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Rapid Analysis of Trace Drugs and Metabolites Using a Thermal Desorption DART-MS Configuration[†]

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Abstract

The need to analyze trace narcotic samples rapidly for screening or confirmatory purposes is of increasing interest to the forensic, homeland security, and criminal justice sectors. This work presents a novel method for the detection and quantification of trace drugs and metabolites off of a swipe material using a thermal desorption direct analysis in real time mass spectrometry (TD-DART-MS) configuration. A variation on traditional DART, this configuration allows for desorption of the sample into a confined tube, completely independent of the DART source, allowing for more efficient and thermally precise analysis of material present on a swipe. Over thirty trace samples of narcotics, metabolites, and cutting agents deposited onto swipes were rapidly differentiated using this methodology. The non-optimized method led to sensitivities ranging from single nanograms to hundreds of picograms. Direct comparison to traditional DART with a subset of the samples highlighted an improvement in sensitivity by a factor of twenty to thirty and an increase in reproducibility sample to sample from approximately 45 % RSD to less than 15 % RSD. Rapid extraction-less quantification was also possible.

Keywords

Thermal Desorption; DART-MS; Ambient Ionization; Trace Narcotics

Introduction

Rapid, specific, and reproducible identification of trace drugs and their metabolites to support applications in both forensic science and trace contraband detection. In the forensic science community, where there exists a significant backlog in controlled substance cases,^{1,2} the ability to rapidly characterize a narcotic sample, from a field collection or laboratory swipe, with a highly specific and reproducible screening technique would provide significant improvements in both case backlog and turnaround time. Direct analysis in real time mass spectrometry (DART-MS) has been shown to be able to detect a large array of drugs and metabolites^{3–10} however traditional DART-MS analysis, commonly completed by dissolving

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the sample and analyzing an aliquot with a glass capillary, suffers from poor reproducibility due to inconsistent sample introduction resulting from the small spatial footprint of the DART sampling jet and variations in sampling geometry as highlighted by Harris *et al.*¹¹

For trace contraband detection using swipe sampling at security checkpoints and border crossings there is an emphasis on rapid and selective analysis that will minimize both wait times and false alarms while being able to cope with complex background matrices such as dust, dirt, and fingerprint residues. Traditionally, ion mobility spectrometry has been used for these applications^{12–15} which, though rapid, lack specificity, especially for the increasing number of chemically similar designer drugs such as synthetic cannabinoids and cathinones. However, the traditional method of sampling for DART⁹, is impractical for this application, where swipe sampling is traditionally used. Previous work has shown confined DART configurations, whereby the DART gas stream is confined to a tube before reaching the mass spectrometer inlet, are possible, but these variations have been implemented mainly for use in detection of volatile compounds from human breath or other objects.^{16–18}

This work presents an initial proof-of-concept of a confined thermal desorption DART-MS (TD-DART-MS) configuration which allows for rapid, specific, and reproducible analysis of trace drug and metabolite samples. The system incorporates a glass junction to confine the DART gas stream and thus enhance reproducibility. A thermal desorber is also coupled to the glass junction to allow for reproducible sample introduction using the sampling swipes commonly encountered in a trace contraband detection setting. A total of 34 different drugs, metabolites, and cutting agents were examined. Their representative spectra and sensitivities are discussed. A direct comparison in sensitivity and reproducibility to the traditional DART configuration is also presented. The potential application for quantification, since this is a closed system which allows for more complete consumption of the analyte, is also highlighted.

Experimental Methods

Instrumentation

A schematic of the TD-DART configuration used in this work is shown in Figure 1. The configuration utilizes an on-axis DART-SVP source (IonSense, Saugus, MA, USA), in line with a Vapur® interface (IonSense). Between the source and the interface is a glass tee junction, the dimensions of which are shown in Figure 1. The junction is wrapped in insulating material (heating tape, heat wrap) to help maintain an elevated temperature. One end of the junction is fitted directly into the Vapur interface, in place of the typical ceramic tube. There is a 2 mm – 3 mm gap in between the DART and the other end of the glass junction to allow airflow into the system, which is necessary for ionization. The thermal desorber (Morpho Detection, Newark, CA, USA) is press-fit directly onto the junction and allows temperature control within the range of 22 °C – 245 °C. The thermal desorption unit consists of a series of cartridge heaters that heat both the top and bottom of a 2 mm by 28 mm sample introduction inlet (Figure 1). The DART supplies nitrogen at a rate of approximately 1.5 L min⁻¹ and the vacuum side of the Vapur interface draws at a rate of 3.0 L min⁻¹, to ensure flow towards the MS interface. The draw of the vacuum through the

Vapur interface is controlled by a needle valve and measured by a mass flow meter (FMA 1700 Series, Omega Engineering Inc., Stamford, CT, USA).

In this study, a temperature of 240 °C was chosen for the thermal desorption unit based on prior published methods using thermal desorption ion mobility spectrometry (IMS) systems.^{12,19} To favor analytes remaining in the gas phase and reduce losses due to recondensation, the DART gas (nitrogen, zero air) was used to heat (350 °C) the glass, and was operated in positive ionization mode.

The TD-DART setup was attached to a JEOL JMST1000-LP AccuTOF mass spectrometer (JEOL USA, Peabody, MA, USA). The system was operated with an orifice temperature of 100 °C, ring lens voltage of +5 V, orifice 2 voltage of +10 V, peaks voltage of 400 V, and detector voltage of +2000 V. The orifice 1 voltage was cycled through +10 V, +30 V, +60 V, and +90 V at a scan rate of 1 scan s⁻¹, to obtain both low fragmentation and high fragmentation spectra. All spectra shown are from the +10 V orifice 1 voltage scan, unless otherwise stated. A mass scan range of 50 *m/z* to 600 *m/z* was used.

Materials

A total of 34 drugs, metabolites, and cutting agents (Table 1) were purchased as 1 mg mL⁻¹ solutions or in solid form and dissolved to a concentration of 1 mg mL⁻¹ with methanol (Chromasolv, Sigma-Aldrich). All samples were further diluted to a range of 0.1 µg mL⁻¹ to 100 µg mL⁻¹ to allow for deposition of the desired mass (0.1 ng to 100 ng) in a 1 µL to 5 µL aliquot. Samples were directly deposited onto PTFE coated fiberglass swipes (DSA Detection, North Andover, MA, USA). The position of the deposition was in the area of the swipe which exhibited maximum signal intensity, based on previous work.²⁰

Results and Discussion

Spectral Response & Sensitivities

To evaluate the system efficacy for the compounds in Table 1, 100 ng of each compound were deposited onto swipes and analyzed. Response of all compounds was rapid (typically within two seconds after insertion) and readily distinguishable from background (S/N exceeding 500:1). Example spectra of methamphetamine and α-pyrrolidinopentiophene (α-PVP) are shown in Figure 2. At a low orifice 1 voltage (+10 V) (Figure 2 A and C and Table 1), all compounds, except ecgonine methyl ester (EME), produced a readily detectable protonated molecule, typical of drugs analyzed by DART-MS.^{3,4} EME preferentially formed a hydronium adduct ion [M+H₃O]⁺ with a nominal mass of 200 *m/z* which was also readily detectable (S/N exceeding 2,000:1). It is important to note, in contrast to conventional DART, a substantially higher (two to three orders of magnitude) signal was obtained by using nitrogen as the ionization gas instead of helium. This may be due to the active pull of the Vapur source which could quench the helium metastables prior to sample or atmospheric water ionization. As the orifice 1 voltage was increased to +60 V and +90 V (Figure 2 B and D and Table 1), most molecules exhibited an expected reduction in the protonated molecule signal as well as more extreme fragmentation. The fragmentation was compound-dependent and included dehydration and/or cleavage of the molecule into smaller fragments.

To compare the mass spectra obtained from the TD-DART-MS configuration to a typical DART-MS configuration, spectra were searched against the NIST DART Forensics Library (Gaithersburg, MD, USA). This library contains mass spectra of narcotics, from the Virginia Department of Forensic Science, analyzed at +20 V, +30 V, +60 V, and +90 V orifice 1 voltages. Sixteen of the compounds studied were present in the library and included methamphetamine, cocaine, 6-AM, methadone, PCP, oxycodone, MDMA, temazepam, oxazepam, amphetamine, naloxone, heroin, buprenorphine, naphyrone, methylone, and 3,4-MDPV. When searched against the library, all peaks at the corresponding voltages (+10 V was compared to the library's +20 V spectra) matched, with identical base peaks in all spectra. The hits for all compounds at all voltages matched the identity of the analyte searched.

Approximate sensitivities were evaluated by determining the lowest level at which the compounds were detected with a signal to noise ratio of at least 10:1, and are shown in Table 1. All sensitivities were obtained using an orifice 1 voltage of +10 V, as higher orifice 1 voltages induce fragmentation, causing a reduction in the base peak. Nearly all compounds were detectable at or below the 1 ng swipe⁻¹ level. This value was lower than levels (single to tens of nanograms) previously reported using a traditional DART-MS configuration.²¹ Larger compounds, such as heroin and 11-nor-9-caboxy- Δ^9 -THC were only detectable at the 5 ng swipe⁻¹ level, likely due to lower volatilities, which limited sample desorption. Increasing the desorption temperature would likely help to increase the sensitivity of these compounds by more readily releasing the chemical off of the surface, however, thermally labile compounds would be more likely to decompose.

A head-to-head comparison of LODs between traditional DART-MS and TD-DART-MS was completed on a small subset of compounds (methamphetamine, temazepam, and 4-MMC). LODs were calculated using ASTM Method E2677.²² To calculate the LODs, ten replicates containing one of five mass levels ((0, 0.25, 1, 10, 100) ng) were analyzed randomly by either depositing onto a swipe (TD-DART-MS) or pipetting onto a glass capillary (traditional DART-MS). Parameters for the traditional DART-MS analysis included a 300 °C gas temperature, helium as the DART gas, and a $\approx$ 0.5 cm sampling distance from the DART source. Peaks areas were calculated and entered into the ASTM E2677 web portal to calculate the LOD90 value (90 % confidence level limit of detection). For all three compounds TD-DART-MS exhibited at least a factor of 20 lower LOD90. LOD90 values for TD-DART-MS were 0.11 ng, 0.16 ng, and 0.07 ng for temazepam, methamphetamine, and 4-MMC respectively. Traditional DART-MS exhibited corresponding LOD90 values of 3.28 ng, 3.35 ng, and 1.59 ng. In addition to improved sensitivity, the TD-DART-MS configuration demonstrated lower sample-to-sample variation. Relative standard deviations (RSDs) of the ten replicates using the TD-DART-MS configuration ranged from 5 % to 14 % while RSDs using traditional DART-MS ranged from 23 % to 80 %. The improvement in reproducibility of TD-DART-MS over conventional DART-MS was increasingly noticeable at low mass levels. In this regime, rapid desorption produced significant variability with inaccurate positioning of the glass capillary in the DART gas stream.

Calibration Curve

One of the major drawbacks to traditional DART-MS analysis is the large response variability from sample-to-sample because of inconsistent sample introduction. In the TD-DART-MS configuration, the system is confined to the desorber and glass junction, allowing for increased reproducibility and efficiency in sample introduction. Improved reproducibility can lead to quantitative analysis by this type of system. To evaluate the systems quantification capability, a six-point calibration curve of MDA was created by pipetting a known mass, (1, 5, 10, 25, 50, or 100) ng of MDA onto 5 swipes in addition to 10 ng of an internal standard (MDA-d5). Analysis of these samples produced a linear calibration curve with an R^2 value exceeding 0.999 independent of the incorporation of internal standard data. Relative standard deviations of the replicate measurements ranged from 2 % to 12 %, exceeding the typical 30 % to 40 % relative standard deviation of traditional DART measurements.

Complex Mixtures

In real-world forensic and trace contraband detection applications, it is unlikely that a pure drug will be analyzed. There may be a number of interferents, cutting agents or multiple drugs, complicating the mass spectrum and increasing the potential for competitive ionization, signal suppression, and false positive or false negative results. To simulate these situations, a number of complex mixtures were analyzed by pipetting known amounts of mixtures onto swipe materials. These samples consisted of common drug mixtures, drugs with cutting agents, drugs with metabolites, and drugs in the presence of a complex matrix.

Figure 3 highlights the spectra of several examples. Figure 3A shows the analysis of multiple drugs (10 ng of naloxone and buprenorphine). In addition to drug mixtures, when dealing with forensic drug identification or trace contraband screening, it is likely that a narcotic with a cutting agent will be encountered. Figure 3B simulates the response of heroin (30 ng) and a common cutting agent, acetaminophen (10 ng). In a forensic setting, it is likely that simultaneous detection of a drug and its metabolites may be required. Figure 3C depicts the concurrent detection of 9-THC and cannabinal with two metabolites, 11-hydroxy-9-THC and 11-nor-9-carboxy-9-THC (10 ng each). From a trace contraband viewpoint, it may also be necessary to detect narcotics, and potentially their metabolites, in the presence of a complex matrix such as a fingerprint. This would be especially useful for hand swiping or direct fingerprint analysis off of swipes. Figure 3D shows the detection of cocaine, EME, and benzoecgonine (10 ng each) in the presence of an artificial fingerprint material²³ (1,000 ng). The artificial fingerprint material contains over forty different chemicals at varying concentrations, to mimic an actual fingerprint, and includes fatty acids, salts, amino acids, and other compounds.²³ In all four examples, detection of the drugs at low levels was rapid, specific, and exhibited minimal negative effects (competitive ionization or signal suppression) from the presence of additional drugs, cutting agents, metabolites, or other complex matrices. Furthermore, system removal of complex matrices was rapid, and occurred in less than thirty seconds, a necessity in a high throughput screening environment.

Conclusion

The TD-DART-MS configuration can readily detect a number of drugs, cutting agents, and metabolites at the level of 0.2 to 5 ng. Complex mixtures, including multiple drugs, drugs and metabolites, and drugs in the presence of fingerprint residue showed minimal negative effects on the detection of the compounds of interest. Because of the confined system and reproducible method of sample deposition, quantification was possible, as highlighted with a MDA calibration curve with relative standard deviations at or below 12 % across replicates. Sensitivity was up to a factor of 30 times better using this configuration, compared to traditional DART-MS, and sample-to-sample reproducibility was improved by up to a factor of 4.

The use of a thermal desorption configuration provides rapid, specific, and reproducible results, has many potential applications including pharmaceutical quality control, forensic controlled substance testing, toxicology and trace contraband security screening. Current work is looking at evaluating the applicability of this technique for additional compound classes, such as explosives, pesticides, phthalates, and biomolecules. Additional configurations, involving accommodation for dopant introduction, different junction geometries and junction lengths, secondary desorption mechanisms, and rapid quantification are also being researched. The role of nitrogen for increased sensitivity over helium is also being investigated. Optimization of the system for both enhanced sensitivity and reproducibility is also being completed.

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Figure 1.

A schematic of the thermal desorption direct analysis in real time (TD-DART) configuration (top) and dimensions of the glass junction (bottom).

Figure 2. Representative mass spectra of methamphetamine (A. and B.) and α -PVP (C. and D.) at a low fragmentation voltage (A. and C.) and a high fragmentation voltage (B. and D.).

Figure 3.
Representative spectra of complex mixtures. Peaks corresponding to the compounds of interest are identified.

Table 1

List of the drugs, metabolites, and cutting agents tested as well as their limits of sensitivity and base peaks from the +10 V (low fragmentation) and +60 V (high fragmentation) spectra. Supplier corresponds to (1) Cayman Chemicals (Ann Arbor, MI, USA), (2) Cerilliant (Round Rock, TX, USA), or (3) Sigma-Aldrich (St. Louis, MO, USA).

Drug	CAS#	Approximate Sensitivity (ng)	Base Peak (+10 V)	Assignment	Base Peak (+60 V)	Assignment	Supplier
Stimulants							
Amphetamine	300-62-9	1.0	136.113	[M+H] ⁺	91.055	[C ₇ H ₇] ⁺	2
Cocaine	50-36-2	0.25	304.155	[M+H] ⁺	182.118	[M-C ₇ H ₅ O ₂] ⁺	1
Methamphetamine	537-46-2	0.10	150.128	[M+H] ⁺	91.055	[C ₇ H ₇] ⁺	3
Methylenedioxymphetamine (MDA)	101-77-9	0.50	180.224	[M+H] ⁺	163.076	[M-NH ₂] ⁺	3
3,4-Methylenedioxymphetamine (MDMA)	42542-10-9	0.75	194.118	[M+H] ⁺	163.076	[M-CH ₄ N] ⁺	3
Opioids							
Buprenorphine	52485-79-7	1.0	468.311	[M+H] ⁺	450.301	[M-OH] ⁺	2
Heroin	561-27-3	5.0	370.165	[M+H] ⁺	370.165	[M+H] ⁺	3
Methadone	76-99-3	0.50	310.217	[M+H] ⁺	265.159	[M-C ₂ H ₆ N] ⁺	2
Naloxone	465-65-6	0.50	328.155	[M+H] ⁺	310.144	[M-OH] ⁺	2
Oxycodone	76-42-6	1.0	316.155	[M+H] ⁺	298.144	[M-OH] ⁺	2
Cannabinoids							
Cannabichromene	20675-51-8	0.25	315.232	[M+H] ⁺	315.232	[M+H] ⁺	1
Cannabinol	521-35-7	0.50	311.201	[M+H] ⁺	295.170	[M-CH ₃] ⁺	1
Tetrahydrocannabinol-9-THC	1972-08-3	1.0	315.232	[M+H] ⁺	315.232	[M+H] ⁺	1
Synthetic Cathinones							
3,4-Dimethylcathinone (3,4-DMC)	1081772-06-6	0.50	192.139	[M+H] ⁺	174.128	[M-OH] ⁺	2
4-Ethylmethcathinone (4-EMC)	1391053-87-4	1.0	192.139	[M+H] ⁺	174.125	[M-OH] ⁺	2
Methylenedioxypyrovalerone (3,4-MDPV)	687603-66-3	0.10	276.150	[M+H] ⁺	276.160	[M+H] ⁺	2
2-Methylmethcathinone (2-MMC)	1246815-51-9	0.25	178.123	[M+H] ⁺	160.113	[M-OH] ⁺	1
4-Methylmethcathinone (4-MMMC)	1189726-22-4	0.25	178.123	[M+H] ⁺	160.113	[M-OH] ⁺	2
Mephedrone (MDMC)	186028-80-8	0.25	208.097	[M+H] ⁺	160.113	[C ₁₁ H ₁₄ N] ⁺	2

Drug	CAS#	Approximate Sensitivity (ng)	Base Peak (+10 V)	Assignment	Base Peak (+60 V)	Assignment	Supplier
Naphyrone	850352-53-3	0.50	282.186	[M+H] ⁺	282.186	[M+H] ⁺	2
α -Pyrrolidinopentiophenone (α -PVP)	5485-65-4	0.10	232.170	[M+H] ⁺	232.170	[M+H] ⁺	2
Hallucinogens							
Phencyclidine(PCP)	87-86-5	1.0	244.206	[M+H] ⁺	86.100	[C ₃ H ₁₂ N] ⁺	2
Benzodiazepines							
Oxazepam	604-75-1	1.0	287.059	[M+H] ⁺	269.048	[M-OH] ⁺	1
Temazepam	846-50-4	0.25	301.074	[M+H] ⁺	301.074	[M+H] ⁺	1
Metabolites							
6-Acetylmorphine (6-AM)	2784-73-8	0.50	328.155	[M+H] ⁺	328.155	[M+H] ⁺	2
Benzocgonine	94-09-7	1.0	290.139	[M+H] ⁺	290.139	[M+H] ⁺	1
Cotinine	486-56-6	0.25	177.103	[M+H] ⁺	177.103	[M+H] ⁺	2
Ecgonine Methyl Ester (EME)	7143-09-1	0.10	200.129	[M+H ₃ O] ⁺	182.118	[M+H] ⁺	2
11-hydroxy- -9-THC	34675-49-5	5.0	331.227	[M+H] ⁺	331.227	[M+H] ⁺	2
11-nor-9-carboxy- -9-THC	64280-14-4	5.0	345.206	[M+H] ⁺	345.206	[M+H] ⁺	2
Other							
Acetaminophen	103-90-2	0.25	152.071	[M+H] ⁺	152.071	[M+H] ⁺	3
Benzocaine	94-09-7	0.50	166.087	[M+H] ⁺	166.087	[M+H] ⁺	3
Levamisole	16595-80-5	0.75	205.080	[M+H] ⁺	205.080	[M+H] ⁺	2
Nicotine	22083-74-5	0.25	163.123	[M+H] ⁺	132.081	[M-CH ₄ N] ⁺	2