive and false negative samples. These inferior results could be expected because both techniques can highly be influenced by interfering agents, present in the tablets, with the

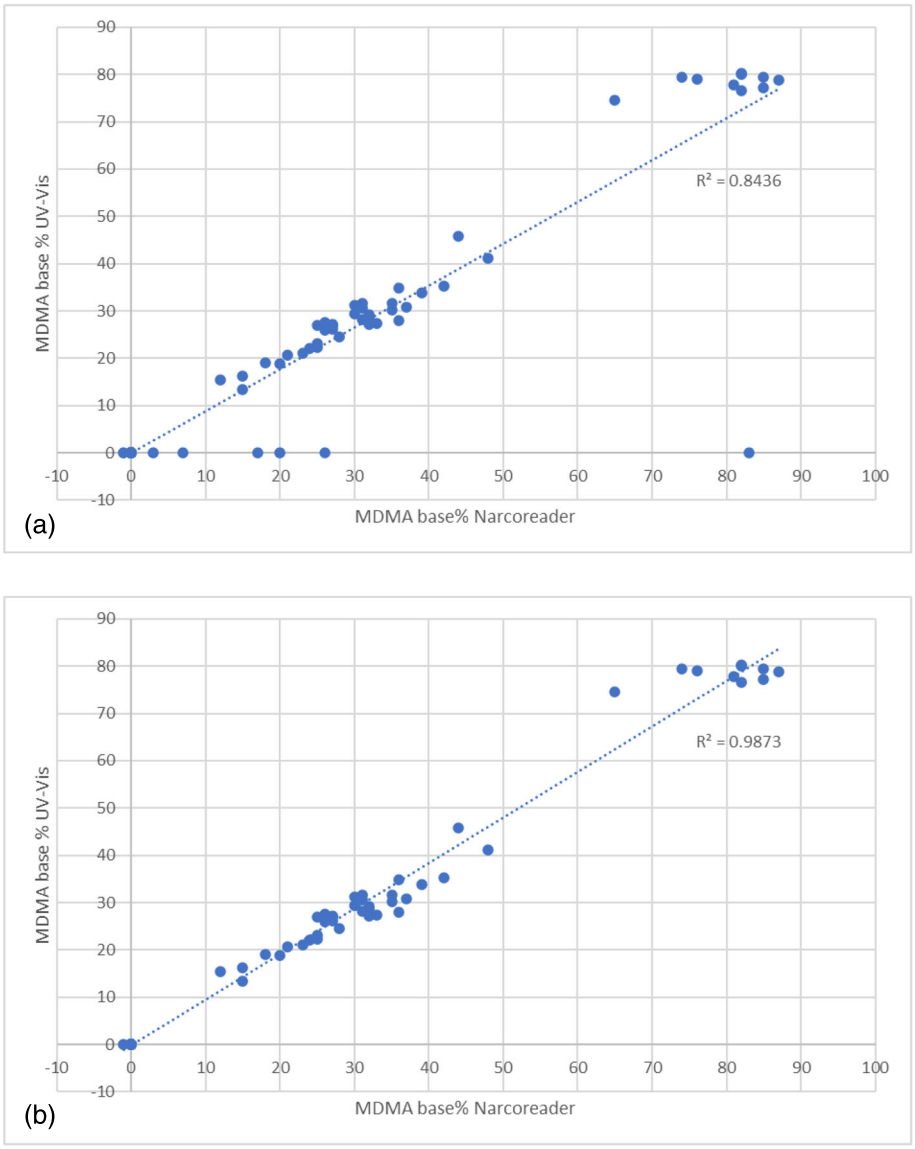

FIGURE 5 (a) Correlation between the quantitative results of ultraviolet–visible (UV–Vis) and the Narcoreader® device and (b) correlation between the quantitative results of UV–Vis and the Narcoreader® device after removal of the false positive samples. MDMA, 3,4-methylenedioxymethamphetamine.

NIR spectrum or causing fluorescence in Raman spectroscopy. It also has to be said that NIR and Raman spectra are much less specific than MIR spectra and therefore not that well suited for simple library comparison applications. Both techniques, however, can benefit a lot from data processing and modelling, but this was out of the scope for this case study in the context of practical harm reduction application.

Due to the results obtained with NIR and Raman, the comparison with the Narcoreader® will be further limited to the MIR results.

3.2.2 | Narcoreader®

Table 2 also represents the true/false positive/negative rates for the Narcoreader® device. Here, a sensitivity of 100% was obtained, meaning that all positive samples were also considered positive by this technique, as was also the case for MIR spectroscopy. Furthermore, this technique showed a specificity of 70% and a precision of 88%, pointing at a comparable performance to that of the classical MIR approach. Focussing on the false positive samples shows that sample 25, which was in fact ibuprofen, tested positive for MDMA with the Narcoreader® device, although quantitative analysis resulted in a negative percentage of MDMA. Samples 5, 15, 20, and 28 all tested positive, but GC–MS could not identify the principal component in these samples. For sure, it is not MDMA, but it seems the Narcoreader® device still see these components as MDMA. Sample 29 tested positive as well, but with a percentage MDMA of 3%, which could be missed by GC–MS, because the GC–MS method was optimised and validated for regular street drugs and so for active amounts of MDMA in the samples. Sample 14, containing 3,4-methylenedioxyamphetamine, a closely related molecule to MDMA, was also found to be a false positive.

The Narcoreader® is the only alternative technique used in this research that allowed for direct quantitative analysis of the MDMA tablets. Figure 5 shows the correlation between the results obtained with the Narcoreader® and UV–Vis analysis. A determination

coefficient (R^2) value of 0.84 could be obtained after removing the samples containing both MDMA and caffeine, which were not dosed with UV–Vis (Figure 5a). After removal of the seven false positive samples from the graph, an even better correlation value of 0.99 could be obtained (Figure 5b). It has to be mentioned here that also MIR, NIR, and Raman spectroscopy allow for semiquantitative analysis, but here, data processing is necessary that is for the moment not available in the software of the equipment used by the drug checking services or not applied. Either way, quantitative analysis with MIR, NIR, and Raman is not that straightforward to be used by nonexperts.

As for MIR, the series of prepared low dosed samples was analysed in order to determine the LOD. However, none of these samples tested positive for MDMA, meaning that the LOD of the Narcoreader® device is higher than 4% and has to be set equal to 13.4% (the dosage of the lowest concentrated positive sample). It has to be pointed out that this is the LOD for the Narcoreader® device as a whole, meaning the combination of the electrochemical sensor and the algorithm. Electrochemistry is typically a very sensitive technique with low detection limits, yet the sensor generates a signal interpreted by the software, which has built-in thresholds based on which the signal is considered to be meaningful. The goal is to filter for noise, leaving only the signal coming from MDMA. For this study, the thresholds were defined based on the typical concentrations found in "real" street drugs, and therefore, very low concentrations might not be seen as positive by the software.

4 | DISCUSSION

The results reported above need to be interpreted within the context of this study: the evaluation of the use of the different instruments in the context of drug checking as part of on-site harm reduction actions in an event setting such as music festivals. Within such a set-up, analysis cannot be done in a laboratory environment and also might be performed by people not sufficiently trained in chemical analysis. Thus, the ideal instrument should be mobile, easy to use—including automatic interpretation of the data—and requiring minimal to no sample preparation. In addition, on-site testing benefits from fast analysis performance (preferably around 5 to 10 min). From the perspective of the event sector, services provided at mass events require utmost efficiency in order to be effective and customer-friendly; while from the perspective of the effectiveness of a harm reduction set-up, enabling a swift consultancy after drug checking and engagement with people who are interested in drug use is essential to maximise the harm reduction strategy of the action. This also means that the instruments were used as they would be used today in this context, that is, using simple library searches for the spectroscopic techniques, not exploiting the possibilities of data processing and the application of chemometric models, which could improve significantly the performance of the spectroscopic techniques and allow them to be used at full potential.[16]

MIR, NIR, and Raman spectroscopy were applied as they would typically be applied on-site. These techniques have the advantage that they are nondestructive, easy to use, do not need any sample preparation, and exist in performant portable versions. Even more, they have proven highly valuable in the analysis of illicit drugs, as reported for cocaine, ketamine, and heroine.[27] For the analysis of MDMA tablets, less literature is available using these techniques, probably due to the previously mentioned interferences, caused by the compounds present in ecstasy tablets. This is also the probable cause why NIR and Raman techniques failed in this study, using only simple library searches. However, it was shown in literature that part of this problem can be solved by coupling these techniques to chemometric modelling. As shown previously by our group, it is possible to preprocess NIR spectra followed by training chemometric models for MDMA tablets.[22] These models, both using MIR as NIR, were able to classify samples in MDMA-containing and non-MDMA-containing ones with a correct classification rate (ccr%) of 96% showing 4% of false positive samples and no false negatives. The NIR models were also able to estimate the percentage MDMA (as base equivalent) present with an error of less than 5%.[23] It was also shown that training of these models should be done using samples of tablets that effectively are circulating on the drug market instead of confining to laboratory-designed products, in order to include as much variability in matrices and colorants as possible into the models.[23] Several other authors focussed on this combination of spectroscopy and chemometrics for the analysis of MDMA and other illicit drugs as was recently reviewed by Deconinck et al.[16] The same approach could be feasible using Raman spectra, but here, the fluorescence phenomenon is more important, and therefore, new instruments that can (partly) compensate for this are necessary. The Raman spectrometer used in this research was not able to do so. Another possible solution is the newly emerging surface enhanced Raman spectroscopy kits, allowing the amplification of the Raman signal and a partial compensation for fluorescence.[16] Sample preparation for such surface enhanced Raman spectroscopy analysis is comparable with that of the chemical sensor, used in this study. Although all of this could enable NIR and Raman to be used for the analysis of ecstasy tablets on-site, it should be kept in mind that in the context of harm reduction, these instruments are operated by personnel with limited knowledge of analytical chemistry. In this case, harm reduction staff needs support for the training of the models and also for the constant updating of these models with new samples in order to keep up with the always increasing variability. Additionally, the vendor software should enable the use of chemometric models in their software and this also for portable devices in order to enable automatic interpretation of the results.

MIR spectroscopy combined with an ATR sampler was one of the two techniques giving promising results within the set-up of this study. Although the machine used in this study was a benchtop model, nowadays, portable versions exist with comparable performance and resolution. ATR–MIR is also a nondestructive, easy to use technique that necessitates only minimal sample preparation, that is, grinding of the tablets or the crystals. In this study, ATR–MIR with a sensitivity of 100%, a specificity of 79%, and a precision of 91% showed the overall best performance. The results could also be improved using

chemometric modelling techniques with the same constraints as described before for NIR and Raman. In this study, it was opted to use the technique as it is nowadays applied by harm reduction organisation in night life settings: The sample was grinded, and the spectrum was measured and compared with a spectral library not only containing a reference spectrum for MDMA but also spectra of samples previously characterised by GC–MS.

Although not evaluated in this study, the three spectroscopic techniques also allow for semiquantitative analysis. This can be performed using external calibration or the use of chemometric models such as multiple linear regression or partial least squares analysis. External calibration is feasible when the variability in the samples is limited. This has been described in literature for white powders, for example cocaine samples.[16,27] In the current case study on MDMA tablets, such an approach will likely not work because the external calibration would be based on the spectrum of MDMA references. Therefore, chemometric modelling would again be necessary as shown by our group in previous research.[22] Once more, the implication of chemometric software in the daily routine of harm reduction services would imply the vendor software to be able to create, update, and use these models in an automatic way in the field and the organisations would need continuous support from specialists to implement this.

Finally, when equipped with an appropriate database, spectroscopic techniques are able to detect and identify a large number of active substances. MIR spectroscopy was, for instance, able to identify ibuprofen in sample 25. This is a huge advantage, because in the context of harm reduction in event settings, a whole range of licit and illicit products can be encountered in various formats going from tablets and capsules to powders and liquids.

The fourth technique used in this comparative study was the Narcoreader® device, developed in the context of law enforcement and applied here for the first time taking harm reduction context and objectives into account. The instrument is small, portable, and easy to use. The interpretability of the results is automatic, and it is the only approach in this study that allows for a direct and straightforward quantitative analysis. For the analysis of the MDMA tablets, the Narcoreader® device showed highly similar results to the ones of MIR with a sensitivity of 100%, a specificity of 70%, and a precision of 88%. However, compared with MIR, the Narcoreader® device came with some important disadvantages. The first being that the method is destructive, and therefore, (part of) the sample can no longer be used for further investigations. Here, it should be kept in mind that in a harm reduction set-up, the sample amount at hand will mostly be limited and follow-up analyses will not be possible due to the lack of substance provided. Though people that make use of a drug checking service easily agree to provide a minimum amount of material, one should take into account that in their opinion, psychoactive substances are pricy and valuable, and therefore, having to hand in large amounts for testing might increase the threshold of making use of the service in the first place. The second is the fact that it is a "one molecule at a time" approach, meaning that currently, for each molecule, another set of parameters, materials, and procedures is required, where MIR can screen different types of samples simultaneously for different molecules. It should also be kept in mind that the synthetic drug market is constantly changing, so it is also important to be able to detect new substances as closely to their appearance on the drug market, and therefore, the availability of a simple method able to perform a more general screening is important. The third is the need for sample preparation, which is more extensive than for the other techniques. Here, it has to be said that for qualitative analysis alone, the sample preparation is limited to powdering the sample, taking a spatula tip of powder, pouring it into a prefilled Eppendorf with buffer, and shaking it. If quantitative analysis is required as well, the more extensive sample preparation as described in Section 2.2 is necessary. For quantitative analysis, an added factor for its application in a harm reduction context, the Narcoreader® device gives highly correlated results with those obtained by traditional accredited analysis techniques.

5 | CONCLUSION

Table 3 summarises the key parameters of this comparative study for MIR, NIR, Raman spectroscopy, and the Narcoreader® device for their use in a harm reduction set-up in event settings. ATR–MIR and the Narcoreader® device gave similar results and are both suited for the analysis of MDMA tablets in drug checking context. MIR has the advantage of no sample preparation, whereas the Narcoreader® device allows for a straightforward and direct quantitative analysis, an

TABLE 3 Comparison of the analytical methods based on different parameters.

	MIR	NIR	Raman	Narcoreader
Portable			x	x
Nondestructive	x	x	x	
No sample preparation	x	x	x	
Easy semiquantitative analysis				x
Sensitivity (%)	100	94	84	100
Specificity (%)	79	9	4	70
Precision (%)	91	69	66	88

Abbreviations: MIR, mid-infrared; NIR, near-infrared.

important factor in the risk evaluation of MDMA tablets. The current challenges on ecstasy tablets remain the monitoring of potential adulterants, but above all the variety of MDMA concentration in tablets circulating on the drug market. High-dosed tablets are at the base of MDMA-related adverse events, and the consultancy on dosage is hence an important element in drug checking.

Looking at the broader context of drug checking for harm reduction in event setting, the applicability of the Narcoreader® device is more limited due to its "one molecule at a time" characteristic. However, Narcoreader® applications were also described for cocaine[19] and heroin.[22] In the future, a combination approach where the sample is prepared in one buffer and applied to different electrodes of either a series of or an all-in-one Narcoreader® device might be worth investigating. Such application would be a powerful, fast, and easy tool, valuable for the future of drug checking in event settings. Currently, ATR–MIR is the more preferred technique as it allows for screening for a series of molecules if a good spectral library is available.[26] However, quantitative analysis is not so straightforward but can be solved by using MIR as initial screening and another technique for quantitation or by enabling the easy implementation and use of chemometric models in the software of the portable MIR spectrometers. Additionally, the use of MIR for screening and the Narcoreader® device as quantitative tool could be considered.

Both approaches show potential for the future of drug checking for harm reduction and could therefore be part of an approach combining different techniques. Though it should always be kept in mind that due to the high diversity of products on the illicit drug market, an ideal approach does not exist and that the choice of an approach or approaches will always be a trade-off to find the best compromise based on the context of the application.

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