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Atmospheric Solids Analysis Probe Coupled to a Portable Mass Spectrometer for Rapid Identification of Bulk Drug Seizures

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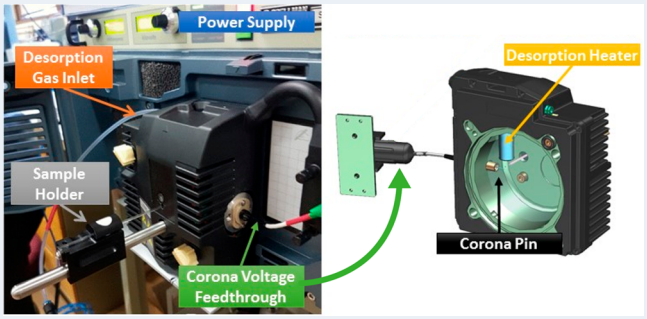
Supporting Information

ABSTRACT: The emergence of ambient ionization techniques and their combination with smaller, cheaper mass spectrometers is beginning to make real the possibility of mass spectrometry measurements being made routinely outside of traditional laboratory settings. Here, we describe the development of an atmospheric solids analysis probe (ASAP) source for a commercially available miniaturized, single-quadrupole mass spectrometer and subsequent modification of the instrument to allow it to run as a deployable system; we further go on to describe the application of this instrument to the identification of the contents of drug seizures. For the drug seizure analysis, a small quantity of the material (powder, tablet, resin, etc.) was dissolved in ethanol and shaken to extract the analytes, the resulting solutions were then sampled by dipping a sealed glass capillary into the solution prior to analysis by ASAP−MS. Identification of the contents of the seizures was carried out using a NIST searching approach utilizing a bespoke spectral library containing 46 compounds representative of those most commonly encountered in UK forensic laboratories. In order to increase confidence in identification the library sample and subsequent analyses were carried out using a four-channel acquisition method; each channel in this method used a different cone voltage (15, 30, 50, and 70 V) inducing differing levels of in-source fragmentation in each channel; the match score across each channel was then used for identification. Using this developed method, a set of 50 real-life drug samples was analyzed with each of these being identified correctly using the library searching method.



INTRODUCTION

Upon making a drug seizure, the first step carried out by law enforcement officers is often to carry out a presumptive test in order to tentatively identify the type of drug which has been seized.[1−5] Presumptive tests are typically simple, inexpensive techniques such as colorimetric "spot" testing which provide rapid results that can be used to guide the next step in the process be that further analysis, preparation of charges, or release of the suspect. While useful for many purposes, the information provided by these presumptive tests can be fairly nonspecific, often limited to compound class rather than a specific molecule; additionally, many of these tests are subject to interference from other compounds such as aspirin and sugar, which can lead to false positives and false negatives. In order to reduce the possibility of such false results it would be desirable, therefore, for law enforcement to have access to more specific detection technology at an earlier stage in the analysis pipeline, for example, at a police station or even at a crime scene.

Mass spectrometry (MS) is one such technology which, when used appropriately, can provide highly specific information for the identification of unknown compounds, and it is therefore defined as one of the "category A" (the most discriminatory) techniques by SWGDRUG (Scientific Working Group for the Analysis of Seized Drugs).[6] As a result, MS (typically combined with gas or liquid chromatography) is generally considered one of the gold standard analytical methods for the identification of drugs of abuse. Until recently, the routine application of MS in nonlaboratory environments has been fairly limited due to a number of factors including the size of the instrumentation, the sample preparation required prior to analysis, the level of expertise required to use the technology, and in particular the cost of purchasing and maintaining the instrumentation. However, two recent advances in MS technology are beginning to address some of these factors, namely, the advent of ambient ionization techniques and advances in MS miniaturization.

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Ambient ionization is a catch all term for the group of techniques which emerged in the early 2000s with the first descriptions of DESI (desorption electrospray ionization)[7] and DART (direct analysis in real time).[8] The key feature of all ambient ionization techniques is the ability to analyse samples directly with minimal sample preparation and no chromatographic separation.[9,10] In DESI, analytes are desorbed and ionized by directing an electrically charged solvent spray (electrospray) toward a surface (e.g., a piece of human tissue), while in DART samples are desorbed and ionized from a surface using a heated plasma of metastable helium (or nitrogen) ions. Since the first descriptions of these techniques many tens of different ambient techniques have been developed which use a variety of ionization mechanisms including electrospray,[11−15] corona discharge,[16,17] dielectric barrier discharge,[18] laser-based ionization,[19] and combinations of these.[20,21] The areas in which these techniques have been applied are manifold but include pharmaceuticals,[22] clinical analysis,[23] food analysis,[24] environmental monitoring,[25] and national security.[26]

One of the main attractions of ambient ionization techniques is their ability to rapidly generate data with total analysis times, including sampling, of often less than 1 min versus the minutes, hours, or even days required for traditional LC− and GC−MS analyses. This ability to rapidly analyze samples lends itself well to the analysis and identification of drug seizures, and it is therefore unsurprising that a large amount of ambient ionization research had fallen in this area.[27−35] DART-MS is the most well-established ionization technique for such analyses, particularly in combination with the JEOL AccuTOF mass spectrometer which has been used to generate a large forensic drug library for use within the NIST-MS search program.[28] It should be noted that the authors of this study suggest that the combination of ambient ionization with a mass spectrometry may not meet the SWGDRUG criteria for a category A technique and may therefore only be accepted as a category B technique.

The development of smaller and more portable mass analyzers has been ongoing almost since the advent of mass spectrometry itself. Many of the key advancements in this area have come from the Cooks group at Purdue University[36−38] who have produced a series of ever smaller ion trap-based instruments up to the current mini-12 instrument, a transportable ion trap which uses a cartridge paper spray device for ionization and has been shown to be a sensitive instrument for the direct analysis of therapeutic drugs in whole blood.[39] The advancements made by the Cooks group and others has led to the commercialization of a variety of miniaturized mass spectrometers from a range of manufacturers; these range from truly hand-portable instruments such as those offered by 908 Devices[40] to larger portable and transportable instruments such as those offered by Advion,[41] Bay Spec,[42] Flir,[35,42] and Microsaic Systems.[43] The combination of ambient ionization with miniaturized mass analyzers offers the potential for MS analysis to be carried out in a range of nonlaboratory environments such as doctors' surgeries, airports, prisons, and police stations. Reports of the combination of ambient ionization with miniaturized mass spectrometers include the combination of DESI with a portable ion trap[44] for the analysis of a range of materials, DART combined with a portable ion trap MS for the identification of drugs of abuse,[45] and on-site screening of evidence from clandestine laboratories using a combination of paperspray ionization, DESI, and APCI on a FLIR AI-MS ion trap.[46] The same group have recently published a validation of the same system for the rapid, in-field identification of drugs of abuse using both DESI and paper spray ionization.[35]

One commercially available miniaturized MS is the Waters QDa (Waters, Wilmslow, UK), a single-quadrupole instrument developed primarily as a detector for nonspecialists such as chromatographers. We have previously demonstrated the use of this instrument in LC−ESI−MS mode for the analysis of trace drugs of abuse in saliva.[47] The QDa has previously been paired with ambient ionization in the form of DART for the authentication of antimalarial tablets[48] and the analysis of a range of analytes in from complex matrices when combined with solid-phase microextraction (SPME) sample preparation.[49] This combination is currently available commercially from Waters.

Here, we present the development of an atmospheric solids analysis probe (ASAP) source for the QDa and the evaluation of the instrument as a device for the rapid identification of drug seizures, with particular consideration to the use of instrumentation outside of a normal laboratory environment. In ASAP, samples (which may be solid or liquid) are introduced to the source via a solid probe such as a glass capillary from where they are desorbed using a heated gas flow (typically nitrogen) prior to ionization via corona discharge.[17] The attractions of ASAP as an ionization technique are manifold but include its relative simplicity and low cost (ASAP can be carried out by making relatively minor modifications to an existing APCI source)[17] and the broad range of analytes it can ionize.[50] Further to this, unpublished work from our laboratory has shown that ASAP works well using ambient air as a desorption gas, removing the need for high-purity gases such as the helium and/or nitrogen required for DART. The combination of ASAP with the QDa was chosen due to its applicability to non-laboratory environments such as police stations which are unlikely to have any of the services available in normal laboratories such as pure gas supplies, exhaust extraction, and the facilities to deal with large volumes of organic solvents.

EXPERIMENTAL SECTION

ASAP Source Design. The standard QDa source is an ESI-only source with a heated nebulizer and separate nebulizer and drying gas flows which are run at fixed flow rates controlled by restriction. This source was modified for ASAP operation by the inclusion of a corona discharge pin to the right of the nebulizer and the removal of the spray capillary and nebulizer housing from the ESI inlet leaving just the drying gas and heater. The nebulizer gas supply was blocked, and the drying gas supply was connected to a manual gas flow controller (Key Instruments, Hatfield, PA) to provide a user-tunable desorption gas flow. The initial source design included a large hole in the front of the source to allow sample to be inserted. The new source geometry was characterized using an XYZ stage to allow the sample position to be altered relative to the position of the heated gas flow, corona pin, and aperture to the mass spectrometer. The result was an optimized source geometry providing spectral quality and sufficient sensitivity for the application. For the final design, a sample introduction rail was added to the front of the source housing positioned such that a glass capillary can be inserted into the source through a smaller hole positioned between the desorption gas

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outlet and corona discharge pin. A schematic of the ASAP-QDa source is shown in Figure 1.

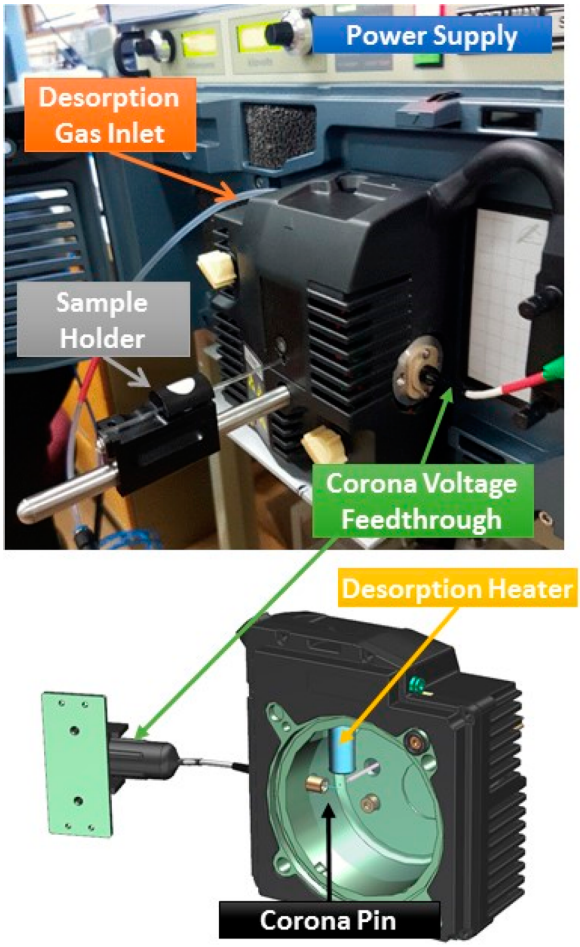

Figure 1. Prototype ASAP-QDa source. The 3D schematic shows the source internals with the locations of the desorption heater, corona pin, and sample. The picture shows the source mounted to the front of the instrument along with the external power and gas supplies.

The power supplies on the standard QDa cannot provide sufficient voltage to maintain a stable corona discharge; the discharge voltage was therefore supplied using an external 8 kV power supply purchased from Spellman High Voltage (Pulborough, West Sussex, UK).

For all experiments, the desorption gas was run at 1 L/min and 450 °C. The corona discharge was operated in positive mode at 2.85 kV in constant voltage mode.

Deployability. A key consideration for this work was the ability to deploy the instrument in nonlaboratory environments where typical laboratory services such as gas supplies will not be available; to address this, we made some minor modifications to the instrument set-up.

The QDa can be configured in two modes: standard, which uses an instrument-mounted diaphragm pump, and performance which uses an external rotary vane backing pump allowing use of a larger diameter inlet orifice. The manufacturer-reported gain in sensitivity on moving from standard to performance mode is around 20-fold under normal conditions (i.e., ESI-MS).

Under normal operating conditions, the QDa uses nitrogen as the system gas; however, as this is unlikely to be available in many field-based scenarios the instrument was moved over to a house compressed air supply (data not shown) which was eventually replaced with a small diaphragm pump (Boxer Pumps, London, U.K.) with a tunable gas flow of between 0.5 and 10 L/min of ambient air.

Initial experiments were carried out in performance mode using nitrogen as the desorption gas; the instrument was then reconfigured into deployable configuration by switching to standard mode and the air from the diaphragm pump. The effect of these changes were assessed using a small set of drugs of abuse standards: diamorphine, MDMA, ketamine, cocaine, methamphetamine, diazepam, and THC (all Sigma-Aldrich, Poole, UK). The compounds were prepared at 100 μg/mL in methanol and sampled by dipping with a 1.9 mm diameter, sealed glass capillary to a depth of ~2 mm; the sample was allowed to dry for 30 s before analysis in full scan mode (m/z 50−650) with a cone voltage ramp used to maximize the $[M + H]^+$ signal for all analytes.

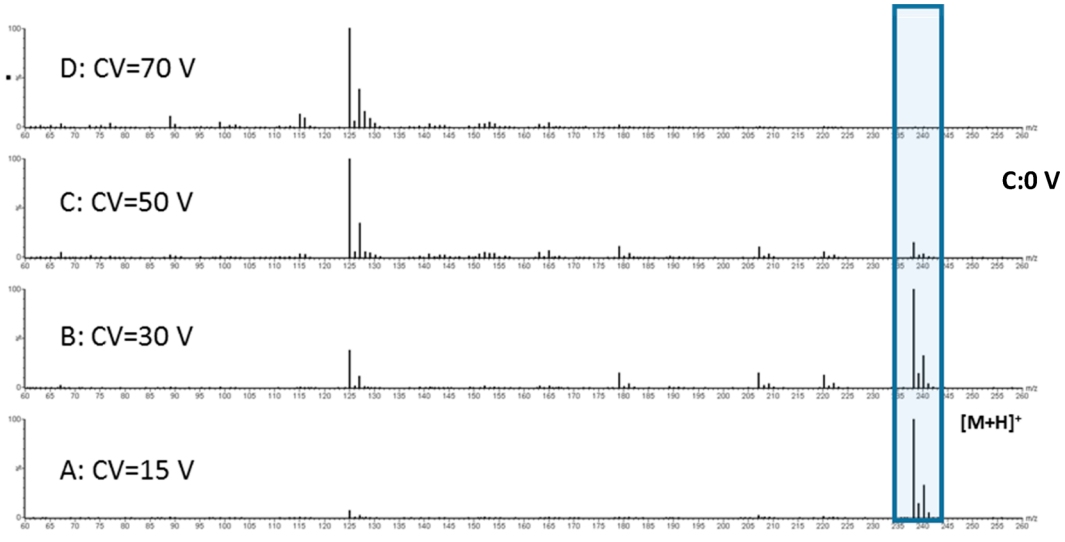

Figure 2. Representative mass spectra for a ketamine standard analyzed by ASAP-QDa at the four standard cone voltages: A, 15 V; B, 30 V; C, 50 V; D, 70 V.

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Library Generation and Identification Criteria. As a single-quadrupole instrument the specificity of the QDa is limited, particularly when no chromatographic separation is included such as in the case of ambient MS. The QDa, however, does offer the possibility of simultaneously analyzing a sample using multiple cone voltages which can be used to induce in-source fragmentation in order to aid specificity.[47] The approach is widely used in ambient ionization to aid identification, for example, for the data contained in the NIST DART-MS forensic database which contains reference DART-ToF data for over 1000 drugs of abuse.[28]

While it is possible to run many tens of different cone voltages in any one experiment, four different voltages were found to provide sufficient information for identification purposes for this application, the voltages chosen were based on those typically used by Waters for these types of experiment namely 15, 30, 50, and 70 V. Figure 2 shows the typical mass spectra obtained for ketamine (100 μg/mL in methanol) using this acquisition method, showing a clear protonated ion at the lowest cone voltage and increasing amounts of characteristic fragment ions as the cone voltage is increased.

This MS method was then used to create a library by analyzing a series of standard solutions (0.1 or 1 mg/mL in acetonitrile or methanol; all Sigma-Aldrich, Poole, UK) of drugs of abuse, adulterants, and cutting agents representative of those most commonly encountered in UK forensics laboratories. The library includes opiates, amphetamines, cathinones, benzodiazepines, stimulants, cannabinoids, and synthetic cannabinoids with a total of 47 compounds currently included; the full list of compounds included can be found the Supporting Information (Table S1. Library spectra were generated using Masslynx (Waters, Wilmslow, UK) by combining the data across the observed TIC chromatogram peak (typically 5−10 s FWHM) without background subtraction. The resulting spectra used an intensity threshold of 2−5% (depending on complexity) with separate spectra being generated for each cone voltage. The resulting library was indexed within Masslynx and converted to NIST format using the Chromalynx module.

Library matching was carried out using NIST 17 (NIST, Gaithersburg, MD) with search spectra generated in the same manner as for the library generation using a fixed 2% threshold; searches were filtered by cone voltage (i.e., 15 V cone voltage unknown spectra were compared against 15 V cone voltage library spectra and so on). Table 1 shows example search scores obtained using forward and reverse searching for a selection of single compounds and in-house produced mixtures of those compounds. We see that for the individual compounds the obtained match scores are high using both forward and reverse matching; however, when mixtures of these compounds are analyzed the forward scores drop significantly in all cases while the reverse match scores are far less affected. This is a direct consequence of the nature of the experiment being conducted here; as there is no chromatographic step included, the spectra generated are representative of all species present. This leads to lower forward match scores as those scores are penalized by the presence of unmatched peaks in the search spectrum. As reverse searching only penalizes for ions which are present in the library spectra but not in the search spectra, the match scores remain high and this approach is therefore better suited to ambient MS analysis. Match criteria were therefore developed using a reverse NIST searching approach with a "hit" requiring a score ≥800 for channel 1 (cone voltage = 15 V), scores of ≥600 in the three remaining channels, and an average score of ≥750.

Table 1. Average Forward and Reverse Match Scores for Individual DoA Standards and Mixtures

sample	analyte	avg forward match score	avg reverse match score
ketamine only	ketamine	897	992
cocaine only	cocaine	913	988
cocaine/ketamine Mix	cocaine	522	964
	ketamine	681	954
diamorphine only	diamorphine	829	985
6-MAM only	6-MAM	687	964
morphine only	morphine	639	848
diamorphine/6-MAM/ morphine mix	diamorphine	517	800
	6-MAM	452	865
	morphine	537	836

Analysis of Drug Seizures. Drug seizures can come in a number of forms including powders, plant material, paper tabs, crystals, and pills, each of which present different challenges for direct analysis, particularly in nonlaboratory environments. To deal with these potential challenges, we developed a simple protocol for the analysis of seizures by ASAP-QDa. Upon receipt of a sample, a small amount of material (~1 mg of powder, one paper tab, one small crystal, etc.) was transferred to a clean 4 mL vial, and 1 mL of ethanol was then added to the vial which was then vortexed for 10 s to aid dissolution. Ethanol was chosen as the solvent thanks to its "catch-all" nature and its perceived lower hazard in comparison to other solvents during handling, meaning the protocol should be easily accepted for use in non-laboratory environments.

A set of 50 representative UK drug seizures were drawn from recent sample submissions to Eurofins Forensic Services. These samples had previously been subjected to full forensic analysis and had assigned identities based on those analyses. The samples included street heroin of various purities, cocaine, ketamine, benzodiazepines, synthetic cannabinoids, cannabis, MDMA (ecstasy), and opium. Each sample was prepared according to the above protocol and analyzed using the described ASAP-MS method prior to database searching. Total analysis time using this approach (including sample preparation) can be as little as 2 min.

RESULTS AND DISCUSSION

Performance in Deployable Configuration. Figure 3 shows the average peak-to-peak signal-to-noise obtained for each of these analytes (N = 5) in performance mode using nitrogen, in standard mode using nitrogen, and in standard mode using ambient air. A considerable drop in S/N is observed for all analytes ranging from 8-fold for THC up to 500-fold for heroin with a median drop in S/N of 52. The observed variation in sensitivity loss is largely a result of differing changes in measured noise across the measured mass range (raw signal loss was between 30- and 60-fold for all analytes; noise increased 12-fold for heroin but decreased 5-fold for THC). Replacing the nitrogen desorption gas with air, however, has virtually no effect on sensitivity with the only significant drop in S/N being observed for cocaine.

Overall, the limits of detection in "deployable mode" (standard configuration using ambient air) were found to be of the order of 5 ng of analyte "on rod" for the species studied

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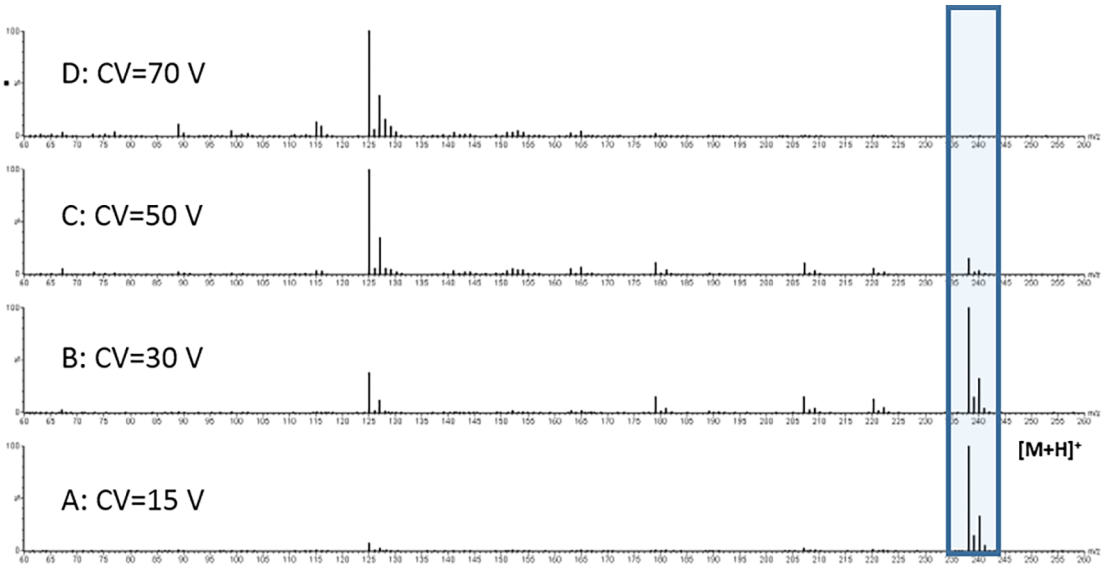

Figure 3. Average peak-to-peak signal-to-noise ratios for a range of DoA standards measured by ASAP-QDa in three different configurations: performance mode with N_2 desorption gas (blue), standard mode with N_2 desorption gas (red), and standard mode with ambient air desorption gas (green). Error bars represent ±1 standard deviation (N = 5). Note that the y-axis scale is logarithmic.

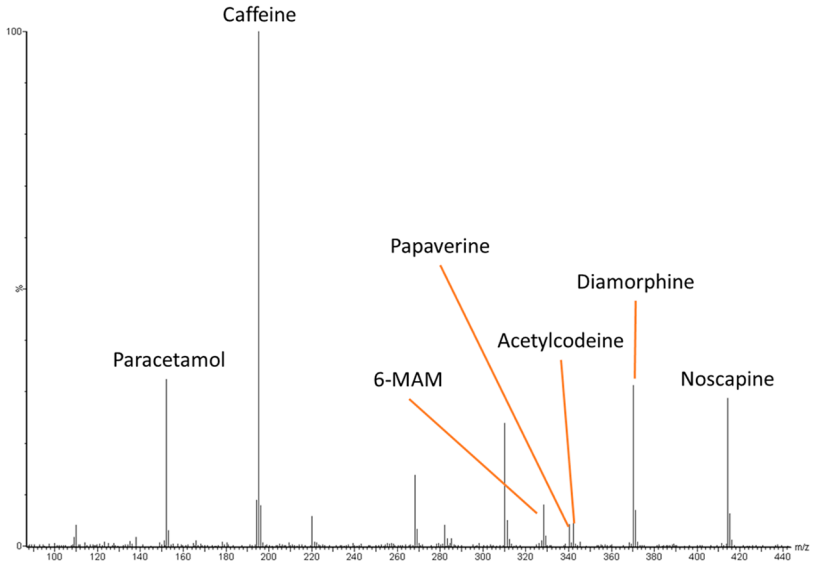

Figure 4. Example low cone voltage (15 V) mass spectrum obtained for a typical street heroin seizure showing evidence of the presence of paracetamol, caffeine, diamorphine (heroin), acetylcodeine, monoacetylmorphine, papaverine, and noscapine.

this was deemed to be sufficient for the analysis of bulk drugs (where concentrations are typically high), and this set-up was used for all subsequent experiments.

Usability and Robustness. One of the key attractions of the QDa as a platform for this work was its reliability and relative simplicity. The instrument pumps down to a useable vacuum within 30 min of start-up and can be configured to perform a mass calibration and resolution tune each time it is switched on, thus ensuring consistency of results.

The instrument has been in use in regular use in our laboratory for a number of years, primarily in combination with a range of ambient ionization sources. During this time, the instrument has been heavily used and found to be reliable and robust with no noted down time. For ASAP operation, we found the corona pin required cleaning every 3−6 months and the sample orifice required replacement approximately every 4 months. The need to replace the sample orifice can be easily diagnosed by monitoring the turbo pump power, which can be seen to decrease when the inlet is partially blocked. Replacing this part is a tool-free operation which takes approximately 45 min including cooling the source and pumping back down to vacuum after installation.

Analysis and Identification of Drug Seizures. The 50 seizure samples were prepared as described and analysed by ASAP-QDa before being searched against the generated library as described. In all cases, matches are based on a single "dip" and analysis. The manual nature of the current database searching approach means this step currently takes around 2 min per samples; however, a software tool is in development to automate this procedure, which will greatly improve analysis speed.

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Figure S1 (Supporting Information) shows an example set of spectra for an MDMA seizure with the reverse search scores for MDMA for each spectrum; the library spectra are shown in Figure S2 for comparison. The search scores for channels 1−4 (low to high cone voltage) were 970, 924, 901, and 904, respectively, with a mean score of 924.75 indicating excellent agreement between the spectra obtained for the seizure and those in the database and resulting in a "hit" for MDMA; no other compound was detected in this sample.

Figure 4 shows an example low cone voltage spectrum of data obtained for a typical street heroin seizure. The spectra obtained here are clearly significantly more complex than those obtained for MDMA. This complexity is due to the presence of a number of different species in the heroin along with the main diamorphine component including other opium alkaloids and derivatives left over from the initial extraction and synthesis (e.g., papaverine) and cutting agents added to bulk out the drug (e.g., paracetamol). From the 15 V cone voltage channel we can see potential $[M + H]^+$ peaks which may correspond to paracetamol (m/z 152), caffeine (m/z 195) , 6-monoacetylmorphine (6-MAM, m/z 328), papaverine (m/z 340), acetylcodeine (m/z 342), diamorphine (m/z 370), and noscapine (m/z 414). Library searching of this data gives hits for 6-MAM, morphine, diamorphine, acetylcodeine, and noscapine with the best matches being for 6-MAM and diamorphine. The hit for morphine, which is not known to be present in this sample, is a result of the similarity in fragmentation patterns between morphine, diamorphine, and 6-MAM (both of which are present in the sample) resulting in high scores for morphine in all channels; similarly, some samples which contain acetylcodeine also gave a hit for codeine. This observation is a key drawback of using in-source fragmentation where no precursor selection can occur. Caffeine and paracetamol both yield high match scores (>850) in channels 1−3 but give no match in channel 4 and are therefore not considered to be hits. This is a consequence of the complexity of the sample and the degree of fragmentation observed for all species at this cone voltage which combine to mask many of the diagnostic caffeine and paracetamol ions at this cone voltage.

Table 2 summarizes the identification results for all 50 seizures analyzed where "sample type" indicates the major illegal constituent as identified by full forensic analysis of the samples. Here, we see that in 49 of the 50 analyzed samples the major constituents identified by ASAP-QDa are in agreement with the full forensic analysis. The single missed identification was for Ritalin (methyl phenidate), which is not currently in the database so correctly gave no hits. As with the example shown in Figure 4, we see that in many cases morphine and/or codeine are incorrectly identified as being present in street heroin. Importantly, in each of these cases diamorphine was also identified as being present in the sample, meaning that no sample would be misclassified on the basis of this data. This does, however, support Steiner and Larson's suggestion that ambient ionization mass spectrometry would likely be considered a "category B" method by SWGDRUG.[28] It may be possible to reduce the incidence of these incorrect identifications by using stricter identification criteria during library searching, although this would likely lead to an increase in false negatives, particularly for samples with lower purity.

The heroin samples included here cover a wide range of purities representative of those typically observed by UK forensics laboratories from street purities (as low as 15% pure) to wholesale purities (as high as 75% pure) demonstrating the ability of the technique to identify diamorphine across a range of sample purities. This ability is further demonstrated by the inclusion of amphetamine in the sample group; these samples were of very low purity (<5%) but were all identified correctly with high scores across the four acquisition channels.

Table 2. Summary of Results from Analysis of Drug Seizures

sample type	no. of seizures	correctly identified	comments
heroin (diamorphine)	16	16	morphine incorrectly identified (5/16), codeine incorrectly identified (4/16)
MDMA	5	5	
LSD	1	1	
alprazolam	2	2	
diazepam	2	2	
ketamine	2	2	
amphetamine	4	4	caffeine also identified 2/4 samples
4-chloroethcathinone	1	1	
MMB-fubinaca	3	3	
oxymetholone/ methandienone	1	1	
Ritalin	1	0	not in library
cocaine	5	5	
benzocaine	2	2	
opium	1	1	morphine, thebaine, papaverine, and noscapine identified as present
tramadol	1	1	
cannabis	3	3	
total	**50**	**49**	

CONCLUSIONS

In this work, we have presented the modification of a commercially available, low-cost, miniaturized mass spectrometer to include a prototype atmospheric solids analysis probe source. We have further shown that by making some simple modifications the instrument can be operated in a deployable configuration using an instrument-mounted diaphragm pump to provide roughing vacuum and a second smaller diaphragm pump to provide a flow of ambient air for desorption. Having made these modifications, the reconfigured instrument only requires a power source in order to operate with no need for exhaust extraction or pure gas supplies, meaning the instrument can easily be used in nonlaboratory environments. While in its current form the added power supply, gas flow controller, and air pump lie outside the instrument form factor, we have identified suitable units such that these could be easily moved within the casing of the instrument.

The development of this instrument had the specific aim of providing an MS-based tool to law enforcement and forensic laboratories for the rapid identification of drugs of abuse that could complement or even supersede current presumptive tests. To meet this goal, we have built a small database of drugs of abuse and common cutting agents which covers around 95% of all UK drugs seizures. The performance of the instrument when tested against a range of real-world drug seizures was shown to be excellent with few false positives and only a single negative result due to the compound of interest not being present in the library. The current identification workflow is somewhat nontrivial due to the manual nature of the search

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process; however, we are currently working on a software tool which will allow this process to be automated for easier identification and further allow the easy addition of new compounds. In the near future, we plan to deploy the next version of this instrument in a forensics laboratory where it will be validated for the routine screening of drugs of abuse in a forensic laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jasms.9b00020..

List of compounds included in the ASAP QDa MS database (Table S1), example mass spectra obtained for an MDMA seizure (Figure S1), and four NIST library spectra for MDMA (Figure S2) (PDF)

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Notes

The authors declare no competing financial interest.

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