Comparative study of the analysis of seized samples by GC-MS, 1H NMR and FT-IR spectroscopy within a Night-Time Economy (NTE) setting

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ABSTRACT

Rapid analysis of surrendered or seized drug samples provides important intelligence for health (*e.g.* treatment or harm reduction), and custodial services. Herein, three *in-situ* techniques, GC-MS, 1H NMR and FT-IR spectroscopy, with searchable libraries, are used to analyse 318 samples qualitatively, using technique specific library-based searches, obtained over the period 24th – 29th August 2019. 259 samples were identified as consisting of a single component, of which cocaine was the most prevalent (n = 158). Median match scores for all three techniques were $\geq$ 0.84 and showed agreement except for metformin (n = 1), oxandrolone (identified as vitamin K by IR (n = 4)), diazepam (identified as zolpidem by FT-IR (n = 2)) and 2-Br-4,5-DMPEA (n = 1), a structural isomer of 2C-B identified as a polymer of cellulose (cardboard) by FT-IR. 51 samples were found to consist of two or more components, of which 49 were adulterated cocaine samples (45 binary and 4 tertiary samples). GC-MS identified all components present in the 49 adulterated cocaine samples, whereas IR identified only cocaine in 88 % of cases (adulterant only = 12 %). The breakdown for 1H NMR spectroscopy was all components identified (51 %), cocaine only (33 %), adulterant only (10 %), cocaine and one adulterant (tertiary mixtures only, 6 %).

1. Introduction

Drug testing of seized or surrendered materials that are believed to contain illicit or controlled materials, is important for harm-reduction [1], treating drug intoxication [2] and information gathering to inform policing policies [3]. Analysis of biological fluids, such as urine [4] or saliva [5], is also a useful indicator of the prevalence of drugs within a population or at an event. Blood sampling can also be useful, such as in the detection of fentanyl analogues and metabolites at low concentration *via* liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) [6]. However, obtaining, and processing, these biological fluids can be onerous. Some drugs are eliminated quickly from the body, and this can render saliva, urine and blood testing redundant or with reduced efficacy. Another method for assessing the usage of illicit drugs is to use self-reported data, although this approach does rely on the user being able to recall exactly what they have taken and that their response may be one that is socially desirable rather than truthful [7]. Self-reported data also relies on the user knowing exactly what they have purchased, or have been given, with absolute certainty. This is often not the case, with the majority of illicit drugs containing adulteration/bulking agents which are not advertised to the users [8].

Qualitative and quantitative analysis of drugs that have been seized or surrendered, by analytical techniques operated in a complimentary

fashion, enables the complete assessment of a sample to be completed. A number of techniques are available for analysis of samples believed to contain illicit drugs, such as Fourier transform infra-red (FT-IR) spectroscopy [9-11], gas-chromatography mass-spectrometry (GC-MS) [12, 13], nuclear magnetic resonance (NMR) [14,15], Raman spectroscopy [9,16] and colorimetric testing [17]. Of these techniques, GC-MS is considered the "gold standard" [1,18] for forensic analysis due to the separation power of the GC component and mass spectral fingerprint afforded by MS component. Derivatization can also be employed to further aid identification [19]. However, the technique does suffer from long run times and can struggle with separating regioisomers successfully e.g. regioisomeric cathinones [20], although linear discriminant analysis can be used to identify individual isomers e.g. mephedrone ring-isomers [19]. As such, the use of other techniques for forensic-linked testing might be desirable.

Nuclear Magnetic Resonance (NMR) spectroscopy is also a viable technique for drug analysis as the exact atom connectivity can be ascertained upon the collection of a suite of spectra. This can be time consuming, especially if the drug being analysed is new. However, due to the nature of the ^{1}H NMR spectrum, being unique for a particular analyte, comparison of an obtained spectrum against a library of spectra enables fast and discriminatory analysis to be completed. This can be done by manual comparison of collected spectra to reference spectra [15,21], or the process can be automated [22]. Furthermore, the requirement of a super-conducting magnet has been negated by the availability of benchtop NMR spectrometers. Benchtop NMR spectrometers also have potential field-deployable [23] utility. Both high-field and benchtop NMR spectrometers have been used for the characterisation of novel psychoactive substances [21], such as the qualitative analysis of nine synthetic cannabinoids at high- and low-magnetic field [24]. The time needed for data acquisition is limited by the amount of available sample or the solubility of the material. Quantification by NMR can be also be achieved readily, with [14] or without [22] an internal standard.

Infra-red analysis has been utilised for a number of analyses of illicit drug materials, including psychoactive substances. A large scale (>200) study that used infra-red and Raman to screen samples has been reported in which 76 % of samples were identified [9]. Surface-enhanced Raman spectroscopy (SERS) has been employed for the detection of novel psychoactive substances as powders or in solution [16]. Furthermore, handheld Raman spectroscopy has been used for the analysis of 13 surrendered samples alongside a questionnaire completed by participants for drug checking purposes as part of a community substance misuse service [25].

Multi-technology approaches have been utilised for drug checking. A recent report has utilised FT-IR, Raman, SERS, GC-MS and test strips and evaluated their use for the analysis of the same sample [26]. Communication of results was cited as being challenging due to database searching producing different hits when analysing FT-IR, Raman and GC-MS data and these results were not always consistent with test strip data. In addition, even when the same compound was identified, the confidence in the outcome could be substantially different. A further study, conducted over two sites, appraised the use of fentanyl test strips, Raman and FT-IR for identifying fentanyl in 210 samples [27]. Fentanyl test strips were found to have the highest sensitivity (96.3 % and 100 %) whereas the Raman spectrometer in "point-and-shoot" mode returned the highest specificity (98.1 % and 100 %) but the sensitivity was only ca. 4 % at both sites and rose to only 38.5 % or 61.1 % when SERS was employed. FT-IR was only tested at one site for which sensitivity and specificity were 83.3 % and 90.2 % respectively. Another study ascertained the concordance of results obtained from colorimetric testing and GC-MS analysis for 120 samples collected from night events in Umbria, Italy [28]. Ketamine, 3,4-methylenedioxymethamphetamine (MDMA), amphetamine, cocaine, heroin and lysergic acid diethylamide (LSD) were detected in the samples analysed.

In this paper, the analysis of 318 samples within a night-time economy (NTE) setting over the period 24th-29th August 2019 are disclosed. NTE refers herein to the illegal trade of illicit drugs in venues such as nightclubs, music events or festivals. Samples are analysed in-situ qualitatively by FT-IR, ^{1}H NMR and GC-MS. For samples in which more than one component was present, the components were quantified by GC-MS. This triangulation of data for each sample enables the identity of any active pharmaceutical ingredient (API) to be ascertained. The complimentary nature of the approach enables a direct comparison to be formed between the three techniques, and by extension, an assessment of their technical readiness to be employed for routine drug testing for events where harm-reduction is the focus. The three techniques employed have associated software that, following automated or manual analysis of the acquired spectrum, reports a 'match score' along with the given compound identification. The exact means by which this is calculated differs with the software packages, but in all cases, these are values on a scale between 0 and 1, with 1 indicating an exact match with a library reference compound(s). The rationale for this choice is that some drug checking services use volunteers to conduct analyses, who may not be scientifically trained, and so these match scores would be heavily relied upon in these circumstances, especially if rapid turn-around is required.

2. Materials and methods

All reagents were of commercial quality and used without further purification. Methanol (>99.9 %) was of analytical grade and was obtained from Fisher Scientific (Loughborough, UK). DMSO-d_6 was obtained from Merck (Poole, UK). 0.45 μm PTFE syringe filters were obtained from Fisher Scientific (Loughborough, UK). The 318 samples were obtained by Greater Manchester Police (GMP), between 24th-29th August 2019, via the MANchester DRug Analysis and Knowledge Exchange (MANDRAKE) partnership in accordance with Manchester Metropolitan University's Home Office license (Ref. No. 423023) requirements and agreed procedures.

2.1. Fourier Transform infra-red (FT-IR) spectroscopy

Infrared spectra were obtained in the range 4000 – 650 cm^{-1} using either a Thermo Scientific Nicolet iS10ATR-FTIR instrument (Thermo Scientific, Rochester, USA) or a PerkinElmer Spectrum Two UATR (PerkinElmer, Beaconsfield, UK) each equipped with diamond attenuated total reflectance (ATR) accessories. 16 scans were acquired of each sample with a resolution of 4 cm^{-1} (line spacing 1.928 cm^{-1}). Qualitative identification of the components present in a sample were performed using OMNIC (Thermo Scientific, Rochester, USA) or Spectrum 10 (PerkinElmer, Beaconsfield, UK) against defined libraries (Scientific database (version 10.5.3.738) and SWGDRUG IR Library (version 2.1)). Both search platforms utilised a correlation search to determine the component(s) present. The highest match score was used for identification purposes.

Samples were analysed in their supplied forms as indicated in Tables S1-S2. All samples were ground using a pestle and mortar prior to analysis to ensure good sample homogeneity.

2.2. ^{1}H NMR spectroscopy

^{1}H NMR spectra were acquired of all samples using a Pulsar benchtop NMR spectrometer (Oxford Instruments, Abingdon, UK) operating at a frequency of 59.7 MHz. The temperature of the probe was calculated to be 308.5 K by measuring the separation (in Hz, $\Delta\delta$) between the CH$_2$ and OH signals of neat ethylene glycol and implementing the equation T [K] = 466.5−102.00 $\Delta\delta$ [29]. For the seized materials, a micro-spatula tip of the material (ca. 5−10 mg) was dissolved in DMSO-d_6 (0.6 mL). All samples were filtered through a 0.45 μm polyvinylidene difluoride syringe filter (Whatman) directly into a NMR tube. After the sample had been inserted, an automated procedure began whereby the instrument

would lock on to the deuterated signature of DMSO (thus used as a chemical shift reference) before acquiring 16 scans. Following acquisition, the data were processed in MNova (Mestrelab Research, Santiago de Compostela, Spain) using an automated script file. The processed FID was then analyzed by the pattern recognition algorithm, NPS Pattern Match (Oxford Instruments, Abingdon), developed using Matlab (The Mathworks Inc., Cambridge, UK). The algorithm employs a minimum distance classifier. The multivariate distance between the sample spectrum and each of the reference spectra is calculated. The sample is identified as the nearest reference compound, provided the "match score" (equal to one minus the distance) exceeds an (empirically determined) threshold; if it does not, then the outcome is considered to be tentative, unreliable, or unknown. Binary mixtures are accommodated by extending the pattern search with synthetically generated mixture spectra of pairwise combinations of the reference library.

2.3. Gas Chromatography-Mass Spectrometry (GC-MS)

GC-MS analysis was performed using an Agilent 7890B GC and a MS5977B mass selective detector (Agilent Technologies, Wokingham, UK). The mass spectrometer was operated in the electron ionisation mode at 70 eV. Separation was achieved with a capillary column (HP5 MS, 30 m Å~ 0.25 mm i.d. 0.25 μm) with helium as the carrier gas at a constant flow rate of 60 mL min^{-1}. The initial oven temperature was set to 50 °C prior to be being ramped to 290 °C in 30 °C min^{-1} intervals. A hold time of 2 min was used at 290 °C to give a total run time of 10 min. A 0.5 μL aliquot of the sample was injected with a split ratio of 50:1. The injector and the GC interface temperatures were both maintained at 265 °C respectively. The MS source and quadrupole temperatures were set at 230 °C and 150 °C. Mass spectra were obtained in full scan mode (40–550 amu). All samples (qualitative analysis) were prepared as 1 mg mL^{-1} solutions in methanol with no derivatisation. Eicosane (0.5 mg mL^{-1}) was used as an internal standard and each sample was injected once.

Qualitative analysis of samples was performed using the inbuilt library search function. The National Institute of Standards and Technology (NIST) database was used to assign the identities of components present within a sample based on both their retention factors and their corresponding mass spectra. Match factors obtained from the mass spectrum are derived from the modified cosine of the angle between the spectra (normalised dot product).

2.4. GC-MS method validation

GC-MS method validation was performed using an Agilent 7890B GC and a MS5977B mass selective detector (Agilent Technologies, Wokingham, UK) employing the parameters detailed in Section 2.4. Mass spectra were obtained under Selected Ion Monitoring (SIM) mode, using three specific fragment ions for each analyte. The GC-MS method was validated in accordance with the ICH guidelines [30] using the following parameters: linearity, accuracy, precision, limit of detection (LOD) and limit of quantification (LOQ). Linearity, precision: six replicate injections of the calibration standards were performed and the data analysed under the same conditions. The RSD % was calculated for each replicate test sample. Accuracy (percentage recovery study): determined from spiked samples prepared in triplicate at three levels over a range of 80–120 % of the target concentration (15 μg mL^{-1}). The percentage recovery and RSD % were calculated for each of the replicate samples. Limits of detection and quantification: six replicate injections of the calibration standards were performed and the data analysed under the same conditions. The limits of detection and quantification were determined based on the signal-to-noise (S/N) ratio, where a signal-to-noise ratio of 3:1 and 10:1 was used to calculate the LOD and LOQ respectively.

3. Results and discussion

3.1. Analysis of samples

To analyse the 318 seized samples that were seized over the period 24th-29th August 2019, FT-IR spectroscopy, ^{1}H NMR spectroscopy and GC-MS were used in tandem. Match scores were obtained for each analysis obtained, and this was used to cross-validate the results obtained.

The vast majority of the samples analysed comprised of a single component, as determined by the number of components identified following GC-MS, given that this technique is considered the "gold standard" for forensic sampling [1,18]. This also provides a suitable reference point from which to assess the other two techniques, ^{1}H NMR and FT-IR spectroscopy, as potential alternative techniques.

Of the 318 samples that were surveyed, eight samples were not analysed due to insufficient material. Of the reminder, 259 samples were found to consist of a single component and 51 of two or more components. For the single component samples (Table S1), the most prevalent drug identified was cocaine (61.0 %), followed by MDMA (18.5 %) and then ketamine (7.7 %). The prevalent nature of these three drugs has been reported in previous studies [31-33]. GC-MS and FT-IR analysis lacked the discriminatory power to differentiate between cocaine free-base and cocaine.HCl, whereas ^{1}H NMR spectroscopy was able to do so. Of the 158 cocaine samples, 66 consisted of cocaine in its free-base form whereas 84 consisted of the hydrochloride salt. The remainder eight samples were returned as a mixture by the ^{1}H NMR analysis; adulterants such as phenacetin and paracetamol were indicated as being present, although these were not detected by GC-MS. Five of these samples indicated cocaine was present as the hydrochloride salt.

The FT-IR analysis of the cocaine containing samples were truncated when reported in Table 1. This is because nine of the samples returned hits that did not match those performed using GC-MS and ^{1}H NMR spectroscopy, in that cocaine was not identified. Insufficient material was available for the analysis of four of these samples. For the remainder, FT-IR analysis indicated that creatine hydrate (n = 2), boric acid (n = 1), cardboard (polymer of cellulose, n = 1) and chlorhexidine (n = 1) were returned with match scores ranging from 0.54 to 0.97. Spectral subtraction of the returned hit did not aid the identification of cocaine within these samples. These nine samples were, therefore, excluded from Table 1.

Four herbal samples (19312 – 19315) were analysed by GC-MS and determined to contain delta-9-tetrahydrocannabinol (THC; t_R = 4.72 min, match score = 0.98) as the principal component, indicating that these samples were cannabis. ^{1}H NMR and FT-IR analysis returned cannabis and tetrahydrocannabinolic acid respectively, although only three samples were correctly identified for the latter; one sample was returned as basil leaf.

One sample (19087) was returned as cardboard (polymer of cellulose) with a median match score of 0.66 (by FT-IR), whereas ^{1}H NMR analysis determined that this sample contained 2C-B (match score = 0.92). A high level of excipients, relative to active ingredient, in a solid dosage form can potentially mask the active ingredient signals and affect the identification of seized drug samples by infrared analysis. Normally, 2 C-B tablets contain dosage ranges of between 5 and 10 mg and based on the weight of the surveyed sample (211 mg) this would equate to 2.4 – 4.7 % w/w of 2 C-B being potentially present within the tablet which is below the detection threshold (*ca.* 10 % w/w) of this technique [1,27]. GC-MS analysis of this sample gave a median match score of 0.78 (2 C-B) which is not conclusive for the presence of this compound.

Evaluation of the EI-MS spectrum for the sample (Fig. 1) indicated that low abundance molecular ions [m/z = 259.0 (^{79}Br-M^{+}) and 261.0 (^{81}Br-M^{+})], for 2C-B, were not visible in the EI spectrum for the sample, however the diagnostic base peak, which results from loss of bromine, was observed at m/z = 180.0 indicating the potential presence of the 2C-B isomer, 2-bromo-4,5-dimethoxyphenethylamine (2-Br-4,5-DMPEA).

Table 1

Median match scores obtained for the 259 samples found to contain a single component from FT-IR, ^{1}H NMR and GC-MS analysis. Key: [1]Retuned as cardboard (polymer of cellulose, match score = 0.66); [2]Retured as 2C-B; [3]Returned as tetrahydrocannabinolic acid; [4]Returned as cannabis; [5]Principle psychoactive component (THC, t_R = 4.72 min) determined in sample; [6]Returned as Ambien (Zolpidem is the API). Match score median = 0.96; [7]Confirmation *via N*-methyl-bis(trifluoroacetamide) [MBTFA] derivatisation and comparison of GC-EI-MS spectral data reported by C. Goedecke et al., *Anal. Methods*, 2017, 9, 1580–1584. [8]Returned as vitamin K (all instances). Match score median = 0.96. [†]GC retention times for compounds identified were consistent with those reported by Antonides et al. [31]. Newly detected compounds in this study are indicated by their retention times (in min) being given in parentheses after their median match scores.

Substance	No. of samples	Median match score obtained		
		FT-IR	^{1}H NMR	GC-MS[†]
2-Br-4,5-DMPEA	1	_[1]	0.92[2]	0.78[2]
4-Methylmethcathinone	2	0.98	0.94	0.96
Aspirin	1	0.99	0.99	0.87
Caffeine	2	0.88	0.90	0.96
Cannabis	4	0.90 (n = 3)[3]	0.95[4]	0.98[5]
Cocaine	158	0.96 (n = 149)	0.96	0.98
Diazepam	2	_[6]	0.94	0.88
Ketamine	20	0.92	0.95	0.98
MDMA	48	0.99	0.98	0.98
Metformin	1	0.78	0.97	_[7]
N-ethylpentylone	1	0.92	0.93	0.98 (7.03)
Oxandrolone	4	_[8]	0.93	0.85 (10.45)
Paracetamol	13	0.99	0.96	0.99
Pregabalin	2	0.92	0.84	0.96 (4.99)

Characteristic fragment ions at m/z = 215.0/217.0, associated with loss of ethylamine and 230.0/232.0 corresponding to α,β-cleavage of the phenethylamine sidechain were also observed confirming that the isomer was likely to be present (see Fig. S10 for proposed fragmentation patterns). When a reference standard of 2-Br-4,5-DMPEA was added to the NMR spectral library, sample (19087) was still returned as 2 C-B with a match-score of 0.92. 2-Br-4,5-DMPEA was listed as the fifth hit with a match-score of 0.90.

These results have to be carefully interpreted. The algorithm allows for a tolerance limit of ± 0.06 ppm for any peak [31]. In DMSO-d$_6$, the two aromatic peaks of 2C-B occur at 7.20 and 6.98 ppm in the ^{1}H NMR spectrum (see Fig. S11). For 2-br-4,5-DMPEA, these peaks are upfield shifted to 7.14 and 6.96 ppm (see Fig. S12). In addition, the difference in chemical shift for each pair of aromatic peaks is very similar (circa. 0.2 ppm). Due to the other ^{1}H NMR signals of 2C-B and its isomer not being located in either the fingerprint or class region that is analysed by the algorithm, these aromatic peaks are key to structural identification by the algorithm. Thus, exact determination is difficult without changing the constraints employed by the algorithm *e.g.*, extending the fingerprint/class chemical shift regions so that more signals are appraised. In this context, the wider picture needs to be considered in that not all drug samples surveyed will contain 2 C-B and therefore the methodology employed cannot be tailored for specific compounds as this pertains to a decision having been taken regarding the identity of the drug sample prior to analysis commencing.

Four tablets were shown to contain oxandrolone by GC-MS (median match score = 0.85). This was also confirmed by ^{1}H NMR (median match score = 0.93). FT-IR analysis returned vitamin K for all of these samples. The structures of vitamin K and oxandrolone are dissimilar in that the former consists of a naphthoquinone ring and a long hydrocarbon chain, whereas the latter possesses a fused-ring system. Oxandrolone is a controlled material in countries such as the USA, Canada and the UK, whereas vitamin K is not.

One sample was detected by ^{1}H NMR and IR spectroscopy to contain metformin (match scores 0.97 and 0.78 respectively). Unlike the other substances identified, metformin was not detected by GC-MS as it requires derivatisation to render it volatile and thermally stable [34]. Subsequent derivatisation of this sample (as its MBTFA derivative) and analysis by GC-MS confirmed the presence of metformin.

The median match scores for all the single component samples are shown in Table 1. GC-MS and ^{1}H NMR spectroscopy possess high correlation scores (*i.e.* close to unity) for all the single component samples surveyed, with the exception metformin (GC-MS). Conversely, there is a large variability in the FT-IR match scores obtained and there were a number of drugs that were mis-identified using this technique. This raises serious questions about the reliability of using FT-IR for harm reduction/drug detection purposes, especially if secondary evidence of identity is not obtained.

3.2. Mixtures

Of the samples surveyed, 51 were found to consist of two or more components. Of these 51 samples, 49 were adulterated cocaine mixtures that were further identified by GC-MS analysis as being binary mixtures (n = 45, Table S2) or tertiary mixtures (n = 4, Table S3). It was found for the binary mixtures that levamisole was by far the most common adulterant (42.2 %), with phenacetin (15.6 %), caffeine (15.6 %) and benzocaine (20.0 %) being the next common. Paracetamol (4.4 %) and benadryl (diphenhydramine, 2.2 %) were the least prevalent. A Spanish survey conducted over the period 2007 – 2014 of 43,196 samples [35] revealed that the most prevalent adulterant was levamisole (46.9 %) which is consistent with the results of the samples surveyed herein; likewise is the proportion of samples found to contain caffeine (13.2 %) and paracetamol (4.1 %). However, the percentage of samples found to contain phenacetin (36.3 %) and benzocaine (2.6 %) are much higher and lower, respectively, than the values reported here. Results from a Manchester, UK, based survey of 432 samples seized in 2017–2018 reported that samples of cocaine were mainly adulterated with levamisole which was identified in 46.2 % of adulterated cocaine samples (n = 26) [31]. Other adulterants identified were ketamine (3.8 %), benzocaine (34.6 %), phenacetin (7.7 %), caffeine (3.8 %), and paracetamol (3.8 %). The latter four adulterants have been identified in the samples surveyed herein, although there is evident variability in the occurrence of different adulterants in comparison with previous studies.

Cocaine content of 45 of these 49 samples was ascertained *via* GC-MS. Four samples could not be quantified due to insufficient material being available. The cocaine content of the levamisole adulterated samples was 82.6–99.0 % (n = 19). The cocaine content of the caffeine (8.5–93.3 %, n = 6) and benzocaine (10.7–92.1 %, n = 11) adulterated samples showed the largest range. Median cocaine content values have been shown to vary considerably as a function of the weight of seizure, with the difference between the maximum and minimum median cocaine content values being the smallest for seizures > 1000 g [35]. Results for the other adulterated samples are shown in Table 2 and are reported alongside the purities of other substances identified in samples surveyed.
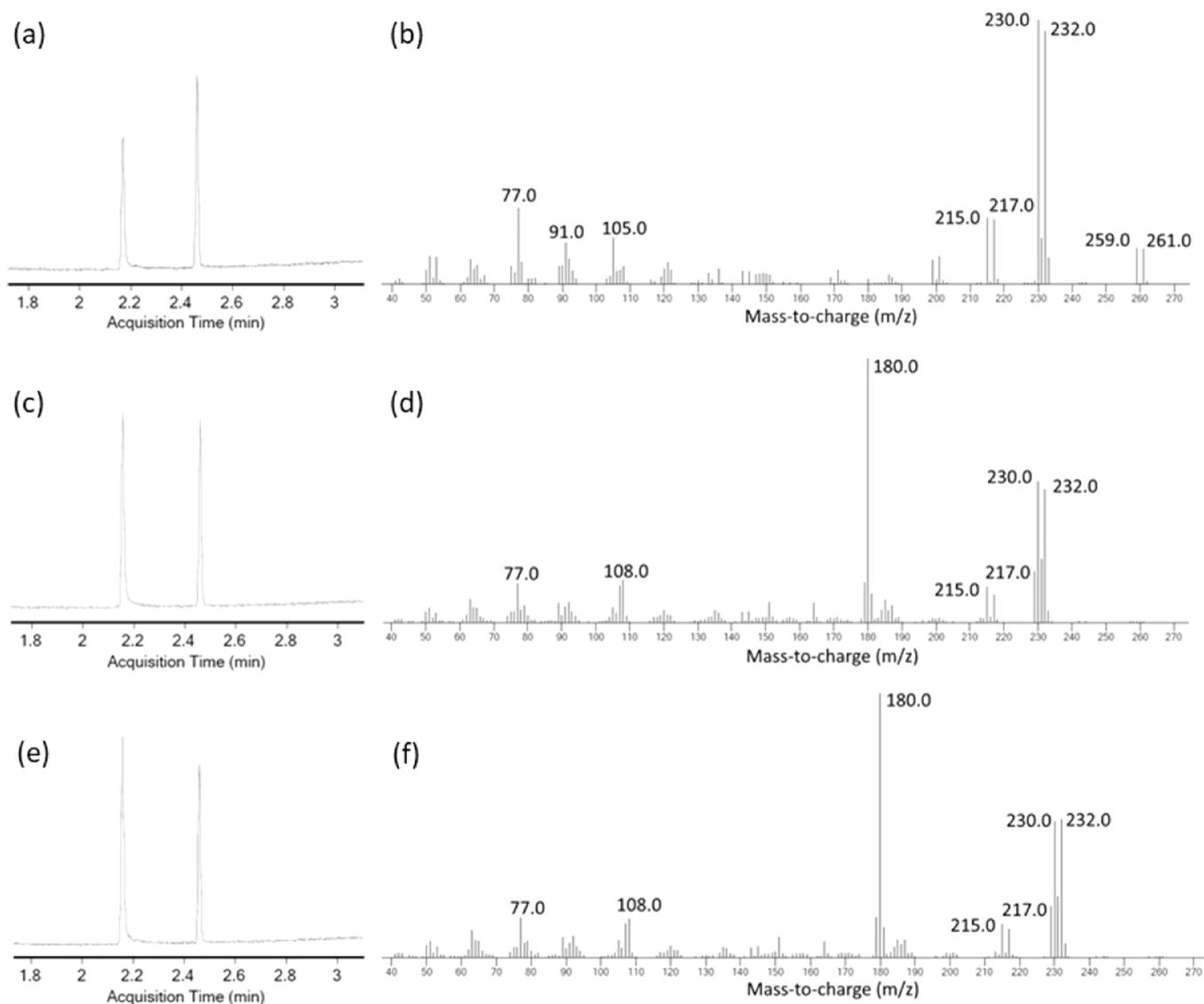
Fig. 1. (a) Chromatogram of 2 C-B reference standard; (b) EI-MS spectrum (t_R = 2.17 min) of 2 C-B (2) reference standard; (c) Chromatogram of 2-Br-4,5-DMPEA reference standard; (d) EI-MS spectrum (t_R = 2.15 min) of 2-Br-4,5-DMPEA reference standard; (e) Chromatogram of sample (19,087); (f) EI-MS spectrum (t_R = 2.15 min) of sample (19,087). Note: t_R = 2.46 min (internal standard, eicosane).

Table 2
Percentage content of main API in cocaine, MDMA and ketamine samples surveyed as part of this study.

Substance	Adulterant	Main API Content (% w/w)
Cocaine	–	92.8–99.0 (n = 161)
	Levamisole	82.6–99.0 (n = 19)
	Phenacetin	71.8–91.1 (n = 7)
	Caffeine	8.5–93.3 (n = 7)
	Benzocaine	10.7–92.1 (n = 9)
	Paracetamol	65.0–92.8 (n = 2)
	Benadryl (diphenhydramine)	97.3 (n = 1)
MDMA (powder)	–	95.0–99.0 (n = 41)
MDMA (tablets)	–	24.3–40.4 (n = 15)
Ketamine	–	96.2–99.1 (n = 18)

The two samples identified as a binary mixture that were not found to contain cocaine consisted of paracetamol and benadryl (diphenhydramine, n = 1), and MDMA and caffeine (n = 1). Paracetamol and MDMA respectively were reported following FT-IR and NMR analysis for these two samples. In both instances, the second component was not detected.

The four tertiary samples were cocaine in the presence of either paracetamol and levamisole (n = 1), benzocaine and caffeine (n = 2) or benzocaine and levamisole (n = 1). The amount of cocaine present varied from 18.3 % to 64.8 % w/w; for a full breakdown see Table S3.

3.2.1. FT-IR analysis of mixtures

The four most common adulterants detected by GC-MS were levamisole, caffeine, phenacetin and benzocaine. Upon inspection of Table 3, there is clearly a distinction between the ability of the NMR and FT-IR analysis to detect the main API as well as the adulterant, with the FT-IR analysis only identifying one or the other but never both. The software utilised for the FT-IR analysis does have the capacity to detect the two components and so these results are somewhat surprising. However, some FT-IR search platforms are better suited to the detection of a single unknown component.

In light of these results, a series of measurements were undertaken whereby a sample consisting of cocaine and a single adulterant (either caffeine, benzocaine or levamisole) in ratios varying from 100:0–0:100 w/w was analysed by FT-IR analysis. The percentage weight for each sample was compared to the percentage obtained for the two components, along with the respective match scores (see Tables S4–6). The

Table 3

Component detection following FT-IR and ^{1}H NMR analysis of samples containing cocaine and one or more adulterants.

Mixture identified by GC-MS	No. of samples	Number of samples analysed by NMR that satisfied:				Number of samples analysed by FT-IR that satisfied:		
		All components identified	Only cocaine identified	Cocaine and one adulterant identified (tertiary mixtures only)	Only adulterant identified	All components identified	Only cocaine	Only adulterant identified
Cocaine and levamisole	19	8	11				19	
Cocaine and paracetamol	2	1	1				2	
Cocaine and phenacetin	7	7					7	
Cocaine and benzocaine	9	7			2		6	3
Cocaine and caffeine	7	2	4		1		5	1
Cocaine and benadryl	1				1			1
Cocaine, benzocaine and caffeine	1			1			1	
Cocaine, levamisole and benzocaine	2			2			1	1
Cocaine, levamisole and paracetamol	1				1	[a]	[a]	[a]

[a] Insufficient material to obtain analysis

results of this analysis were quite striking.

Firstly, in samples consisting of *ca.* 80 % w/w or more cocaine irrespective of adulterant, the adulterant is never detected. Similarly, when the sample consists of $\geq$ 90 % adulterant w/w, cocaine is not detected either. Between these extremes, for samples consisting of cocaine and caffeine or benzocaine, both cocaine and the adulterant are detected (Tables S4 and S5, and Figs. S1 and S2). Corresponding ^{1}H NMR and gas chromatograms are shown in Figs. S4, S5, S7 and S8. The percentages of the two components shows some agreement over this range with the sample matrix composition, although there is a degree of variability. In terms of the cocaine and caffeine samples surveyed (Table S3), five of the seven samples possess cocaine either > 85 % or < 10 % w/w. Only two samples, therefore, could be reasonably expected to return caffeine and cocaine as the result by FT-IR analysis. One of these samples returned alpha lactose (70 % cocaine) whilst the other returned cocaine (51 % cocaine). Analysis of the samples by NMR returned the correct result (cocaine and caffeine) for these two samples; all other samples were identified as cocaine solely (>69 % w/w cocaine) or caffeine (8.3 % w/w cocaine).

In an analogous controlled study where the amount of cocaine and benzocaine was varied (Table S5), it was found that at ~80 %+ w/w cocaine, benzocaine was not detected. For cocaine to be detectable, approximately 20 % w/w is needed. This can be explained upon inspection of the FT-IR spectra (Fig. S1) by considering the spectral features of cocaine and benzocaine. For example, at $\geq$ 20 % w/w, the diagnostic C=O stretches of cocaine at *ca.* 1700 cm^{-1} are distinguishable readily from the baseline, whereas at 10 % w/w, these two stretches are less intense and the C=O stretch (*ca.* 1680 cm^{-1}) associated with benzocaine dominants. Comparing these findings to the results for the nine cocaine and benzocaine samples listed in Table S3 again provides rationale for the results produced from the FT-IR spectroscopic analysis and library search outcomes. Three samples were returned as containing benzocaine solely (33 % (n = 3)) by FT-IR analysis. All three samples possessed the lowest amount of cocaine present from GC-MS analysis (12 % (n = 1) and 27 % (n = 2)), although the latter is the region where benzocaine should be detectable. Two of these samples were returned as consisting of benzocaine solely by NMR analysis. All the other samples consisted of $\geq$ 60 % cocaine and were returned as solely consisting of cocaine following FT-IR analysis; all of these samples were correctly identified by ^{1}H NMR analysis to contain cocaine and benzocaine. Manual subtraction of cocaine's FT-IR signature from the FT-IR spectrum did not assist the detection of the adulterant in any of these cases.

The data for the simulated cocaine and levamisole samples (Table S6 and Fig. S3) is perhaps the easiest to interpret given the high cocaine content of the samples surveyed that were found to consist of cocaine and levamisole (>85 % w/w cocaine). At this threshold, levamisole was not detected at all in the simulated samples; levamisole was only detected when present at *ca.* 70 % w/w or higher. It is therefore not surprising that levamisole wasn't detected in the FT-IR analysis of the seized samples. However, the ^{1}H NMR analysis of the seized samples was able to detect levamisole in eight of the 19 samples (Table S3), despite these samples being $\geq$ 89 % cocaine. ^{1}H NMR spectra and gas chromatograms for the simulated samples are shown in Figs. S6 and S9.

Subtraction of the main component identified in the FT-IR spectrum can provide a route to the identification of a secondary component. This was explored using mixtures of cocaine hydrochloride and either caffeine, benzocaine or levamisole of varying percentage weight (0 – 100 %). Using the default subtraction approach worked well for caffeine and benzocaine (Tables S7 and S8) as caffeine and benzocaine were identified following subtraction of cocaine from the original spectrum. Match scores for caffeine and benzocaine range identified in these mixtures are similar (0.78–0.87 for caffeine, 0.73–0.80 for benzocaine). When the adulterant was subtracted from the spectrum cocaine hydrochloride was identified with match scores of 0.80–0.97 (caffeine subtracted) and 0.76–0.92 (benzocaine subtracted). These match scores improve if the subtraction factor is applied manually (shown in Tables S10 and S11). Match scores for caffeine and benzocaine after manual subtraction were 0.79–0.96 and 0.78–1.00 respectively. Match scores for cocaine hydrochloride were similarly improved.

The default subtraction approach to identifying levamisole and cocaine hydrochloride in a mixture resulted in styrofoam being identified when the percentage by weight of levamisole in the mixture was greater than 0 % but less than 30.5 % following subtraction of cocaine hydrochloride from the acquired spectrum (Table S9). Interestingly, when the percentage weight of levamisole was 89.3 %, subtraction of levamisole from the spectrum also resulted in styrofoam being identified and not cocaine hydrochloride. Conversely, manual subtraction (Table S12) enabled levamisole to be detected at every percentage weight greater than 0 %. Cocaine hydrochloride was also identified in every single mixture when it was present. None of the subtractions resulted in styrofoam being identified. Furthermore, the match scores for the identification of levamisole are higher when subtraction is performed manually (median = 0.88) compared to the default approach (software driven subtraction, median = 0.80).

Based on the data obtained from these studies, re-evaluation of a subset of binary samples (37) by the manual subtraction methods was completed. The results of this study are shown in Table S13. For the samples identified as cocaine and levamisole (n = 17), levamisole was identified after subtraction of the cocaine spectrum for only one sample. The resulting match score was 0.63. This sample was 95.3 % w/w cocaine (samples surveyed ranged from 87 – >99 % w/w of cocaine). Using a more aggressive subtraction factor did enable levamisole to be identified in a further four instances. However, this approach relies upon the fact that sample composition is already known and thus is not practical in terms of identifying adulterants present in a sample of unknown provenance. Samples where the adulterant was caffeine (n = 5) and paracetamol (n = 2) lead to the adulterant being identified twice and once respectively. For the caffeine samples, the percentage composition of the sample that was cocaine was 51 % and 8 % w/w, whereas for the phenacetin sample, it was 64 % w/w. The other samples surveyed where the adulterant was caffeine or phenacetin all possessed higher amounts of cocaine. The one sample that was identified as being cocaine and Benadryl did not return the adulterant when subtraction was employed. Again, the samples consisted of a large amount of cocaine (98 % w/w).

For the cocaine and phenacetin samples (n = 5), subtraction of cocaine from the FT-IR spectrum resulted in phenacetin being identified each time. The median match score and subtraction factor were 0.85 and 0.55 respectively. The percentage of cocaine present in these samples ranged from 71 % to 90 % w/w. Similarly, for the cocaine and benzocaine samples surveyed (n = 7), benzocaine was identified each time following subtraction of cocaine (median match score and subtraction factor was 0.77 and 0.49 respectively). The percentage of cocaine present in these samples was smaller compared to the cocaine and phenacetin samples as the range was 11 – 77 % w/w.

The analysis of these 37 binary samples highlights that identification of the secondary component is dependent on the amount of cocaine present and the chemical identity of the adulterant. Furthermore, optimisation of the subtraction factor employed can enable the adulterant to be identified but this requires the sample composition to be known prior to analysis rather than the approach being used to identify the adulterant present.

3.2.2. Tertiary mixtures

Four samples were found to comprise of three compounds; two contained benzocaine, caffeine and cocaine, one contained paracetamol, cocaine and levamisole and the final sample consisted of benzocaine, levamisole and cocaine (Table S3). The amount of cocaine in the samples, from GC-MS analysis, ranged from 18.3 % to 64.8 % w/w. ^{1}H NMR analysis identified cocaine in three of the four samples whereas FT-IR analysis only identified it thrice (although only three samples analysed by FT-IR due to insufficient material being available). ^{1}H NMR analysis of the sample deduced to contain cocaine, paracetamol and levamisole in a ratio of 64.77:32.69:2.54 by GC-MS was returned as paracetamol and 2,3-dimethyldiphenidine with a match-score of 0.92 (0.9211–4 d.p.). However, cocaine and paracetamol were also indicated as a possible match; the match score was also 0.92 (0.9151–4 d.p.), so not too dissimilar from, in terms of the match score, the highest ranked match. For the remainder three samples, NMR analysis identified cocaine and benzocaine but not the second adulterant (levamisole or caffeine). Given that the amount of levamisole and caffeine present in the samples was ≤ 2.45 % w/w, this result is perhaps not unexpected.

Evaluation of three of the four tertiary samples using the manual subtraction method identified benzocaine in every single instance following subtraction of cocaine from the FT-IR spectrum (Table S13). The second adulterant (caffeine or levamisole was not identified; again this can be reflected upon in terms of low amount of caffeine (*ca.* 2 %) and levamisole (1 %) present in these samples.

4. Conclusion

Herein, 318 samples obtained over the period 24th – 29th August 2019 were analysed *in situ* by GC-MS, ^{1}H NMR and FT-IR spectroscopy. 259 samples were identified as consisting of a single component, 47 as binary and four as tertiary. Eight samples could not be analysed due to insufficient material. Cocaine samples were very prevalent, accounting for 158 of the single component samples, 45 of the binary samples and all of the tertiary samples.

The analysis of the single component samples showed good agreement between the three techniques, in the majority of cases, with median match scores ≥ 0.84. Exceptions to this were samples containing metformin (not identified by GC-MS (n = 1)), oxandrolone (identified as vitamin K by FT-IR (n = 4)), diazepam (identified as zolpidem by FT-IR (n = 2)) and 2 C-B (identified as cardboard by FT-IR (n = 1)).

Analysis of the binary and tertiary samples showed lower agreement between the three techniques as FT-IR and ^{1}H NMR did not always detect the adulterant and / or the API. The latter proved more capable in that all components were identified in 51 % of cases, cocaine only was identified in 33 % of cases, the adulterant only in 10 % of cases, and cocaine and one adulterant (tertiary mixtures only) in 6 % of cases. Conversely, FT-IR identified only cocaine in 88 % of cases and the adulterant only in 12 %. Use of manual subtraction to identify the second component in FT-IR spectra did improve the capacity of FT-IR spectroscopy to identify the second component, but this transpired to be very much dependent on the chemical identity of the adulterant and the percentage of cocaine present. In samples where cocaine was adulterated with benzocaine and phenacetin, subtraction enabled the adulterant to be detected each time (n = 7 and 5 respectively). However, cocaine samples adulterated with levamisole, caffeine and paracetamol only resulted in the adulterant being identified in 29 %, 40 % and 50 % of instances, respectively.

From a harm reduction perspective, FT-IR is the most rapid in terms of data acquisition and analysis (*ca.* a few mins), followed by ^{1}H NMR (*ca.* 5 mins) and then GC-MS (*ca.* 20 mins). However, the rapid nature of data collection must be considered against the accuracy of the data obtained. In this respect, GC-MS provides the most insightful, and accurate, analysis of sample composition for the samples analysed herein, followed by ^{1}H NMR spectroscopy and then finally IR spectroscopy. Furthermore, this study highlights the need to analyse samples using two (or more) analytical techniques to fully validate the component(s) present qualitatively.

CRediT authorship contribution statement

David I. Dixon: Methodology, Investigation, Validation, Formal analysis. **Lysbeth H. Antonides:** Formal analysis. **Andrew Costello:** Resources. **Benjamin Crane:** Resources. **Arran Embleton:** Formal analysis. **Mark L. Fletcher:** Resources. **Nicolas Gilbert:** Formal analysis. **Matthew C. Hulme:** Formal analysis. **Molly J. James:** Formal analysis. **Michael A. Lever:** Resources. **Conner J. Maccallum:** Formal analysis. **Molly F. Millea:** Formal analysis. **Jessica L. Pimlott:** Formal analysis. **Thomas B. R. Robertson:** Formal analysis. **Nathan E. Rudge:** Formal analysis. **Christopher J. Schofield:** Resources. **Filip Zukowicz:** Formal analysis. **E. Kate Kemsley:** Software, Conceptualization, Methodology, Writing – review & editing. **Oliver B. Sutcliffe:** Resources, Supervision, Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Ryan E. Mewis:** Supervision, Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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

Data Availability

The data that has been used is confidential.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpba.2022.114950.

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