UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Portable near infrared spectroscopy for the isomeric differentiation of new psychoactive substances

Kranenburg, R.F.; Ramaker, H.-J.; van Asten, A.C.

DOI
10.1016/j.forsciint.2022.111467

Publication date
2022

Document Version
Final published version

Published in
Forensic Science International

License
CC BY

Link to publication

Citation for published version (APA):
Kranenburg, R. F., Ramaker, H.-J., & van Asten, A. C. (2022). Portable near infrared spectroscopy for the isomeric differentiation of new psychoactive substances. *Forensic Science International*, *341*, Article 111467. https://doi.org/10.1016/j.forsciint.2022.111467

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)

Download date:05 Sep 2026

Forensic Science International 341 (2022) 111467

Contents lists available at ScienceDirect

Forensic Science International

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

Portable near infrared spectroscopy for the isomeric differentiation of new psychoactive substances

Ruben F. Kranenburg[a,b,*,1], Henk-Jan Ramaker[c], Arian C. van Asten[b,d,2]

[a] Dutch National Police, Unit Amsterdam, Forensic Laboratory, Kabelweg 25, Amsterdam 1014 BA, the Netherlands
[b] Van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Postbus 94157, Amsterdam 1090 GD, the Netherlands
[c] TIPb, Koningin Wilhelminaplein 30, Amsterdam 1062 KR, the Netherlands
[d] Co van Ledden Hulsebosch Center (CLHC), Amsterdam Center for Forensic Science and Medicine, Postbus 94157, Amsterdam 1090 GD, the Netherlands

ARTICLE INFO

Article history:
Received 19 July 2022
Received in revised form 1 September 2022
Accepted 15 September 2022
Available online 23 September 2022

Keywords:
Ring-isomers
Forensic drug analysis
Mobile detection
Cathinone analogues
MDMA analogues
Mephedrone
Chemometrics

ABSTRACT

Rapid and efficient identification of the precise isomeric form of new psychoactive substances (NPS) by forensic casework laboratories is a relevant challenge in the forensic field. Differences in legal status occur for ring-isomeric species of the same class, thus leading to different penalties and judicial control. Portable systems such as near-infrared (NIR) spectroscopy recently emerged as suitable techniques for the on-scene identification of common drugs of abuse such as cocaine, MDMA and amphetamine. This way, the overall forensic process becomes more efficient as relevant information on substance identity becomes available directly at the scene of crime. Currently, no NIR-based applications exist for the rapid, on-scene detection of NPS isomers. Herein, we present the differentiation of cathinone and phenethylamine-type NPS analogues based on their NIR spectrum recorded in 2 seconds on a portable 1350 – 2600 nm spectrometer. A prior developed data analysis model was found suitable for the identification of the methylmethcathinone (MMC) isomers 2-MMC, 3-MMC and 4-MMC. In 51 mixtures and 22 seized casework samples, the correct isomeric form was detected in all cases except for a few mixtures with an active ingredient content of 10 wt %. These results show the feasibility of on-site NPS detection as presumptive test performed directly at the scene of crime with a small size NIR-spectrometer. Additionally, in the illicit drug analysis laboratory the combination of NIR and GC–MS analysis might be suitable for robust identification of NPS isomers and analogues.
© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

On-scene illicit-drug detection by portable instrumentation is an important topic in forensics. A result directly available at the scene-of-crime can steer the investigation process and provide important information for decisions such as search warrants, arrests, and requests for laboratory analysis. Additionally, early information on substance identity increases the safety of investigators. Ultimately, a result admittable as court evidence generated on-site will significantly reduce the costs and will increase the speed of the forensic process as transport, administration and analysis in dedicated laboratory facilities can be avoided. Currently, forensic laboratories often apply a colorimetric test to gain a rapid first indication for the possible presence of narcotics. These chemical tests yield a specific color with traditional illicit-drugs, such as an orange-brown color when the Marquis reagent reacts with amphetamine [1]. The applicability of colorimetric spot tests is however restricted due to their limited selectivity and availability only for a confined set of traditional illicit drugs such as cocaine, heroin, MDMA and amphetamine [1,2].

Portable spectroscopic techniques are suitable to detect a wide range of different substances by a single instrument as long as the substances yield significantly different spectral signals. In the last decade, multiple spectroscopic platforms emerged for presumptive on-scene drug testing, such as Raman and Near-Infrared (NIR) spectroscopy [3–7]. Raman spectroscopy is reported as a technique capable of both common drug and NPS detection [8–10]. NIR is a particularly promising technique due to its potential for miniaturization [11,12], portability [13,14], implementation in a decentralized analytical platform [15–17], and its limited hindrance by fluorescent samples that are challenging when applying Raman spectroscopy

* Corresponding author at: Dutch National Police, Unit Amsterdam, Forensic Laboratory, Kabelweg 25, Amsterdam 1014 BA, the Netherlands.
E-mail address: ruben.kranenburg@politie.nl (R.F. Kranenburg).
[1] **ORCiD:** https://orcid.org/0000–0003-1472–3739
[2] **ORCiD:** https://orcid.org/0000–0001-5392–3982

https://doi.org/10.1016/j.forsciint.2022.111467
0379-0738/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

[3,4]. The applications of NIR spectroscopy within and outside of the forensic field were recently reviewed by Giussani et al. [11] Multiple recent studies specifically reported on the applicability of NIR spectroscopy for presumptive drug testing as a possible replacement for colorimetric spot tests due both to its more generic spectral nature and the elimination of chemicals and consumables required for testing [15,18–21]. It is noteworthy that various (portable) NIR spectrometers differ in resolution and the wavelength range in which they operate and wise sensor selection is required for specific forensic applications [7,22]. In earlier work, our group showed that NIR spectrometers operating above 1000 nm and up to 2600 nm are optimal for drugs of abuse detection due to specific spectral features within this range for a broad set of psychoactive compounds of interest [20,22].

However, the influx of over 1000 different new psychoactive substances (NPS) in the last decade significantly impacted the drugs of abuse market and the analytical requirements of forensic drug testing laboratories worldwide [23]. NPS emerge as uncontrolled analogues of illicit drugs that have similar psychoactive properties. The pharmacological properties and toxicity of these novel substances are often unknown and this leads to severe health issues and deaths among consumers [24]. Additionally, forensic laboratories face challenges in NPS analysis due to closely related molecular structures (*e.g.* ring-isomers, positional isomers) that lead to almost similar analytical characteristics (*e.g.* similarities in retention time and mass spectrum). This is further complicated by differences in legal control that may lead to different penalties for isomeric analogues. For example, in The Netherlands 4-methylmethcathinone (4-MMC, mephedrone) is a list 1 'hard drug' controlled substance since 2012, its isomer 3-methylmethcathinone (3-MMC) is since 2021 controlled as a list 2 'soft drug' leading to a lower maximum penalty for possession or trade, and 2-methylmethcathinone (2-MMC) currently is an unregulated substance [25]. Failure to confidently identify the correct isomeric form may thus have severe judicial consequences such as erroneous convictions.

The increased chemical diversity and complexity encountered in case work currently still requires dedicated laboratory-based analytical techniques for confirmatory NPS identification. Spectroscopy-based detection techniques are particularly suitable for ring-isomeric differentiation due to highly discriminating spectral signals for the ortho-, meta- and para-isomers. Two main spectroscopy-based techniques used in the field of NPS ring-isomer differentiation are gas chromatography – infrared spectroscopy (GC–IR) [26–30] and GC – vacuum ultraviolet spectroscopy (GC–VUV) [31–35]. Another technique successfully applied for NPS isomeric differentiation is infrared ion spectroscopy (IRIS) [36,37]. Conventional mass spectrometry (MS) based approaches are more challenging for isomeric differentiation due to similarities in both nominal mass and fragmentation pattern of NPS ring isomers. Since GC–MS has been the golden standard technique for illicit drug identification in forensic practice, most forensic laboratories have extensive experience utilizing this technique. Additionally, this may regularly be the only technique available within smaller high-volume casework laboratories. To evade the investment in new instrument hardware, various approaches using traditional GC–MS methods with slight modifications were introduced. These include softer ionization techniques [35,38–40], chemical derivatization [28,41,42] and the application of chemometric approaches on mass spectra analyzed by conventional GC–MS instruments [40,43–46]. The paramount benefit of the latter is that no additional investment in laboratory infrastructure, analytical instrumentation and employee expertise is required. However, the lack of both extensive validation and routine software platforms to perform these advanced calculations currently still limits its usability in forensic casework laboratories. Bottomline, forensic laboratories currently need to invest in sophisticated instrumentation or data analysis techniques to maintain the required robustness of chemical identification of a continuously expanding number of psychoactive compounds encountered in street samples.

Although some studies have reported on the use of NIR spectroscopy for NPS detection, none of these specifically focused on the differentiation of closely related NPS analogues [18,47–49]. Therefore, the central research question of this study is whether challenging NPS isomers can sufficiently be differentiated by means of rapid NIR spectroscopic analysis on a portable spectrometer. Mixtures and casework samples were analyzed on a portable NIR spectrometer (sensor size 2×2 x 0.5 cm) operating in the relatively broad 1300–2600 nm wavelength range. Our results show that the NPS isomers yield sufficient spectral features to allow differentiation of even challenging closely related analogues and isomers. An analytical scheme incorporating both portable NIR (to elucidate the ring-isomeric form *e.g.* ortho, meta or para substituted) and GC–MS (to identify the NPS class *e.g.* MMC) may thus allow for unequivocal identification. This way, additional analysis using advanced analytical techniques or data analysis can be avoided.

2. Materials and methods

2.1. Chemicals and casework samples

Reference substances of 2-fluoroamphetamine HCl (2-FA); 3-fluoroamphetamine HCl (3-FA); 3-fluoromethamphetamine HCl (3-FMA); 4-fluoromethamphetamine HCl (4-FMA); 2-methylethcathinone HCl (2-MEC); 3-methylethcathinone HCl (3-MEC); 4-methylethcathinone HCl (4-MEC); 2,3-methylenedioxy-methamphetamine HCl (2,3-MDMA); 2,3-methylenedioxy-amphetamine HCl (2,3-MDA); 3,4-methylenedioxy-ethylcathinone HCl (3,4-ethylone) and 2,3-methylenedioxy-methcathinone HCl (2,3-methylone) were obtained from Cayman Chemical Company (Ann Arbor, MI, USA). 4-Fluoroamphetamine HCl (4-FA); 2-fluoromethamphetamine HCl (2-FMA); 2-methylmethcathinone HCl (2-MMC); 3-methylmethcathinone HCl (3-MMC); 4-methylmethcathinone HCl (4-MMC); 3,4-methylenedioxy-amphetamine HCl (3,4-MDA); 3,4-methylenedioxy-methamphetamine HCl (3,4-MDMA); 3,4-methylenedioxy-methcathinone HCl (3,4-methylone) and 3,4-methylenedioxy-ethylamphetamine HCl (3,4-MDEA) were obtained from the Amsterdam Police Laboratory and originated from high purity casework samples as confirmed by the laboratory's validated analytical methods.

Mixtures of 2-MMC, 3-MMC, 4-MMC and 4-MEC with the tablet filler microcrystalline cellulose were prepared from high purity casework samples obtained from the Amsterdam Police. Microcrystalline cellulose Avicel® PH-101 was purchased from Merck (Darmstadt, Germany). Binary mixtures of each drugs with Avicel were prepared from 10 wt% to 100 wt% in steps of 10 wt% (as HCl salts) by weighing proportional amounts of each substance up to a total of 100 – 120 mg. Including a 0 wt% (pure microcrystalline cellulose) sample, this led to a set of 41 samples. Additionally, a set of 10 mixtures of two drug isomers was prepared at the given ratios in wt%: 2-MMC: 3-MMC (50:50); 2-MMC: 3-MMC (75:25); 2-MMC: 4-MEC (50:50); 2-MMC: 4-MEC (75:25); 2-MMC: 4-MMC (50:50); 3-MMC: 4-MEC (50:50); 3-MMC: 4-MEC (75:25); 3-MMC: 4-MMC, (50:50); 3-MMC: 4-MMC (75:25); 4-MMC: 4-MEC (50:50). All mixtures were prepared by grinding the powders in a mortar.

A total of 22 casework samples seized between 2020 and 2022 were provided by the Amsterdam Police. These samples were all identified as containing either an MMC or MEC isomer by the ISO 17025 accredited routine GC–MS based methods of this laboratory. Additionally, the correct isomeric form was identified by Fourier transform infrared spectroscopy (FTIR) and a dedicated GC–MS-based isomeric test following derivatization as reported in earlier work [42].

2.2. Instrumentation and data analysis model

All reference substances, mixtures and casework samples were stored and analyzed in 4-mL borosilicate glass vials with a 15 mm diameter (VWR, Amsterdam, The Netherlands). Reference substances and the set of casework samples were also analyzed in plastic LDPE reclosable bags by placing the plastic bag containing the material directly on top of the sensor. Samples were analyzed on the Powder Puck analytical platform that includes a NeoSpectra sensor (Si-WARE, Cairo, Egypt) operating in the 1300 – 2600 nm range with a 16 nm resolution (at 1500 nm). A single analysis takes approximately 2 s. The second derivatives of the spectral signals were processed by the calibration-friendly multi-stage linear discriminant analysis (LDA) – net analyte signal (NAS) identification model described elsewhere [20]. In this study, a dedicated model was used by recording reference spectra of NPS in 15-fold and storing them in dedicated spectral libraries. These libraries are the only prerequisite to calibrate a new model. After processing scanned sample data, a model result and a similarity score were obtained for every analyzed spectrum. The model result consists of both compound name(s) and predicted concentration(s) of the identified substances. The similarity score is the overall fit score of the measured spectrum against the best combination of spectra in the library. For example, the 40 wt % 3-MMC - 60 wt% microcrystalline cellulose mixture was predicted as: '3-MMC (38%) + Cellulose (57%)' with a similarity score of 0.95. Similarity scores < 0.70 are considered inconclusive. Similarity scores between 0.70 and 0.80 are used for indicative purposes only and are considered as (false) negative for the purpose of this study. Samples were all analyzed in triplicate by placing the glass vials or plastic bags containing the material on top of the NIR sensor. Vials were shaken and bags were repositioned between the individual measurements. Three different library designs were used throughout this study. In library option 1, reference spectra of 2-MMC, 3-MMC, 4-MMC, 2-MEC, 3-MEC, 4-MEC, microcrystalline cellulose, and low-density polyethylene (LDPE) plastic were used for spectral identification and a decision rule was implemented to exclude combinations of multiple drug substances in mixture detection. In library option 2, the same reference spectra were supplemented with the spectrum of hydrated 4-MMC (see Section 3.4) and the consideration of multiple drug substances in a mixture was included. In library option 3, the same full spectral set as in option 2 was used, but with the restriction of identifying only one drug substance in the mixture. Results on all three library options are reported in the Supplemental Information for all analyses in this study. The results of the most relevant library option are shown in black, others are shown in gray.

3. Results

3.1. Differences in NIR spectra of closely related analogues

Reference NIR spectra of the isomeric sets 2-MMC, 3-MMC, and 4-MMC as well as 2-MEC, 3-MEC, and 4-MEC are shown in Fig. 1. As expected, the overall shape of the spectra is much more similar for these closely related substances compared to common drugs of abuse [20,22]. However, differences can already be spotted in the normalized raw spectra upon more detailed visual inspection. Distinguishing features are visible especially in the 1600 – 1800 nm, 2200 – 2600 nm wavelength range and the relative intensity and location of the shoulder peak at ~2150 nm. It must be noted that the NIR data is further preprocessed as part of the identification model. Derivative spectra is commonly calculated to emphasize spectra features such as peak differences. In the chemometric data analysis performed in this study, a second derivative spectrum is processed by the model. Fig. S1 in the Supplemental Information shows the second derivative spectra of 5 replicate scans of the isomeric cathinone sets in Fig. 1. These plots clearly show compound-specific diagnostic spectral features for all individual cathinone substances. Interestingly, no clear correlation is visible between the methylated and ethylated isomeric pairs (*e.g.* 2-MMC and 2-MEC) as is the case for most spectroscopic techniques such as VUV [31,32], FTIR [26] and IRIS [36]. This can possibly be explained by the more generic nature of the bands in the NIR spectrum originating from various overtones and combination-bands of molecular vibrations. Overall, these results show the potential of NIR to differentiate both NPS ring isomers and alkyl chain analogues.

Similar to the cathinone isomers, differences in NIR spectrum can be found for the amphetamine-type NPS analogues of conventional ecstasy (*i.e.* 3,4-MDMA). Fig. 2 presents the NIR spectra of seven drugs that are closely related to 3,4-MDMA with the NIR spectrum of 3,4-MDMA itself as overlay. The minor differences in molecular structure of these analogues towards 3,4-MDMA are depicted by the orange shade in the structures shown in Fig. 2. In line with the cathinones, both the 1600 – 1800 nm and 2200 – 2600 nm wavelength range yield diagnostic differences in the NIR spectrum. Similarly, the second derivative spectra (Fig. S2) clearly shows distinguishing spectral features for all individual analogues demonstrating the potential of NIR analysis for their differentiation. It must be noted that the presented spectra originate from the anhydrous hydrochloride salts of the drug. Especially for 3,4-MDMA HCl is it known that multiple polymorphous crystalline forms with a different degree of hydration exist [50,51]. The crystalline form commonly encountered in The Netherlands is the hydrated form that shows a notable spectral peak at 2020 nm [22,52,53]. Fig. S3 in the Supplemental Information shows the same MDMA-analogue spectra as Fig. 2, but now overlayed with the spectrum of hydrated 3,4-MDMA HCl. The corresponding second derivative spectra can be found in Fig. S4. The large differences between the hydrated and anhydrous crystalline form illustrate that care needs to be taken in the development of NIR-based models and libraries for substances that exist in various crystalline forms (*e.g.* salt forms, hydration polymorphisms).

3.2. NIR-based identification of cathinones in diluted samples

Methylmethcathinone-isomers were selected as the candidate set in the mixture study due to their relatively high occurrence in forensic casework [54] and their remarkable judicial status in The Netherlands where each isomer is subject to a different legal condition [25]. The compound 4-MEC (a list I controlled substance) was added to the set in order to assess potential mix-up between the ethylated (*i.e.* 4-MEC) and methylated (*i.e.* 4-MMC) analogues by the model.

The 41 binary mixtures of 2-MMC, 3-MMC, 4-MMC and 4-MEC in microcrystalline cellulose (tablet filler), ranging from 0 wt% to 100 wt% in steps of 10 wt% as described in **2.1** were all analyzed in triplicate on the NIR spectrometer. Spectra were subsequently processed by the chemometric models described in **2.2** using a library that consists of spectra of all MMC and MEC isomers (six in total), and microcrystalline cellulose. The obtained individual identification results for all samples are shown in Table S1 in the Supplemental Information. From all 120 scans of drug-containing samples, 119 scans were correctly identified as containing the exact isomer as present in the mixture. For all samples originating from mixtures with a drug-content of 20 wt% up to 80 wt%, both the correct cathinone isomer and the presence of microcrystalline cellulose was predicted. (*e.g.* for the first replicate of the 20 wt% 4-MMC sample the result '4-MMC (23%) + Cellulose (73%)' with a similarity score of 0.96 was obtained.) The only erroneous result originated from a sample with a 10 wt% 4-MEC content. Herein, one of the three replicate scans was mistakenly identified as '2-MEC (11%) + Cellulose (86%)' with a 0.98 similarity score. The same spectra were also

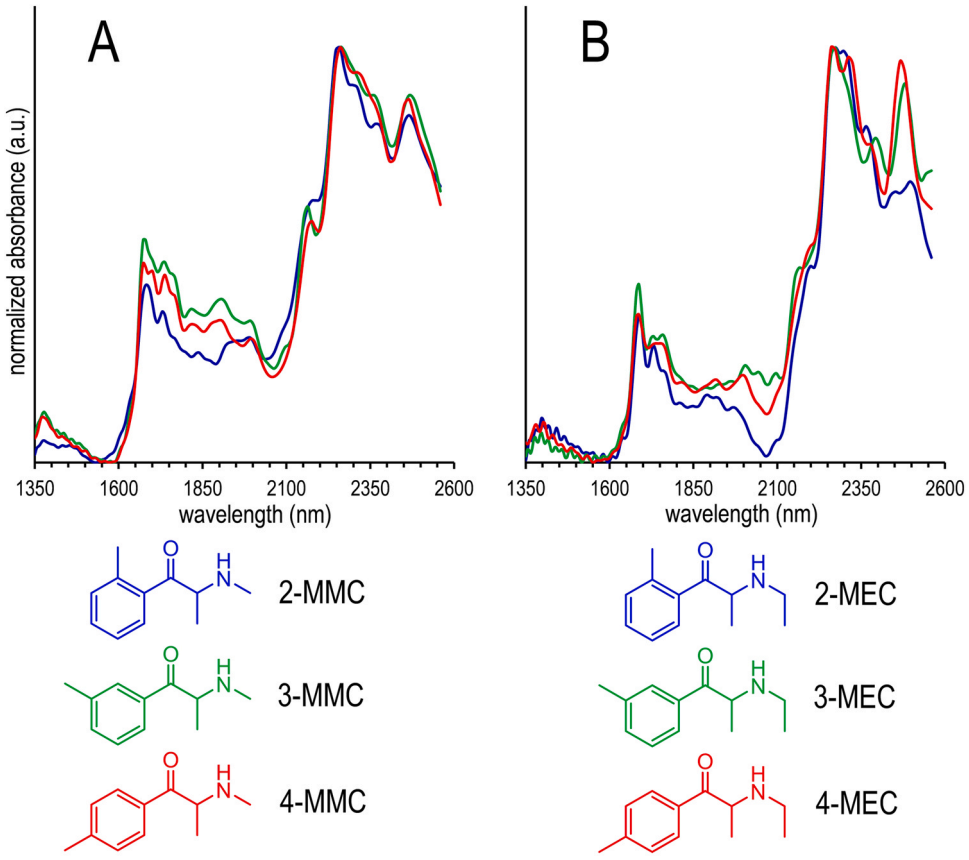

Fig. 1. Normalized NIR spectra of two sets of cathinone isomers. Panel A: 2-MMC (blue), 3-MMC (green), 4-MMC (red); panel B: 2-MEC (blue), 3-MEC (green), and 4-MEC (red).

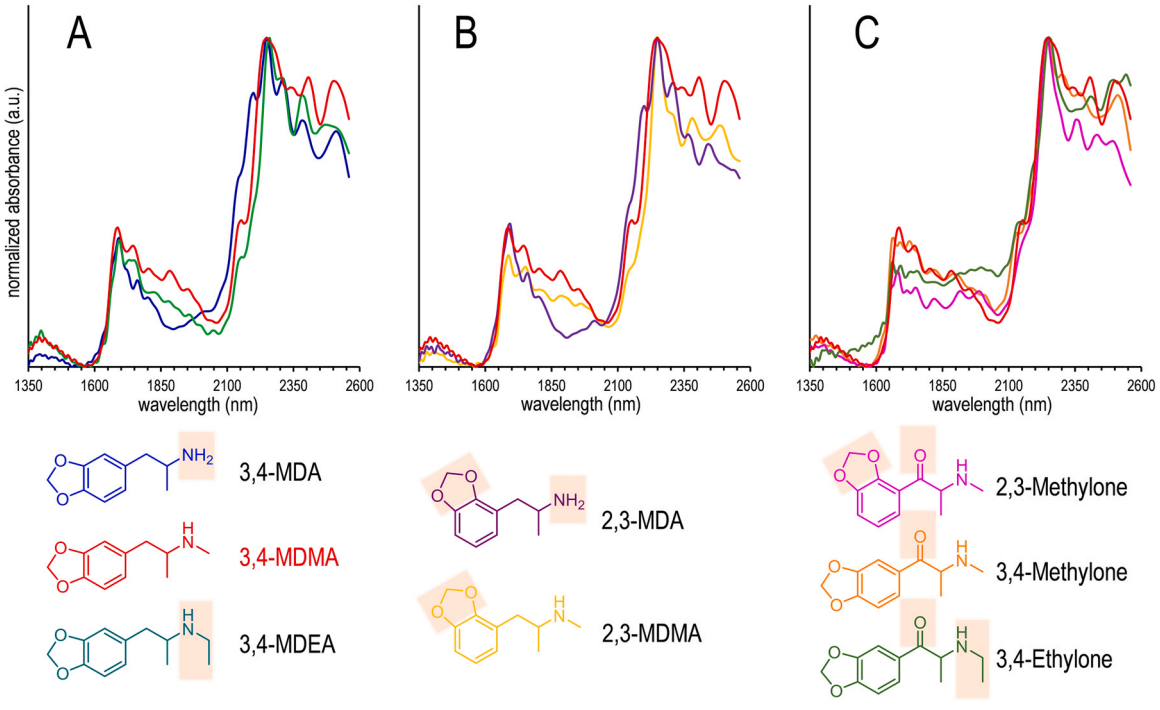

Fig. 2. Normalized NIR spectra of MDMA analogues in overlay with 3,4-MDMA HCl (anhydrous) in red in all panels. Panel A: 3,4-MDA (blue), 3,4-MDEA (green); panel B: 2,3-MDA (purple), 2,3-MDMA (yellow); panel C: 2,3-methylone (pink), 3,4-methylone (orange), and 3,4-ethylone (dark green). The orange shade in the molecular structures emphasizes the difference with MDMA. Note that the spectra of the commonly encountered hydrated 3,4-MDMA HCl form is not shown. A similar figure with hydrated MDMA can be found as Fig. S3 in the Supplemental Information.

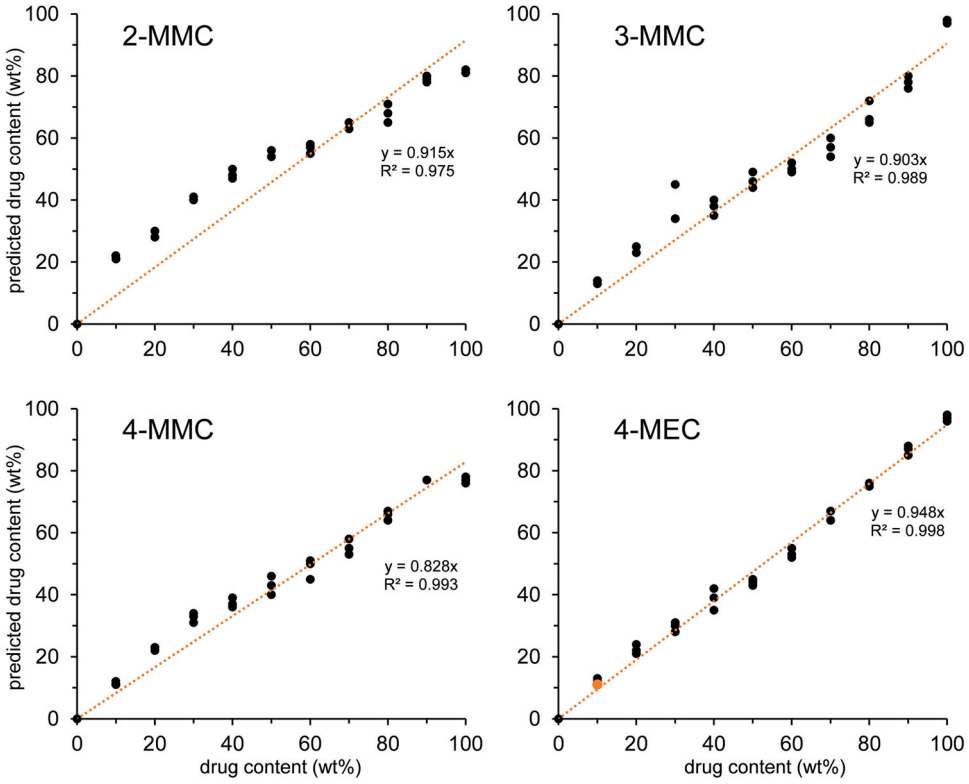

Fig. 3. Plots of the predicted concentration of cathinone by the NIR-based model *versus* the actual drug content of the binary mixtures with microcrystalline cellulose. Black dots are correctly identified samples. The orange dot is the single misidentification of 10 wt% 4-MEC as 2-MEC. The trendline is based on the correctly identified samples only.

processed on library options 2 and 3, that focus on drug-mixture detection (see **3.3**) and the appearance of different hydrated forms (see **3.4**). Similar results were obtained for these library options (Table S1, results in gray) with only slight differences for the low-level drug samples.

Besides an identity, the chemometric model also predicts a concentration from the best fit to ascribe the spectral signal. This concentration should be taken as an indication since the model is only trained on pure reference spectra. Fig. 3 shows the predicted concentrations of 2-MMC, 3-MMC, 4-MMC and 4-MEC in their respective cellulose mixtures plotted against the actual concentrations. The predicted model concentrations are in good accordance with the true mixture concentrations. Note that only a very small volume fraction of the mixture is actually sampled at the focus area of the NIR sensor. It is highly likely this volume fraction does not represent the true mixture concentration. This explains the differences between precited and actual concentrations as shown in Fig. 3. The orange dot in Fig. 3 depicts the single misidentification of 10 wt% 4-MEC. It is evident from this plot and the results in Table S1 that erroneous results are generated at lower actual concentrations (10 wt%). This insight may be useful to further tune the performance of the model with respect to false positives and false negatives by *e.g.* implementing a cut-off threshold on the predicted concentration [14]. Since seized forensic casework samples typically contain active ingredient levels well above 20 wt%, such a threshold may reduce false positive results without increasing the number of false negatives due to the rarity of low level samples. However, in other applications and settings, low levels might occur more frequently. It is not expected for instance that the presented NIR methodology will work effectively when these drugs are added at moderate levels to food stuffs.

Overall, these results indicate that differentiation of ring-isomeric cathinones by NIR spectra is well possible. This requires a spectral library that accurately represents the actual composition of the samples in order to correctly perform the mixture deconvolution.

3.3. NIR-based identification of cathinones in drug-isomer mixtures

Due to the spectral similarities, a more challenging test for the possibilities of NIR-based mixture detection is the analysis of samples that consist of mixtures of the isomers. As a proof of principle, a set of 10 binary mixtures of 2-MMC, 3-MMC, 4-MMC and 4-MEC in 50:50 and 25:75 wt% ratios was prepared, analyzed and processed by the software. Fig. 4 shows the obtained spectra for the 3-MMC: 4-MMC mixtures. The zoom on *e.g.* the 2100 – 2400 nm range (panel B) showed that despite the minor overall differences, the spectra of the mixtures are recognizable as combinations of the pure substances. This effect is even more pronounced in the second derivative spectra (panel C). One of the model decision rules in the processing software involves combinations of drug substances. That is, only a single drug substance can be used to predict the composition of an unknown powder. The reason for this is morefold: the rare occurrence of drug-mixtures in casework, the fact that for generic drugs the presence of a single controlled active ingredient will already lead to an illicit status of the sample and to prevent erroneous results by the model attributing unknown residual signals to (a mixture of) various drug substances. Nonetheless, for the purpose of this specific experiment with deliberately prepared drug mixtures, the possibility to detect multiple drug substances in a single sample was enabled through library option 2. Table S2 in the Supplemental Information gives the individual results of all replicate scans. For clarity and to gain insight in the model performance, the results on all three library options are presented for all samples in this study. However, due to the inability of library options 1 and 3 to detect drug-mixtures, these results are less relevant for this set. Overall, the presence of both cathinones in the mixtures was correctly identified in 29 out of the 30 spectra with similarity scores ≥ 0.92. For one out of the three replicate scans of

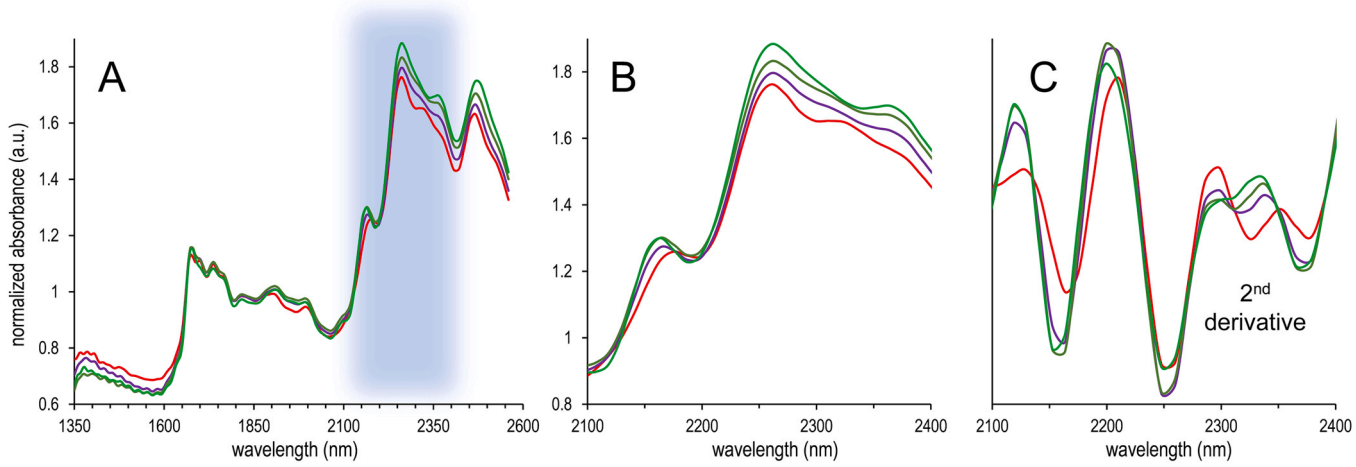

Fig. 4. NIR spectra of pure 3-MMC (green), a 75:25 mixture of 3-MMC and 4-MMC (dark green), a 50:50 mixture of 3-MMC and 4-MMC (purple), and pure 4-MMC (red). Panel A depicts the full spectrum; panel B shows a zoom of the 2100 – 2400 nm range depicted by the blue shade in panel A; panel C shows the second derivative spectrum of the 2100 – 2400 nm range.

sample '2-MMC (75 wt%): 3-MMC (25 wt%)' only the presence of most abundant 2-MMC was detected while the presence of 3-MMC was not reported. It is unknown if this error is caused by spectral limitations or due to inhomogeneity of the sample. These results nevertheless show that NIR-based detection of NPS mixtures is well possible. Care must be however be taken by allowing the combination of two drugs in a sample. This may slightly increase erroneous results as can be seen by the 'library option 2′ results on the other sample sets. For example, 30 wt% 4-MMC in cellulose was mispredicted as a mixture of 4-MMC (23%), 2-MMC (15%) and Cellulose (60%) using this library (Table S1).

3.4. Identification of cathinone isomers in casework samples

The performance of the NIR-based identification model was further assessed on 22 seized forensic casework samples for which the presence of a cathinone isomer was established by GC–MS analysis. This set of samples contained both crystalline powders -the most common form of appearance of cathinone samples- and tablets in various colors and shapes. The results of all individual analyses (scanned in glass vials) can be found in Table S3, library option 1, in the Supplemental Information. Summarized, the correct substance and isomeric form were identified in all 2-MMC, 3-MMC and 4-MEC containing samples with typical similarity scores above 0.90. Spectra of these casework samples in comparison with the present isomer are shown in Fig. 5. These convenient results show that identification of the precise isomeric form in relatively pure seized casework samples is possible using a rapid and non-destructive NIR-analysis. Only for 4-MMC, in 2 out of the 6 casework samples the model was inconclusive on the presence of a cathinone-isomer. The spectra of these samples significantly deviated from the 4-MMC reference spectra as depicted by the asterisk in the 4-MMC panel in Fig. 5. The strong signal around 2000 nm indicates the presence of crystalline water. It is therefore hypothesized that both an anhydrous and hydrated polymorphous crystalline structure of 4-MMC HCl exist in casework samples, similarly as for MDMA HCl [50,51,53]. This hypothesis was tested by heating the perceived hydrated 4-MMC HCl casework sample MM006 at 150 °C for 3 h in an attempt to remove the coordinated water from the crystalline structure. Fig. 6 presents the NIR-spectra of both reference 4-MMC, the original sample MM006 and the spectrum after drying. The spectral signals around 1400 nm and 2000 nm, both attributed to water, disappeared after heating. When processed on the identification model, the dried MM006 sample was identified as 4-MMC with similarity scores between 0.86 and 0.90. Fig. S5 also confirms the presence of water of crystallization and its removal after heating visible in the infrared spectra. The water of crystallization is visible as a peak at ~3500 cm^{-1}.

This insight in the existence of a hydrated 4-MMC HCl polymorph yielding a significantly different NIR-spectrum than the anhydrous analogue, demonstrates the importance of library design in NIR-based spectral modelling. In line with different salt and base forms of common drugs that yield different NIR-spectra, attention also need to be given to the possible existence of hydrated polymorphs and their inclusion in the spectral library. As a proof of principle, the spectrum of the hydrated 4-MMC HCl sample MM006 was added to the cathinone library and all spectra from the casework samples were reprocessed on this library (library option 3). This way, the formerly inconclusive sample MM018 was also identified as 4-MMC HCl hydrate with both a predicted 99% purity and a 0.99 similarity score for all three replicates. Interestingly, with the additional 4-MMC spectrum added to the library, all other samples remained correctly identified. No false positives were thus introduced by this approach. All individual identification results on the cathinone spectral library including both 4-MMC forms can be found in Table S3, for library option 3, in the Supplemental Information.

3.5. Cathinone casework samples analyzed through plastic bags

Earlier work showed the possibilities for NIR-detection of regular drugs-of-abuse samples directly through LDPE plastic bags [20]. As forensic drugs samples are commonly seized in plastic bags, analysis of the materials directly through the packaging is both convenient and safe for the operator. All casework samples described in **3.4** as well as pure reference materials were additionally analyzed through an LDPE plastic reclosable bag as a proof of principle. The results for all three replicate scans of all samples can be found in Table S4 in the Supplemental Information. When processed by library option 3 (single drug compound, both 4-MMC types included in library) the best results were obtained. In all cases, the obtained spectrum was identified as a mixture of a cathinone drug and LDPE-plastic. In 72 out of the 78 scans, the correct isomer was detected (in combination with plastic). The remaining 6 scans were inconclusive because the similarity score was below the 0.80 threshold. For 5 out of 6 of these scans, the best match (score between 0.70 and 0.80) still indicated 4-MMC as the correct isomer. In the remaining scan, the best match (score 0.78) was for 4-MEC in combination with LDPE plastic. These results show that NIR-based detection of drugs in plastic bags is

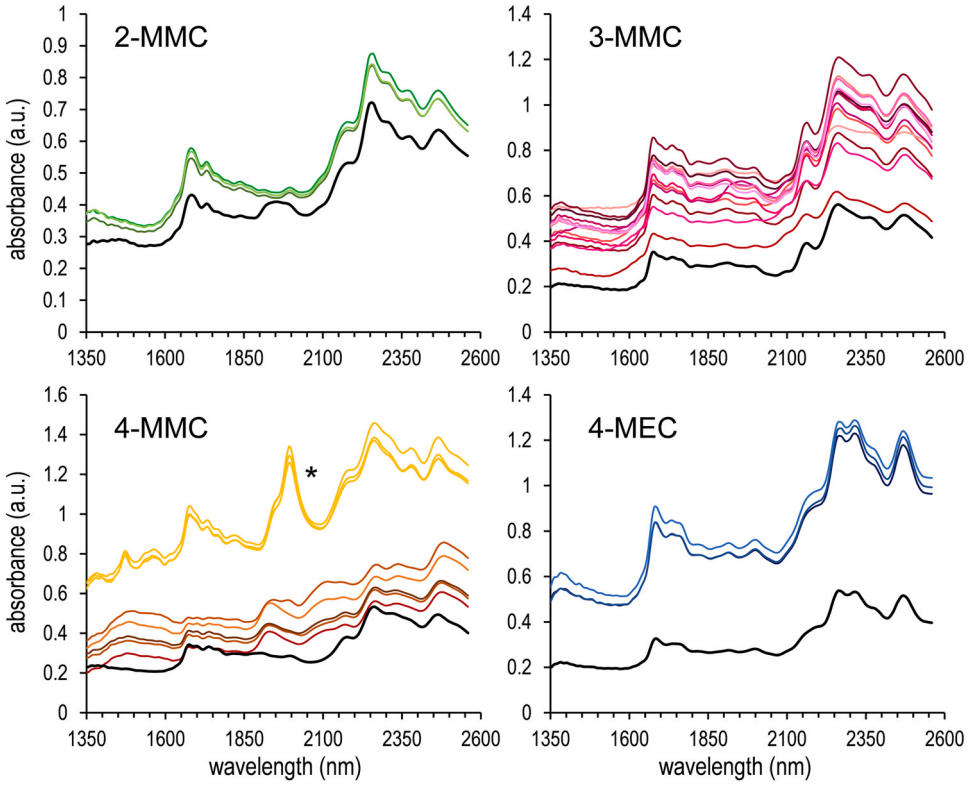

Fig. 5. NIR spectra of seized casework samples (colored plots) with the reference spectra of the present cathinone isomer in black. The asterisk marks sample MM006 that was identified as a hydrated crystalline form of 4-MMC HCl.

possible, even for these closely related cathinones. It must however be noted that less pure samples such as crushed tablets were clearly more challenging than relatively pure crystalline samples. Since the plastic sheet absorbs a significant part of the NIR radiation, less energy remains available to be absorbed by other substances such as drugs. This challenges the analysis of drug samples contained in plastic bags. For crushed tablets in plastic bags, both the lower similarity scores and high percentage of unexplained signal (*i.e.* the sum of predicted percentages of the detected substances is well below 100%) show the limitations of this approach. It is also noteworthy that microcrystalline cellulose was not detected in the samples in plastic bags, although its presence was confirmed (and is expected) in tablet samples.

4. Conclusions

Despite minor differences in molecular structure, analysis on a portable NIR spectrometer operating in the 1350 – 2600 nm wavelength range was suitable for NPS isomeric differentiation. Although spectral differences for NPS analogues and isomers are smaller compared to conventional drugs-of-abuse, sufficient spectral differences exist to facilitate and support correct identification. The previously developed data-analysis approach based on LDA (Linear Discriminant Analysis) and NAS (Net Analyte Signal) for spectral identification of mixtures was found suitable for cathinone isomeric differentiation. Sets of cathinone-containing mixtures and actual casework samples were analyzed leading to a 100% correct identification of the precise isomeric form in seconds for samples consisting of compounds present in the spectral reference library and containing more than 10 wt% of the psychoactive substance of

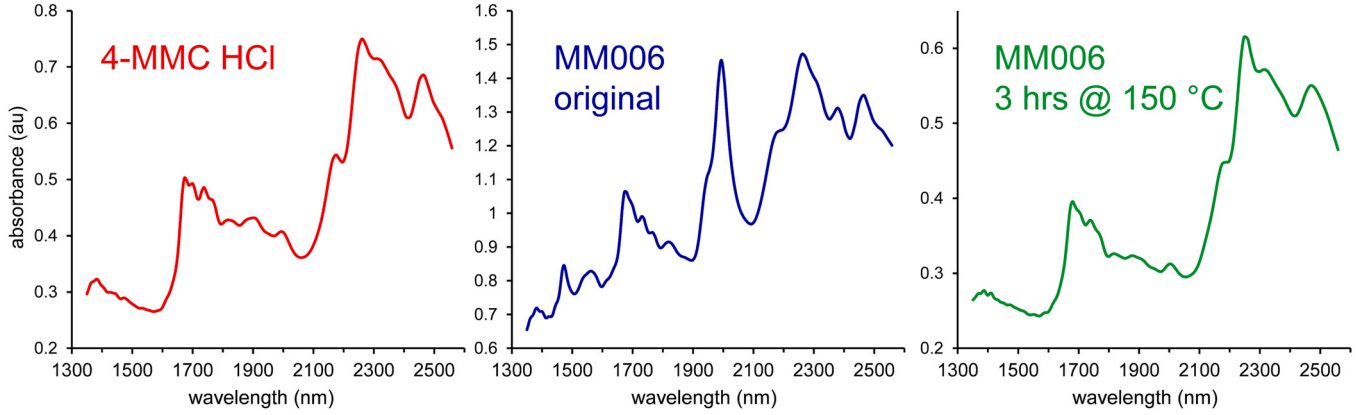

Fig. 6. NIR spectra of the 4-MMC HCl reference, sample MM006, and sample MM006 after 3 h of heating at 150 °C.

interest. Additionally, the results show that NIR-based identification of the correct isomer is possible for high-purity samples analyzed directly though their plastic packaging.

Mixtures of two cathinone isomers or analogues were also correctly predicted by the identification model. This shows that minor spectral differences suffice to detect and deconvolute NPS. The option to include the detection of multiple drug substances as a mixture in a single sample comes at the costs of increasing the risk of misidentification. This is due to the myriad of combinations possible to explain the spectral features. NPS mixture detection is therefore only suggested in specific situations. E.g. when prior knowledge on the probability to encounter mixtures is available in advance, or as an additional check for the presence of drug isomer mixtures in a laboratory-based analytical scheme. This limits the possibilities for robust on-scene isomeric identification by NIR alone.

Rapid identification of both the substance and its isomeric form is important for routine forensic drug laboratories as the legal status (controlled *vs*. uncontrolled) may differ among isomeric forms. Currently, routine casework laboratories perform GC–MS analysis in automated sequences for efficient analysis. Routine GC–MS screening methods are unable to confidently identify the isomeric form due to similarities in mass spectra. Therefore, these laboratories need to perform inefficient additional analysis on expensive dedicated instrumentation such as GC–IR or GC–VUV for confirmation. This study shows that a rapid (2 s) NIR-analysis is able to identify the ring-isomeric form in high-purity samples as demonstrated for the MMC-analogues. Since routine casework laboratories start their workflow with weighing and sub-sampling the material for GC–MS analysis, it is little effort to additionally scan the sample on a portable NIR-sensor located at the workplace. Currently, most casework laboratories also perform an indicative colorimetric test to obtain a rapid first indication of the material's identity and for additional conformation in their analytical scheme. The emergence of NPS for which no colorimetric test is available already fueled the implementation of spectroscopic tests (Raman, infrared) for this purpose. Since rapid and reliable NIR-based drug detection is possible for a vast amount of drugs [20,53], replacement of the colorimetric tests by NIR is envisioned. This way, the obtained NIR-data can not only be used for (preliminary) identification of the main drug but also to predict the isomeric form in case an NPS is detected. The class of this NPS (*e.g.* MMC or MEC) is than later on in the process confirmed by GC–MS. It must be noted that we do not intent to propose confirmatory NPS identification based on NIR-data alone. The sole purpose of the NIR analysis is to further differentiate among the ortho-, meta- or para-isomer of the class analyzed by GC–MS since this technique has limited selectivity for cathinone ring-isomeric differentiation [31,40,43].

As a possible future development, NIR-analysis can also be performed on-scene by police officers directly after they encounter the substance. The small size, portable nature and easy connection to cloud-based data systems allow for the generation of a (preliminary) identification result directly at the scene-of-crime (*e.g.* visible on the screen of the police officer's smartphone). Decent validation and a wise selection of identification thresholds may lead to three different outcomes from on-scene instruments: I) drug identified (high purity), no laboratory confirmation needed; II) no drug detected; and III) inconclusive, possible drug (mixture) detected, laboratory analysis needed. Given the minor spectral differences between analogues and the challenges in complex mixtures, it is foreseen that for NPS additional laboratory analysis is required, although subsequent data-analysis of the previously recorded NIR-spectrum on a dedicated NPS model may already provide a first indication for the laboratory staff to aid efficient analysis. The use of different reference libraries and decision threshold and rules, demonstrate how the knowledge and experience of the forensic illicit drug expert can be used to optimize the performance of NIR-based on-site, instant identification of suspect samples. As the illicit drug market is dynamic, with the regular introduction of new psychoactive compounds, additives and formulations, this expert knowledge needs to be exploited continuously to keep the models up-to-date and the results of the on-site analysis trustworthy.

CRediT authorship contribution statement

RFK: Investigation, Conceptualization, Methodology, Project administration, Data curation, Writing – original draft; HJR: Software, Modelling, Writing – review & editing; ACvA: Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: HJR is managing partner at TIPb, the company commercializing the Powder Puck sensor. The other authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Laboratory staff of the Police laboratory in Amsterdam is acknowledged for their help in selecting suitable casework samples. The illicit-drug department of the Netherlands Forensic Institute and members of the Dutch governmental institutes council are gratefully acknowledged for discussions and insights on the water of hydration experiments. The UvA forensic PhD team at the EAFS 2022 meeting in Stockholm is acknowledged for fruitful discussions and motivational support during the writing process.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.forsciint.2022.111467.

References

[1] M. Philp, S. Fu, A review of chemical "spot" tests: a presumptive illicit drug identification technique, Drug Test. Anal. 10 (2018) 95–108, https://doi.org/10.1002/dta.2300
[2] E. Cuypers, A.-J. Bonneure, J. Tytgat, The use of presumptive color tests for new psychoactive substances, Drug Test. Anal. 8 (2016) 136–140, https://doi.org/10.1002/dta.1847
[3] R.A. Crocombe, Portable spectroscopy, Appl. Spectrosc. 72 (2018) 1701–1751, https://doi.org/10.1177/0003702818809719
[4] W.R. de Araujo, T.M.G. Cardoso, R.G. da Rocha, M.H.P. Santana, R.A.A. Muñoz, E.M. Richter, T.R.L.C. Paixão, W.K.T. Coltro, Portable analytical platforms for forensic chemistry: a review, Anal. Chim. Acta 1034 (2018) 1–21, https://doi.org/10.1016/j.aca.2018.06.014
[5] G.S. Bumbrah, R.M. Sharma, Raman spectroscopy – basic principle, instrumentation and selected applications for the characterization of drugs of abuse, Egypt. J. Forensic Sci. 6 (2016) 209–215, https://doi.org/10.1016/j.ejfs.2015.06.001
[6] R.F. Kranenburg, J. Verduin, R. de Ridder, Y. Weesepoel, M. Alewijn, M. Heerschop, P.H.J. Keizers, A. van Esch, A.C. van Asten, Performance evaluation of handheld Raman spectroscopy for cocaine detection in forensic case samples, Drug Test. Anal. 13 (2021) 1054–1067, https://doi.org/10.1002/dta.2993
[7] K.B. Beć, J. Grabska, C.W. Huck, Principles and applications of miniaturized near-infrared (NIR) spectrometers, Chem. – Eur. J. 27 (2021) 1514–1532, https://doi.org/10.1002/chem.202002838
[8] J. Calvo-Castro, A. Guirguis, E.G. Samaras, M. Zloh, S.B. Kirton, J.L. Stair, Detection of newly emerging psychoactive substances using Raman spectroscopy and chemometrics, RSC Adv. 8 (2018) 31924–31933, https://doi.org/10.1039/C8RA05847D
[9] A. Guirguis, S. Girotto, B. Berti, J.L. Stair, Identification of new psychoactive substances (NPS) using handheld Raman spectroscopy employing both 785 and 1064nm laser sources, Forensic Sci. Int. 273 (2017) 113–123, https://doi.org/10.1016/j.forsciint.2017.01.027
[10] H. Muhamadali, A. Watt, Y. Xu, M. Chisanga, A. Subaihi, C. Jones, D.I. Ellis, O.B. Sutcliffe, R. Goodacre, Rapid detection and quantification of novel psychoactive substances (NPS) using raman spectroscopy and surface-enhanced

raman scattering, Front. Chem. 7 (2019), https://doi.org/10.3389/fchem.2019.00412
[11] B. Giussani, G. Gorla, J. Riu, Analytical chemistry strategies in the use of miniaturised NIR instruments: an overview, Crit. Rev. Anal. Chem. 0 (2022) 1–33, https://doi.org/10.1080/10408347.2022.2047607
[12] R.F. Kranenburg, F. Ou, P. Sevo, M. Petruzzella, R. de Ridder, A. van Klinken, K.D. Hakkel, D.M.J. van Elst, R. van Veldhoven, F. Pagliano, A.C. van Asten, A. Fiore, On-site illicit-drug detection with an integrated near-infrared spectral sensor: a proof of concept, Talanta 245 (2022) 123441, https://doi.org/10.1016/j.talanta.2022.123441
[13] R. Deidda, F. Coppey, D. Damergi, C. Schelling, L. Coïc, J.-L. Veuthey, P.-Y. Sacré, C. De Bleye, P. Hubert, P. Esseiva, É. Ziemons, New perspective for the in-field analysis of cannabis samples using handheld near-infrared spectroscopy: a case study focusing on the determination of Δ9-tetrahydrocannabinol, J. Pharm. Biomed. Anal. 202 (2021) 114150, https://doi.org/10.1016/j.jpba.2021.114150
[14] R.F. Kranenburg, J. Verduin, Y. Weesepoel, M. Alewijn, M. Heerschop, G. Koomen, P. Keizers, F. Bakker, F. Wallace, A. van Esch, A. Hulsbergen, A.C. van Asten, Rapid and robust on-scene detection of cocaine in street samples using a handheld near-infrared spectrometer and machine learning algorithms, Drug Test. Anal. 12 (2020) 1404–1418, https://doi.org/10.1002/dta.2895
[15] F. Coppey, A. Bécue, P.-Y. Sacré, E.M. Ziemons, P. Hubert, P. Esseiva, Providing illicit drugs results in five seconds using ultra-portable NIR technology: an opportunity for forensic laboratories to cope with the trend toward the decentralization of forensic capabilities, Forensic Sci. Int. 317 (2020) 110498, https://doi.org/10.1016/j.forsciint.2020.110498
[16] R. Risoluti, G. Gullifa, A. Battistini, S. Materazzi, "Lab-on-click" detection of illicit drugs in oral fluids by MicroNIR–chemometrics, Anal. Chem. 91 (2019) 6435–6439, https://doi.org/10.1021/acs.analchem.9b00197
[17] R. Risoluti, S. Pichini, R. Pacifici, S. Materazzi, Miniaturized analytical platform for cocaine detection in oral fluids by MicroNIR/Chemometrics, Talanta 202 (2019) 546–553, https://doi.org/10.1016/j.talanta.2019.04.081
[18] S. Assi, A. Guirguis, S. Halsey, S. Fergus, J.L. Stair, Analysis of 'legal high' substances and common adulterants using handheld spectroscopic techniques, Anal. Methods 7 (2015) 736–746, https://doi.org/10.1039/C4AY02169J
[19] C. Liu, Y. Han, S. Min, W. Jia, X. Meng, P. Liu, Rapid qualitative and quantitative analysis of methamphetamine, ketamine, heroin, and cocaine by near-infrared spectroscopy, Forensic Sci. Int. 290 (2018) 162–168, https://doi.org/10.1016/j.forsciint.2018.07.008
[20] R.F. Kranenburg, H.-J. Ramaker, S. Sap, A.C. van Asten, A calibration friendly approach to identify drugs of abuse mixtures with a portable near-infrared analyzer, Drug Test. Anal. 14 (2022) 1089–1101, https://doi.org/10.1002/dta.3231
[21] M.C. Hespanhol, C. Pasquini, A.O. Maldaner, Evaluation of a low-cost portable near-infrared spectrophotometer for in situ cocaine profiling, Talanta 200 (2019) 553–561, https://doi.org/10.1016/j.talanta.2019.03.091
[22] R.F. Kranenburg, Y. Weesepoel, M. Alewijn, S. Sap, P.W.F. Arisz, A. van Esch, P.H.J. Keizers, A.C. van Asten, The importance of wavelength selection in on-scene identification of drugs of abuse with portable near-infrared spectroscopy, Forensic Chem. 30 (2022) 100437, https://doi.org/10.1016/j.forc.2022.100437
[23] United Nations Office on Drugs and Crime, Early Warning advisory on new psychoactive substances, (n.d.). ⟨https://www.unodc.org/LSS/Page/NPS⟩ (accessed February 5, 2022).
[24] M. Kraemer, A. Boehmer, B. Madea, A. Maas, Death cases involving certain new psychoactive substances: a review of the literature, Forensic Sci. Int. 298 (2019) 186–267, https://doi.org/10.1016/j.forsciint.2019.02.021
[25] Dutch Opium Act (Opiumwet), (n.d.). ⟨https://wetten.overheid.nl/BWBR0001941/2021-10-28⟩ (accessed February 18, 2022).
[26] R.F. Kranenburg, L.I. Stuyver, R. de Ridder, A. van Beek, E. Colmsee, A.C. van Asten, Deliberate evasion of narcotic legislation: Trends visualized in commercial mixtures of new psychoactive substances analyzed by GC-solid deposition-FTIR, Forensic Chem. 25 (2021) 100346, https://doi.org/10.1016/j.forc.2021.100346
[27] Y. Abiedalla, A.J. Almalki, J. DeRuiter, C.R. Clark, GC–MS and GC–IR analysis of methylenedioxyphenylalkylamine analogues of the psychoactive 25X-NBOMe drugs, Forensic Chem. 23 (2021) 100314, https://doi.org/10.1016/j.forc.2021.100314
[28] A.J. Almalki, C.R. Clark, Y. Abiedalla, J. DeRuiter, GC–MS analysis of N-(bromodimethoxybenzyl)-2-, 3-, and 4-methoxyphenethylamines: Inverse analogues of the psychoactive 25B-NBOMe drug, Forensic Chem. 21 (2020) 100277, https://doi.org/10.1016/j.forc.2020.100277
[29] Y. Abiedalla, A.J. Almalki, J. DeRuiter, C.R. Clark, GC–MS and GC–IR analysis of substituted N-benzyl 4-bromo-2,5-dimethoxyphenylisopropylamines, Forensic Chem. 24 (2021) 100326, https://doi.org/10.1016/j.forc.2021.100326
[30] T.M.G. Salerno, P. Donato, G. Frison, L. Zamengo, L. Mondello, Gas chromatography—Fourier transform infrared spectroscopy for unambiguous determination of illicit drugs: a proof of concept, Front. Chem. 8 (2020), https://doi.org/10.3389/fchem.2020.00624
[31] R.F. Kranenburg, A.R. García-Cicourel, C. Kukurin, H.-G. Janssen, P.J. Schoenmakers, A.C. van Asten, Distinguishing drug isomers in the forensic laboratory: GC-VUV in addition to GC-MS for orthogonal selectivity and the use of library match scores as a new source of information, Forensic Sci. Int. 302 (2019) 109900, https://doi.org/10.1016/j.forsciint.2019.109900
[32] R.F. Kranenburg, C.K. Lukken, P.J. Schoenmakers, A.C. van Asten, Spotting isomer mixtures in forensic illicit drug casework with GC–VUV using automated coelution detection and spectral deconvolution, J. Chromatogr. B. 1173 (2021) 122675, https://doi.org/10.1016/j.jchromb.2021.122675
[33] L. Skultety, P. Frycak, C. Qiu, J. Smuts, L. Shear-Laude, K. Lemr, J.X. Mao, P. Kroll, K.A. Schug, A. Szewczak, C. Vaught, I. Lurie, V. Havlicek, Resolution of isomeric new designer stimulants using gas chromatography – vacuum ultraviolet spectroscopy and theoretical computations, Anal. Chim. Acta 971 (2017) 55–67, https://doi.org/10.1016/j.aca.2017.03.023
[34] Z.R. Roberson, J.V. Goodpaster, Differentiation of structurally similar phenethylamines via gas chromatography–vacuum ultraviolet spectroscopy (GC–VUV), Forensic Chem. 15 (2019) 100172, https://doi.org/10.1016/j.forc.2019.100172
[35] S. Buchalter, I. Marginean, J. Yohannan, I.S. Lurie, Gas chromatography with tandem cold electron ionization mass spectrometric detection and vacuum ultraviolet detection for the comprehensive analysis of fentanyl analogues, J. Chromatogr. A. 1596 (2019) 183–193, https://doi.org/10.1016/j.chroma.2019.03.011
[36] R.F. Kranenburg, F.A.M.G. van Geenen, G. Berden, J. Oomens, J. Martens, A.C. van Asten, Mass-spectrometry-based identification of synthetic drug isomers using infrared ion spectroscopy, Anal. Chem. 92 (2020) 7282–7288, https://doi.org/10.1021/acs.analchem.0c00915
[37] F.A.M.G. van Geenen, R.F. Kranenburg, A.C. van Asten, J. Martens, J. Oomens, G. Berden, Isomer-specific two-color double-resonance IR2MS3 ion spectroscopy using a single laser: application in the identification of novel psychoactive substances, Anal. Chem. 93 (2021) 2687–2693, https://doi.org/10.1021/acs.analchem.0c05042
[38] J.L. Tanen, I.S. Lurie, I. Marginean, Gas chromatography with dual cold electron ionization mass spectrometry and vacuum ultraviolet detection for the analysis of phenylethylamine analogues, Forensic Chem. 21 (2020) 100281, https://doi.org/10.1016/j.forc.2020.100281
[39] M.P. Levitas, E. Andrews, I. Lurie, I. Marginean, Discrimination of synthetic cathinones by GC–MS and GC–MS/MS using cold electron ionization, Forensic Sci. Int. 288 (2018) 107–114, https://doi.org/10.1016/j.forsciint.2018.04.026
[40] R.F. Kranenburg, D. Peroni, S. Affourtit, J.A. Westerhuis, A.K. Smilde, A.C. van Asten, Revealing hidden information in GC-MS spectra from isomeric drugs: chemometrics based identification from 15 eV and 70 eV EI mass spectra, Forensic Chem. 18 (2020) 100225, https://doi.org/10.1016/j.forc.2020.100225
[41] A.J. Almalki, C.R. Clark, J. DeRuiter, GC–MS analysis of regioisomeric substituted N-benzyl-4-bromo-2,5-dimethoxyphenethylamines, Forensic Chem. 14 (2019) 100164, https://doi.org/10.1016/j.forc.2019.100164
[42] R.F. Kranenburg, J. Verduin, L.I. Stuyver, R. de Ridder, A. van Beek, E. Colmsee, A.C. van Asten, Benefits of derivatization in GC–MS-based identification of new psychoactive substances, Forensic Chem. 20 (2020) 100273, https://doi.org/10.1016/j.forc.2020.100273
[43] J. Bonetti, Mass spectral differentiation of positional isomers using multivariate statistics, Forensic Chem. 9 (2018) 50–61, https://doi.org/10.1016/j.forc.2018.06.001
[44] J.L. Bonetti, S. Samanipour, A.C. van Asten, Utilization of machine learning for the differentiation of positional NPS isomers with direct analysis in real time mass spectrometry, Anal. Chem. (2022), https://doi.org/10.1021/acs.analchem.1c04985
[45] J.T. Davidson, G.P. Jackson, The differentiation of 2,5-dimethoxy-N-(N-methoxybenzyl)phenethylamine (NBOMe) isomers using GC retention indices and multivariate analysis of ion abundances in electron ionization mass spectra, Forensic Chem. 14 (2019) 100160, https://doi.org/10.1016/j.forc.2019.100160
[46] R.E. Liliedahl, J.T. Davidson, The differentiation of synthetic cathinone isomers using GC-EI-MS and multivariate analysis, Forensic Chem. 26 (2021) 100349, https://doi.org/10.1016/j.forc.2021.100349
[47] S. Materazzi, G. Peluso, L. Ripani, R. Risoluti, High-throughput prediction of AKB48 in emerging illicit products by NIR spectroscopy and chemometrics, Microchem. J. 134 (2017) 277–283, https://doi.org/10.1016/j.microc.2017.06.014
[48] R. Risoluti, S. Materazzi, A. Gregori, L. Ripani, Early detection of emerging street drugs by near infrared spectroscopy and chemometrics, Talanta 153 (2016) 407–413, https://doi.org/10.1016/j.talanta.2016.02.044
[49] L. de, O. Magalhães, L.C. Arantes, J.W.B. Braga, Identification of NBOMe and NBOH in blotter papers using a handheld NIR spectrometer and chemometric methods, Microchem. J. 144 (2019) 151–158, https://doi.org/10.1016/j.microc.2018.08.051
[50] A.T. Shulgin, The background and chemistry of MDMA, J. Psychoact. Drugs 18 (1986) 291–304, https://doi.org/10.1080/02791072.1986.10472361
[51] B.H. Morimoto, S. Lovell, B. Kahr, Ecstasy: 3,4-methylenedioxymethamphetamine (MDMA), Acta Crystallogr. C. 54 (Pt 2) (1998) 229–231, https://doi.org/10.1107/s0108270197012390
[52] R.F. Kranenburg, Y. Weesepoel, M. Alewijn, S. Sap, P.W.F. Arisz, A. van Esch, P.H.J. Keizers, A.C. van Asten, Dataset of near-infrared spectral data of illicit-drugs and forensic casework samples analyzed by five portable spectrometers operating in different wavelength ranges, Data Brief. (2022).
[53] R.F. Kranenburg, H.-J. Ramaker, A.C. van Asten, On-site forensic analysis of colored seized materials: detection of brown heroin and MDMA-tablets by a portable NIR spectrometer, Drug Test. Anal. (2022), https://doi.org/10.1002/dta.3356
[54] L. Hondebrink, J.J.N. Lonkhuyzen, C.C. Hunault, J. van den Berg, D. van der Gouwe, A.J.H.P. van Riel, New psychoactive substances (NPS) in the Netherlands: occurrence in forensic drug samples, consumer drug samples and poisons center exposures between 2013 and 2017, Addiction 115 (2020) 716–725, https://doi.org/10.1111/add.14868