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Forensic applications of DART-MS: A review of recent literature

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ABSTRACT

The need for rapid chemical analyses and new analytical tools in forensic laboratories continues to grow due to case backlogs, difficult-to-analyze cases, and identification of previously unseen materials such as new psychoactive substances. To adapt to these needs, the forensics community has been pursuing the use of ambient ionization mass spectrometry, and more specifically direct analysis in real time mass spectrometry (DART-MS), for a wide range of applications. From the inception of DART-MS forensic applications have been researched with demonstrations ranging from drugs of abuse to inorganic gunshot residue to printer inks to insect identification. This article presents a review of research demonstrating the use of DART-MS for forensically relevant samples over the past five years. To provide more context, background on the technique, sampling approaches, and data analysis methods are presented along with a discussion on the potential future and research needs of the technology.

1. Introduction

Since its inception direct analysis in real time mass spectrometry (DART-MS) has been a powerful tool for the field of forensic chemistry due the ability to rapidly obtain a near complete chemical profile of a sample. While traditionally considered a screening tool, recent advances in sample preparation and sample introduction techniques, along with advances in mass spectrometry and chemometric analyses, have shown that DART-MS may be capable of providing quantitative or confirmatory results. These advances include the use of solid phase extraction (SPE) to simplify complex mixture analysis, high-temperature thermal desorption to unlock detection of low-volatility compounds and confined thermal desorption for repeatable and safe analyses. Implementation of advanced mass spectrometers as well as ion or differential mobility spectrometry preceding MS detection has allowed for additional dimensionality to the data which can increase confidence in the results. Additionally, the adoption of statistical or chemometric approaches for data analysis have shown the viability of DART-MS to be used for classification of samples, whether that be cocaine attribution, ignitable liquid classification, or timber species identification. In few fields has the use of DART-MS been so widely demonstrated as in forensic chemistry. Analysis of nearly all types of evidence has been demonstrated, including drugs, explosives, gunshot residues, ignitable liquid residues, inks, paints, polymers, lubricants, bank dyes, beverages, and insects.

As applications for DART-MS in forensic chemistry continue to be researched, the field continues to expand. There have been previous reviews of forensic applications of DART-MS[1,2] (and broader applications of DART-MS[3–5]) that have been published since the inception of the technique. This review does not intend to reiterate the content of the past review articles, but instead supplement them by providing insight into the recent (2015 to present) advances of the technique for forensic chemistry. This review is organized by the main focus of applications in the literature. To provide greater context for those who may be less familiar with DART-MS, a brief discussion on the fundamentals of the technique, alternate approaches to sample analysis, and commonly employed chemometric tools are included. A summary of additional resources relevant to forensic chemists is also provided along with the perceived research needs and discussion of the potential future of the technique.

2. Fundamentals, alternate approaches to sample analysis, and chemometric techniques

2.1. Fundamentals of DART-MS

The fundamental process behind DART-MS is the use of heated metastable gas atoms to desorb and ionize a compound or material of interest. The creation of metastable gas atoms is accomplished by generating a plasma, using a high-voltage needle, to create both charged and metastable species. The charged species are neutralized via an

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electrode within the source, resulting in a stream of metastable atoms, which are heated prior to exiting. A final grid electrode can be found at the exit of the DART source and is used to prevent ion-ion recombination. Fig. 1 presents a cross-sectional view of the DART ionization source. The source, typically, sits several millimeters away from the inlet of the mass spectrometer and samples are directly introduced into the open-air sample region. Gas flows of the DART source are considerably higher than those found in gas chromatography mass spectrometry (GC–MS) systems, with consumption rates of 1.5 L/min to 3.0 L/min, though recent advancements in the technology which utilize a "pulsed" DART may reduce consumption up to 95%.

Helium is the most commonly used source gas because the energy of the metastable atom is sufficient to ionize water. The ionization mechanism, for positive ionization mode, is thought to be driven by ionization of water in the atmosphere (eqn. (1)) which generates charged water clusters (eqn. (2) and (3)) that subsequently ionize the sample (eqn. (4)) [3].

$$He^{*} + H_2O \rightarrow He + H_2O^{+\cdot} + e^{-} \quad (1)$$

$$H_2O^{+\cdot} + H_2O \rightarrow H_3O^{+} + OH^{\cdot} \quad (2)$$

$$H_3O^{+} + nH_2O \rightarrow \left[(H_2O)_{n+1} + H\right]^{+} \quad (3)$$

$$M + \left[(H_2O)_{n+1} + H\right]^{+} \rightarrow [M + H]^{+} + (H_2O)_{n+1} \quad (4)$$

Other source gases, including nitrogen [6–8], argon [9,10], and air [11] have also been demonstrated, with varying degrees of success. These gases do not have metastable atoms with sufficient energy to directly ionize water. Direct ionization of the analyte, or dopant, is required and therefore ionization of the analyte is typically less efficient (eqn. (5) and (6))[12]. Additionally, the use of air as a source gas can lead to the generation of ozone which has a deleterious effect on the source hardware.

$$N_2^{*} + M \rightarrow N_2 + M^{+\cdot} + e^{-} \quad (5)$$

$$M^{+\cdot} + M \rightarrow [M - H]^{\cdot} + [M + H]^{+} \quad (6)$$

2.2. Alternate approaches to sample analysis

While DART-MS has typically been used on-axis with sample introduction completed either directly or via a glass microcapillary (herein referred to as direct sampling), multiple different geometries and analysis approaches have been developed over the past 15 years to address a wide range of samples. These include the use of off-axis or non-proximate configurations, mechanisms for sample preconcentration or sample cleanup, and thermal desorption couplings to allow increased reproducibility and/or increased maximum desorption temperature.

Analysis of larger samples has been demonstrated through off-axis DART-MS, where the source is placed at a non-parallel angle (typically 30° to 60° relative to mass spectrometer inlet) in a configuration much like that used for desorption electrospray ionization (DESI)-MS. This type of modification can allow for movement of large surface areas underneath the source to accomplish wide-area screening. A similar approach for large samples has been demonstrated by Newsome *et al.* in which an extended capillary on the inlet of the mass spectrometer allows for the analysis of samples meters away[13]. While this approach has not been demonstrated for forensic applications, it may prove useful for instances such as body fluid identification on large surfaces (*e.g.,* rugs, garments, etc.) when cutting or portioning is not desired. In a unique application, DART has been coupled with laser desorption (aptly named LADI-MS or Laser Ablation DART Ionization Mass Spectrometry) to allow for chemical imaging at a finer resolution than is obtainable using solely the DART source[14].

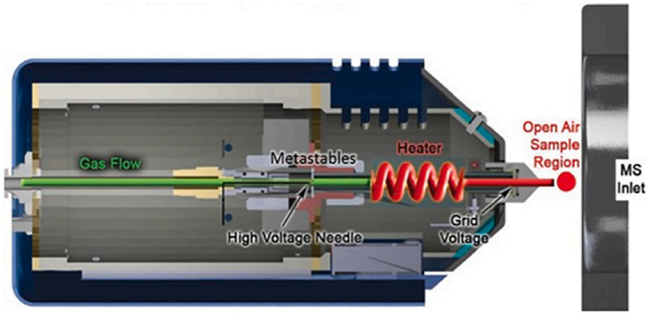

Fig. 1. Cross-section of the DART ionization source. Reprinted with permission from IonSense.

Complex matrices can present challenges due to the lack of chromatographic separation. To overcome this, a number of sample concentration and clean-up techniques have been demonstrated[15–17]. Nearly all these variations focus on some form of SPE utilizing either plastic tips, coated metal meshes or wire, or solid phase microextraction (SPME) tips that are common to GC–MS analyses. With these approaches, not only can samples be cleaned up, but shot to shot reproducibility can typically be enhanced. In addition to cleaning up a sample through SPE or SPME, increasing signal reproducibility has also been achieved. Many of the traditional sampling tools (capillary tubes, metal meshes, etc.) can be mounted on a linear or multiple dimensional rail and scanned through the DART gas stream. Using rails allows for the same area of the sampling tool to be analyzed every time, which can greatly enhance reproducibility. Another approach that has been demonstrated to increase reproducibility is thermal desorption (TD)-DART-MS, which uses an auxiliary thermal desorption unit, typically mounted to a T-junction, that is placed in line with the DART source and MS inlet and allows for samples to be introduced on wipes[8,18]. The enclosed auxiliary thermal desorber allows for controlled and reproducible sample insertion and desorption.

Typical DART-MS settings are not sufficient to desorb many analytes such as those found in paints, polymers, and inorganic explosives. This limitation has led to the investigation of modifications to increase desorption temperatures. Three approaches, all of which provide sample heating independent of the DART source, have been developed. Like the TD-DART configuration described above, infrared thermal desorption (IRTD)-DART allows for samples to be introduced into a thermal desorber via wipes, but instead of using a resistive heater, an IR lamp is employed[19,20]. The use of the IR lamp for heating allows for temperatures in excess of 600 °C and has been demonstrated in analysis of inorganic explosives. Joule-heating thermal desorption (JHTD)-DART-MS has also demonstrated analysis of inorganic explosives and achieves heating temperatures in excess of 750 °C and ramping rates of 450 °C/s by depositing liquid sample onto a nichrome wire which is then ohmically heated[21]. A third approach to achieve higher temperature desorption is the ionRocket which uses a heated copper pot to provide temperature programmed desorption up to 600 °C. A number of applications, forensic and otherwise, have been demonstrated on this platform [22–24].

2.3. Data analysis trends

In addition to the development and use of an array of sample preparation and sample introduction techniques, data analysis tools are routinely applied to DART-MS data. Most methods are implemented to aid in classification or differentiation of samples based on unique characteristics in their mass spectra. These approaches typically use either raw or processed full scan mass spectra from multiple samples of known origin to generate a mass spectral data matrix that is then analyzed. One of the most frequently used data analysis approaches is principal component analysis (PCA). This is an unsupervised approach for feature extraction that takes the mass spectral data matrix and reduces the dimensionality to highlight features which aid in

distinguishing the data. This results in the creation of principal components (consisting of multiple *m/z* values) that are used to explain and separate the data. One of the outputs of PCA is a multi-dimensional plot on which samples (represented as data points) will, if successful, be grouped or clustered together based on commonalities (*i.e.,* same origin, species, etc.)[25].

Hierarchical clustering or hierarchical clustering analysis (HCA) is another unsupervised approach that is often used to find groupings of similar samples. In HCA, a mass spectral data matrix is fed into the algorithm which attempts to identify how similar or different the mass spectra of individual samples are from one another[25]. The output of HCA is a dendrogram showing the overall similarity between all samples that were analyzed. With this information, the user can identify groupings in a similar fashion to PCA. If the desire is to develop a classification model that can be applied to unknown spectra, a supervised method such as random forest analysis (RFA) is commonly used. In RFA, a large number of decision trees are created, with each decision tree containing a set of rules to differentiate samples within the mass spectral data matrix[25]. A subset of the uncorrelated decision trees is compiled to create a classification model that can be used to classify mass spectra from unknown samples. While this briefly describes some of the more commonly employed multivariate statistical methods, many more of varying complexity exist. The interested reader should refer to detailed books and reviews in the literature[26,27].

Two other non-statistical data treatments that are employed are Kendrick mass defect (KMD) and neutral loss spectra. These approaches provide a new way to view mass spectral data that can aid in comparison of samples. KMD analysis is typically applied to polymeric species and takes a given molecular fragment and sets it as an integer value (defined as the Kendrick mass). The defect between the Kendrick mass and nominal mass is then obtained and plotted[28]. The KMD plot can then identify polymers with the same repeating units by their horizontal alignment. Neutral loss spectra are used to identify similar fragmentation patterns amongst compounds. Spectra are created by taking the molecular mass of the compound (which is either known or obtained by using a low fragmentation setting on the MS) and subtracting the *m/z* value of each fragment ion in a high fragmentation spectra[29]. The resulting masses are then plotted to create a spectrum of the neutral part of the compound lost in the creation of each fragment ion. This approach can be useful for identifying similar fragmentation pathways for compounds that have similar core structures but different substitutions.

3. Forensic applications of DART-MS

3.1. Seized drug analysis

Analysis and detection of drugs of abuse is one of the most widely researched applications of DART-MS. First demonstrated in the seminal paper by Cody *et al.*[30], research involving this class of compounds has steadily continued and grown. In recent years several novel applications have been demonstrated such as species identification for psychoactive plants, the use of TD-DART-MS to presumptively identify the contents of drug evidence, classification of cathinones through neutral loss spectra, and quantitation of a suite of different compounds. This section has been sub-sectioned based on drug class or application due to the wide range of areas of research.

3.1.1. Analysis of novel psychoactive substances, traditional drugs, and other compounds of interest

One of the major recent challenges for drug chemists is the ever-changing novel psychoactive substance (NPS) landscape. NPSs, which include classes such as synthetic cannabinoids, synthetic cathinones, and synthetic opioids present a number of analytical challenges including high toxicity, low concentration in samples (relative to cutting agents) and changing chemical structures through the creation of new analogs. Recent papers have demonstrated how DART-MS can not only detect these compounds but also begin to address some of these analytical challenges. Studies that highlight detection capabilities for these compounds include Habala *et al.* who investigated a suite of six synthetic cannabinoids in both pure form and plant material preparations and demonstrated detection of these NPSs from street samples [31]. Moore *et al.* also looked at synthetic cannabinoids on sprayed plant materials, noting issues with sample heterogeneity[32]. They found that a simple extract from 10 mg to 25 mg of plant material was sufficient for producing consistent results. Polkis *et al.* established the ability to detect N-methoxybenzyl (NBOMe) compounds, another NPS class consisting of powerful synthetic hallucinogens, on blotter paper[33]. Direct sampling of the blotter paper was possible (as was analysis of paper extracts), with detection of multiple NBOMe's in a single sample.

The ability to detect low level NPSs in the presence of cutting agents was shown by Sisco *et al.* who demonstrated the ability of TD-DART-MS to detect a range of fentanyl analogs (synthetic opioids)[34]. A series of studies were conducted to demonstrate that mixtures of fentanyl and fentanyl analogs with heroin, cutting agents, and background matrices exhibited minimal competitive ionization effects, as shown in Fig. 2. Sub-nanogram detection limits were also found. A similar study was also recently completed, this time targeting benzodiazepines[35]. Approaches to identify new NPSs was shown by Fowble *et al.* who classified synthetic cathinones using neutral loss spectra[29]. The study leveraged in-source collisionally induced dissociation (is-CID) to produce fragmentation spectra to aid in classification. Using is-CID for analyte fragmentation is accomplished by increasing the potential difference between the orifices within the differentially pumped region of the mass spectrometer resulting in ions colliding more frequently and with higher energy, thereby causing molecular fragmentation. Neutral loss spectra of 44 synthetic cathinones from five different subclasses were derived from the intact, low fragmentation spectra and high fragmentation is-CID spectra. Correct classification of three unknowns was achieved using HCA, as shown in Fig. 3, though difficulties in differentiating pyrrolidine substitutions and di-substituted nitrogen compounds were noted. This approach may prove valuable in identifying NPSs that have never been seen before. Fragmentation pathways of cathinones has also been studied in-depth by Davidson *et al.* [36].

Detection of more traditional drug classes has also been explored in recent years. Chen *et al.* analyzed a suite of drugs commonly spiked into beverages including γ-hydroxybutyrate (GHB) and γ-butyrolactone (GBL)[37]. Recoveries of 40% to 90% out of spiked beverages, compared to water, were found and differentiation between GHB and GBL in negative ionization mode was demonstrated. Watt and Sisco also looked into detection of drugs in baby formula using SPME-DART-MS [38], Suige *et al.* analyzed *tert*-butoxycarbonyl (*t*-Boc)-protected phenethylamines[39]. These compounds are difficult to detect using traditional analytical tools like GC–MS because they readily convert to unprotected compounds in the inlet of the GC or undergo McLafferty rearrangement in the electrospray source of liquid chromatography mass spectrometry (LC-MS) source. Detection of the intact *t*-Boc compounds was accomplished by utilizing a low DART source temperature of 200 °C and sample introduction through a micro syringe. While detection of drugs in samples is the foremost focus in many forensic analysis, detection of other compounds in the sample may be equally valuable. Robinson *et al.* examined detection of rodenticides, which have been reported to be incorporated into drugs of abuse, using TD-DART-MS[40]. These compounds were demonstrated to have higher detection limits than typical drugs, potentially due to higher molecular weights, and were difficult to detect in mixtures using generic screening parameters due to competitive ionization with drugs. Analysis of samples in negative ionization mode, however, eliminated competitive ionization effects and provided sensitive detection of the rodenticides even in the presence of high amounts of drugs like cocaine.

3.1.2. Steroids and supplements

Steroids and supplements represent another group of compounds of

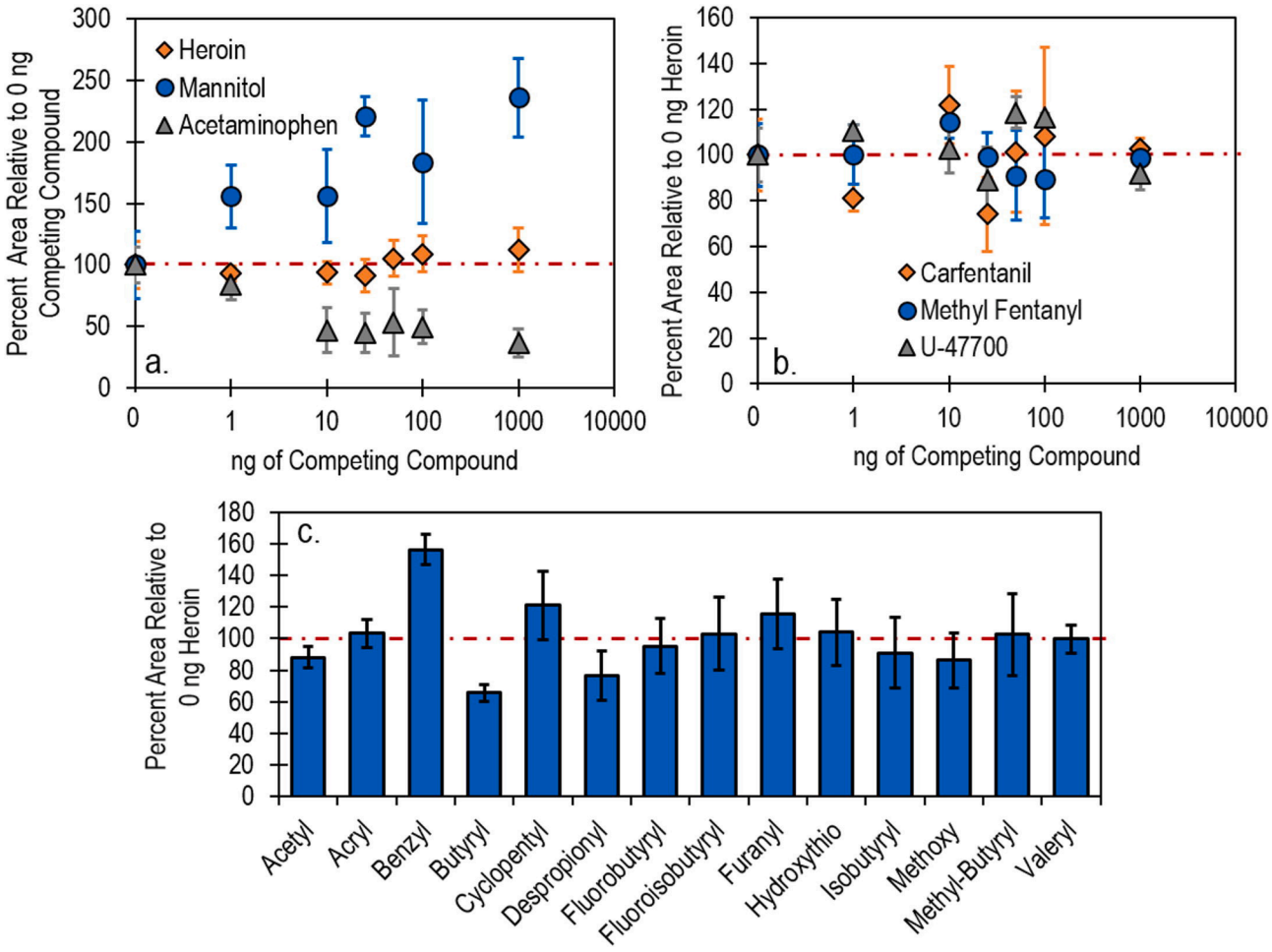

Fig. 2. Demonstration of competitive ionization studies investigating the effect of heroin and cutting agents on the response of fentanyl (a.) and the effect of heroin of other synthetic opioids (b.). In these studies, increasing masses of heroin or the cutting agent are added to a constant mass of fentanyl or fentanyl analog and the response, relative to the response when no heroin or cutting agent is present, is measured. The competitive ionization effects of heroin on a range of fentanyl analogs (c.) is also shown. Error bars are the standard deviation of 5 (a and b) or 3 (c) replicates. Reprinted with permission from (E. Sisco, J. Verkouteren, J. Staymates, J. Lawrence, Rapid detection of fentanyl, fentanyl analogues, and opioids for on-site or laboratory based drug seizure screening using thermal desorption DART-MS and ion mobility spectrometry, Forensic Chemistry. 4 (2017) 108–115.). Copyright (2017). Elsevier.

interest to the drug community that have been explored by DART-MS. Prokundia *et al.* demonstrated detection of testosterone, testosterone analogs, and other steroids in tablets and oils, with verification by GCxGC-MS[41]. Doue *et al.* completed an extensive look at over twenty steroids, focusing on oil-based preparations[42], and showed both qualitative detection and quantitation. The researchers noted that thermal decomposition of steroid esters was observed with DART gas temperatures above 400 °C and highlighted the importance of the, sometimes overlooked, source-to-MS distance parameter. The use of is-CID for enhanced identification was also discussed.

Lesiak *et al.* analyzed a number of Kanna supplements noting the ability to detect a number of the common alkaloids (mesembranol, hordenine, etc.)[43]. Differentiation of materials made from the *Piper betle* species, versus other species, was possible due to the presence of α-terpinene, isoeugenol, and other terpenes. Detection of ephedrine as an adulterating agent was also noted. Screening for ephedrine and other dietary supplements was demonstrated by Santos *et al.*[44]. Using DART coupled with a triple quadrupole mass spectrometer, ephedrine, synephrine, caffeine, sibutramine, methylphenidate, and 1,3-dimethylamylamine (DMAA) were identified from 108 samples including capsules, liquid capsules, and tablets. Thermal degradation of ephedrine above 300 °C was noted along with carryover from direct sample analysis. One strategy to minimize the potential of carryover presented by direct sampling was highlighted in a recent paper by Zhou *et al.* [45]. In this work, the use of micropunching, in which a small amount (milligrams) of material is bored out of a tablet, was investigated as a way to control the amount of sample introduced into the DART stream and detection of modafinil (a nootropic) in tablets was readily achieved.

3.1.3. *E-liquids*

An emerging area of research for drug analysis over the past five years has sprouted around the increased use, and misuse, of electronic cigarettes (e-cigarettes). E-cigarette liquids (e-liquids) are commonly comprised of propylene glycol, glycerin, nicotine, and flavor additives but can be easily modified to contain other drugs of abuse. In 2016, Peace *et al.* highlighted the ability to directly analyze e-liquids using a combination of DART-MS and LC-MS. DART-MS successfully detected the major constituents (propylene glycol and glycerin) as well as nicotine and flavor additives (*e.g.,* carvone, ethyl vanillin, and methyl salicylate)[46]. Peace *et al.* also demonstrated the analysis of e-liquids containing marijuana, with detection of multiple cannabinoids and terpenes in addition to the previously mentioned compounds[47]. These studies were expanded in 2017 to include e-liquids containing synthetic cannabinoids and different sampling methods. Utilizing three commercially available e-liquids, all containing MDMB-FUBINACA, Peace *et al.* demonstrated that placing the e-liquid under the DART gas stream allowed for detection of the volatile flavoring compounds while direct sampling of the liquid provided a more complete chemical profile and

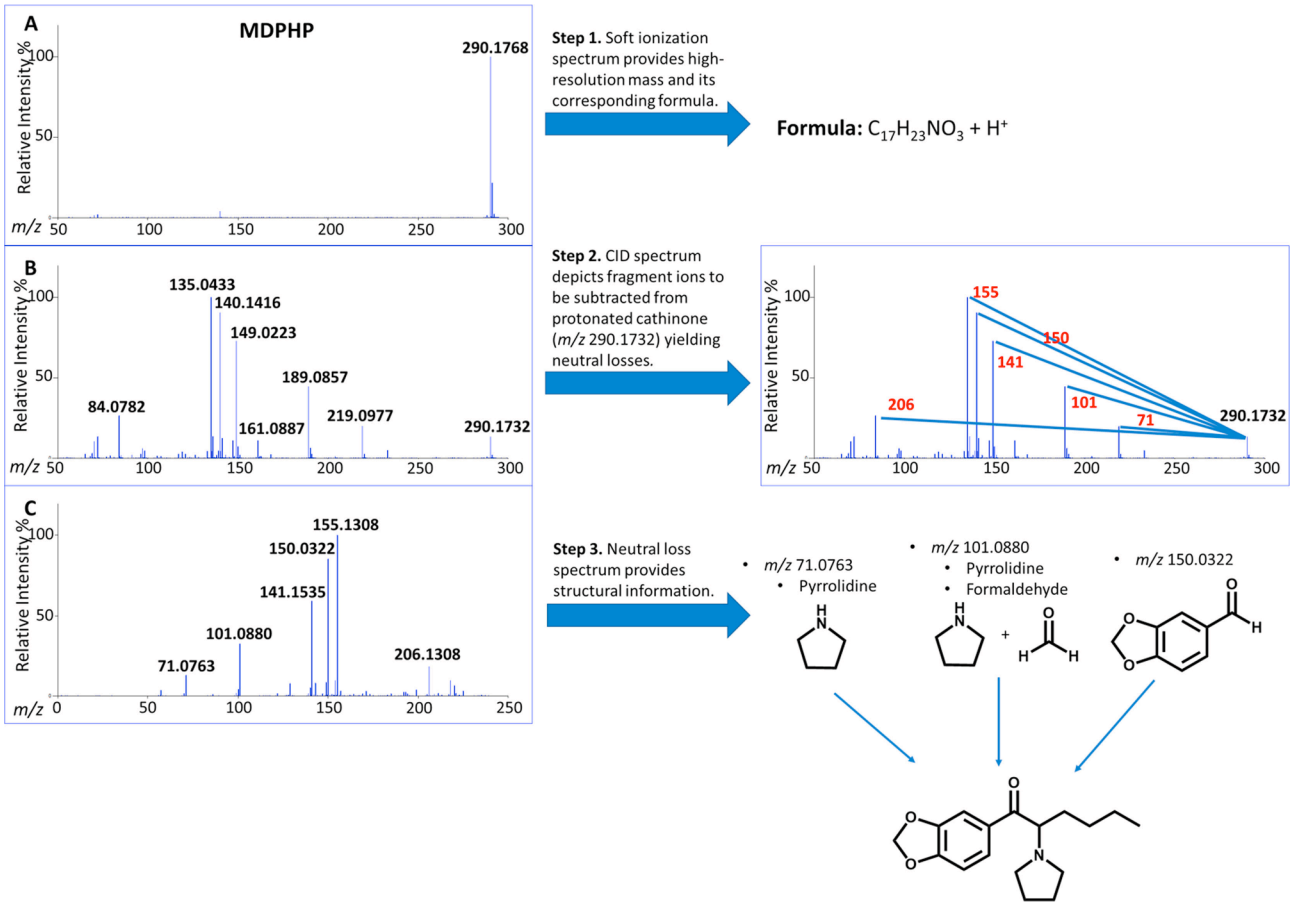

Fig. 3. Demonstration of the use of neutral loss spectra for compound reconstruction. Spectrum A is the low fragmentation spectrum used to obtain the molecular mass of the compound. Spectrum B is the high fragmentation spectrum from which the neutral loss spectrum (Spectrum C) is created. Structural information can then be obtained from the neutral loss spectrum (right side of figure). Reprinted with permission from (K.L. Fowble, J.R.E. Shepard, R.A. Musah, Identification and classification of cathinone unknowns by statistical analysis processing of direct analysis in real time-high resolution mass spectrometry-derived "neutral loss" spectra, Talanta. 179 (2018) 546–553.). Copyright (2018). Elsevier.

sampling of solid material within the liquid produced a signature of predominantly MDMB-FUBINACA[48]. Analysis of e-cigarettes and e-liquids has also been demonstrated by Poklis *et al.*, who described a unique case study where 5-fluoro-ADB and dextromethorphan were found[49], and by Krakowiak *et al.* who studied aerosols from a methamphetamine-containing e-cigarettes to better understand dose delivery[50].

3.1.4. *Analysis of psychoactive plants*

Analysis of plants containing psychoactive compounds has also been an active area of research over the last several years. Dhabbah *et al.* demonstrated detection of cathinone and cathine in the stems and leaves from the Khat plant through direct sampling[51]. Fowble *et al.* developed a quantitative method to measure mitragynine in kratom plants [52]. Utilizing deuterated mitragynine as an internal standard, the samples (which consisted of fresh plant material, dried plant material, and powder) were soaked overnight in methanol, prepared, and analyzed. Mitragynine concentrations from 2 mg/g to 20 mg/g were found but were not independently verified. A similar study was completed by Longo *et al.* targeting quantitation of mescaline in cacti of the *Echinopsis* genus[53]. The mass percent of mescaline was found to be less than 2% of the dry weight, which was consistent with values from previously reported work using GC–MS and LC-MS.

While detection of drugs and other psychoactive substances in, and on, plants has been shown, a number of studies have investigated the ability to use mass spectra for species identification. For this type of analysis, full scan mass spectra are typically processed (either by selecting peaks above a pre-determined threshold or by applying a transformation to the dataset to enhance low intensity peaks) and then one or more multivariate statistical approaches are applied to the resulting data matrix. Lesiak *et al.* demonstrated this approach through the analysis of five different Ayahuasca plant species, which contain *N, N*-dimethyltryptamine[54]. Differentiation of the mass spectra resulting from the five species was possible and classification of the species using PCA produced an accuracy exceeding 98%. The study was taken a step further through the analysis of brews created from a combination of leaves from different species. Again, differentiation and identification of the individual species was possible. The same year Lesiak *et al.* also presented the use of PCA on DART-MS data for the identification of psychoactive pepper in a range of supplements[55]. Their approach highlighted the ability to identify *P. methysticum* versus *P. betle* in powder, tinctures, and raw plant material. Differentiation of these species was driven by the presence of kavalactones in the *P. methysticum* containing samples. Beyramysoltan *et al.* similarly looked at twenty-four nightshade plant species (which produce atropine and scopolamine) across five genera using HCA and partial least squares discriminant analysis (PLS-DA) with direct sampling of the cross-section of seeds[56]. The approach had 95% accuracy in correctly identifying the species. A similar approach for seed analysis was pursued by Lesiak *et al.* for the differentiation of seeds from the *Datura* genus[57].

Plant species identification has also been attempted using more unique sampling approaches. Appley *et al.* investigated the use of SPME sampling of 11 different psychoactive plants to achieve species differentiation[58]. While the traditional approach of bulk sampling was also

investigated, SPME sampling was the focus of the work as it provided a simplified spectral signature. The resulting data matrix was then subjected to PCA and t-distributed stochastic neighbor embedding to identify clusters, followed by development of a model using RFA, as shown in Fig. 4. Complementarities of the different statistical analysis approaches were noted and an accuracy of 99% was obtained. It was found that terpenes, sesquiterpenoids, and estragole best facilitated separation. Dong *et al.* took a different sampling approach in their attempt to differentiate hemp cultivars, using the ionRocket for a temperature programmed thermal desorption[59]. The group achieved differentiation of four different cultivars and noted spectral reproducibility issues with traditional direct sampling and poor data quality using an off-axis approach. Utilization of the ionRocket provided the greatest level of reproducibility and also provided an additional time-dimension to the data. Using PCA for statistical analysis along with a cubic data transformation led to a 99% accuracy rate. Dong *et al.* did note limitations for DART-MS analysis of hemp material including the inability to separate cannabidiol (CBD) from Δ9-tetrahydrocannabinol (THC) or cannabidivarin (CBDV) from tetrahydrocannabivarin (THCV) (using low fragmentation spectra) and the decarboxylation of acidic cannabinoids due to the heated desorption. Sample aging was found to be a source of uncontrollable variance which could complicate classification.

3.1.5. Combining DART-MS with other analytical techniques

Several studies have demonstrated that fusing data from DART-MS with data from other techniques can provide greater confidence in identification. One such study was completed by Marino *et al.* who investigated detection of synthetic cannabinoids from incense samples using a combination of DART-MS and nuclear magnetic resonance spectroscopy (NMR)[60]. Here, DART-MS provided molecular formula information while NMR provided isomeric differentiation. It was noted, however, that sample heterogeneity required multiple samplings to obtain a representative chemical makeup. Nei *et al.* successfully screened for synthetic cathinones, phenethylamine, and synthetic cannabinoids using a combination of DART-MS and fast LC-MS[61]. The combination of techniques resulted in a total run time of 5.5 min, with successful detection of compounds of interest in all samples.

Both Gwak *et al.*[62] and Lian *et al.*[63] investigated the benefits of using DART-MS and ion mobility spectrometry (IMS) for analysis. Using both techniques, Gwak and colleagues studied 35 drugs (synthetic cathinones and cannabinoids). The use of multiple collision energies in the quadrupole time-of-flight (Q-TOF) mass analyzer allowed DART-MS to differentiate constitutional isomers that IMS could not[62]. IMS also produced false alarms that DART-MS was not prone to, especially for compounds with a difference in reduced mobility of less than 0.007 cm^2/Vs. The study by Lian and colleagues looked at 53 drugs and 50 case samples, proposing IMS as a pre-step to DART-MS for screening purposes [63].

Ayodeji *et al.* demonstrated the potential utility of incorporating differential mobility spectrometry (DMS) into the DART-MS configuration[64]. Investigating the amphetamine class of compounds, the researchers were able to show separation and analysis of amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and 3,4-methylenedioxy-N-ethylamphetamine (MDEA) in under five minutes. Given the lack of a traditional chromatographic step, the utilization of a separation tool such as DMS could aid in increasing confidence of identification by providing an additional time dimension to the data.

3.1.6. Nitrogen DART-MS for drug analysis

In recent years there has been an increased interest in the use of nitrogen as the DART source gas driven by the desire to make the DART source more portable and by the increased cost of helium gas. A number of publications have highlighted the ability to use nitrogen for the analysis of drugs. Brown *et al.* used nitrogen DART coupled to a mini mass spectrometer aimed at field applications and found that detection

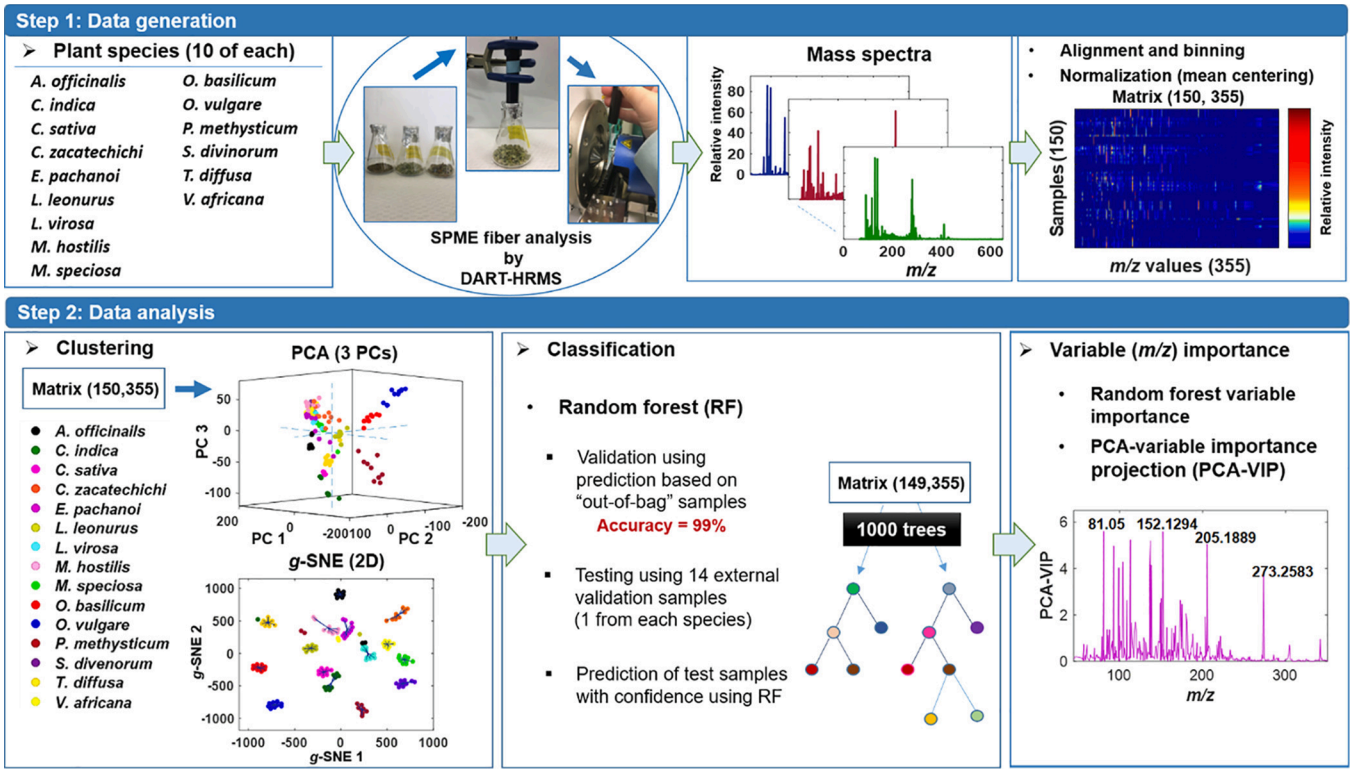

Fig. 4. Workflow from headspace analysis of psychoactive plant material for species identification. Reprinted with permission from (M.G. Appley, S. Beyramysoltan, R.A. Musah, Random Forest Processing of Direct Analysis in Real-Time Mass Spectrometric Data Enables Species Identification of Psychoactive Plants from Their Headspace Chemical Signatures, ACS Omega. 4 (2019) 15636–15644.). Copyright (2019). American Chemical Society.

of all drugs examined was possible[11]. Like helium DART, production of protonated molecules ($[M + H]^+$) was the dominant mechanism though $[M-H + OH]^+$ ions, caused by oxidation, were also observed. Brown *et al.* also noted that air could be used as a DART ionization gas, but the production of ozone caused degradation of drugs like amphetamine and methamphetamine. Multiple studies by Sisco *et al.* have demonstrated the use of TD-DART-MS with a nitrogen source gas for sensitive detection of drugs[18,34]. The platform demonstrated enhanced sensitivity and reproducibility compared to traditional DART-MS analysis. Additionally, the use of the enclosed configuration provided comparable, or improved, results when using nitrogen as the source gas[8]. Finally, a recent study by Song *et al.* looked at nitrogen DART for 22 different drugs and noted excellent sensitivity and production of protonated molecules, confirming previous work[6]. This study also noted the formation of some unusual ions ($[M + H + O]^+$ and $[M + H + 2O]^+$) that are not commonly observed with helium DART.

3.1.7. Forensic intelligence applications

One of the exciting and promising areas where DART-MS is gaining traction is in forensic intelligence applications, due to the ability to rapidly obtain a near-complete chemical fingerprint of a sample. Two recent studies by Cui *et al.* used the spectral profiles created by DART-MS for correlation of cocaine[65] and heroin[66] samples. For the cocaine study, the researchers looked at 47 seized samples from China and were able to identify 20 manufacturing impurities and cutting agents. Development of an HCA model from this data was then used to analyze spectra from an additional 46 samples, and clustering of samples from the same cases was accomplished[65]. Region of origin (southeast Asia versus southwest Asia) of heroin samples was also demonstrated using a similar approach with greater than 93% accuracy[66]. Another study that highlighted the ability to use DART-MS for forensic intelligence purposes was completed by Sisco *et al.* This study identified that the trace residue on drug evidence could be used as a predictor of the contents[67]. Using wipe sampling and TD-DART-MS, analysis of nearly 200 pieces of drug evidence was completed. An overall accuracy of 92% was achieved for correct identification of at least one drug within the packaging from the residue spectra and 100% accuracy was obtained for determining the presence of synthetic opioids. Noted limitations of the approach were samples containing plant material or those packaged in heat-sealed foil bags due to lack of sufficient residue on the exterior packaging.

3.2. Toxicology

While the utility of DART-MS for the analysis of seized drugs has been extensively investigated, work in the field of toxicology appears to only be beginning. Implementation of DART-MS for toxicology is appealing for both rapid screening of samples and, potentially, rapid quantitation. Over the last five years, urine has been the biological fluid most frequently analyzed using DART-MS, though oral fluid and blood have also been analyzed. Beck *et al.* investigated the ability of DART-MS to replace traditional analytical approaches (enzyme immunoassay screens and GC–MS or LC-MS confirmation) for the analysis of methadone in urine[68]. They employed an approach using DART ionization with dual mass analyzers – screening with a TOF mass spectrometer and confirming with a triple quadrupole mass spectrometer. Analysis of unprocessed urine provided an overall positive identification rate at the limit of detection (LOD) of 86% for the screening method and 91% for quantitation method. This approach showed enhanced sensitivity and specificity compared to traditional techniques. Robustness, stability, and recovery were also investigated in this work and showed excellent results. Direct analysis of urine and blood samples was also demonstrated by Zhang *et al.* who investigated nine drugs and metabolites and obtained LODs ranging from sub ng/mL to hundreds of ng/mL[69]. A simple precipitation and removal of proteins using acetonitrile and methanol was employed prior to analysis and was successfully applied to twenty case samples.

While direct analysis has been demonstrated, the use of extraction techniques may be better suited for samples composed of complex matrices such as blood and urine. The use of polydimethylsiloxane (PDMS)-based SPE tips for urinalysis was studied by Olivieri who looked at samples donated from volunteers who had reported drug use[70]. While use of THC, cocaine, benzodiazepines, and amphetamines was reported, successful detection was only achieved for amphetamines. Studies of masking agents showed detection of dextroamphetamine could not be accomplished in the presence of bleach, drain cleaner, and eye drops, though signatures of adulteration were readily observed in the mass spectra, indicating tampering. Other studies utilizing SPE demonstrated more promising results for toxicological analyses. Vasiljevic *et al.* demonstrated SPME-DART-MS for low-level analysis of drugs in oral fluid and blood using custom-made polyacrylonitrile meshes[71]. Investigation of 11 different drugs and metabolites found sub ng/mL to tens of ng/mL detection limits. Quantitation of drug levels was accomplished using deuterated standards, with limits of quantitation (LOQs) at or below the levels set forth in the Driving Under the Influence of Drugs (DRUID) standards disseminated by the European Commission. Vasiljevic furthered this work with the development of a manufactured 96-well SPME brush used for blood and urine analysis[72]. Using a C18 extraction phase, detection of 10 drugs was readily accomplished, with the exception of dihydrocodeine in urine. The SPME-brush that was created allowed for multiple desorption cycles of a sample from a single pin.

Additional novel uses of DART-MS for toxicological analysis have been demonstrated by Evans-Nguyen *et al.* and Phatak[73,74]. Evans-Nguyen *et al.* used functionalized antibodies deposited onto nanogold wires for toxicological analysis[73]. Sensitive analysis of amphetamine and benzodiazepine, using their respective antibodies, allowed for detection levels on par or better than LC-MS/MS techniques. The nanogold wires were shown to be small enough not to perturb the DART gas stream and could be recoated with antibodies after use. Phatak used DART-MS as an investigative tool along with LC-MS/MS to assess the metabolism of fentanyl-related compounds using a biomimetic catalyst [74]. These advances in toxicological analyses have shown that there is a great deal of promise in this type of application.

3.3. Explosives, gunshot residue, and fire debris

3.3.1. Explosives

Since the technique's introduction, DART-MS has demonstrated rapid analysis of liquid- and solid-based explosives[30]. DART-MS has predominantly been employed for rapid presumptive screening, direct analysis of evidentiary materials (*i.e.,* in an ambient ionization configuration), or source attribution investigations. Ionization pathways of organic nitrated explosives, including nitroaromatics, nitroamines, and nitrate esters (negative mode), as well as peroxide-based explosives (positive mode) were determined in early studies[75]. The pathways identified by Nilles *et al.* using helium gas and dopant additions (*e.g.*, chlorine species) have generally been confirmed by subsequent studies. More recent works have expanded to use nitrogen as the ionization gas, demonstrating changes in the ion distributions and dominant adducts [7,19]. An array of studies have exhibited the robust capabilities of DART-MS to directly interrogate surfaces of interest for pre- and post-blast residues[24,75–77]. These studies have demonstrated detection off surfaces including various metals, wood, glass, foam, asphalt, tape, Nomex, polytetrafluoroethylene (PTFE), polymer/metal wires, cell-phone components, and batteries. Sisco and Forbes took a deeper look at the importance substrate properties played on desorption efficiencies and overall detection[76]. Specifically, rough or porous materials more frequently retained target compounds and disrupted the DART gas stream, overall reducing signal. The thermal properties also played a role. For example, thermally conductive substrates heated quicker and over a larger area than insulators, effectively increasing the interrogated

desorption area.

A couple of recent studies also established the utility of DART-MS for source attribution from post-blast debris. This important aspect of forensic analysis can provide critical source attribution information, identifying source material links or directing ongoing investigative efforts. Black *et al.* examined post-blast residues from a number of peroxide-based homemade explosives (HME)[77,78]. These improvised explosive devices (IEDs) included either triacetone triperoxide (TATP), hexamethylene triperoxide diamine (HMTD), or methyl-ethyl ketone peroxide (MEKP) with a pentaerythritol tetranitrate (PETN) blasting cap. Post-blast debris was both directly analyzed by DART-MS or indirectly by wipe sampling with cotton swabs followed by DART-MS. As prior studies have demonstrated, the irregularities on the surface of sample substrates caused difficulties with direct analysis and gas stream disruption, resulting in superior results from dry swab collected samples [77]. Gaiffe *et al.* also investigated post-blast debris from plastic explosives and polymer materials using multivariate statistics and Kendrick mass defect (KMD) analysis[79]. The implementation of KMD analysis provided an untargeted approach focusing on the polymeric components of each sample instead of attempting to identify each peak. In conjunction with PCA, Gaiffe *et al.* observed changes in the polymeric composition of pre- versus post-blast plastic explosives. Most notably, post-blast residues were less oxygenated and more unsaturated.

The evolution of DART-MS has also seen an increase in the number of custom and commercial hybrid or alternative sample introduction techniques (*e.g.,* TD-DART, QuickStrip, ionRocket, SPE-it Tips). An *et al.* presented a cursory investigation comparing TD-DART of PTFE-coated fiberglass weave wipe-based samples to traditional DART for explosives detection[7]. Similar to earlier investigations on narcotics [18], An *et al.* confirmed superior performance of the hybrid wipe insertion TD-DART configuration. Frazier *et al.* also characterized a range of commercial and custom sampling introduction platforms coupled with DART-MS for screening explosives, demonstrating their utility as presumptive techniques for forensic analysis[24]. Hybrid techniques employing high temperature desorption components have also enabled detection of propellants, pyrotechnics, and tertiary explosive fuel-oxidizer mixtures based on inorganic oxidizers. The nonvolatile components of these HMEs present difficulty for the common temperatures achievable with the traditional DART configuration. Forbes *et al.* developed a Joule heating thermal desorption (JHTD) system based on ohmically heating a nichrome wire at rates up to 400 °C/s and reaching 750 °C[21]. The JHTD-DART-MS system demonstrated the detection of nitrate-, chlorate-, and perchlorate-based oxidizers, identifying regimes of vapor generation and thermal decomposition. The multi-second heating ramp feature of the platform enabled organic explosives to be desorbed at lower temperatures without degradation. In a related technique, Forbes *et al.* coupled infrared thermal desorption (IRTD) with DART-MS to achieve elevated heating of wipe-based samples[19]. Similar to the JHTD system, the IRTD-DART-MS platform created a discrete temperature profile, desorbing species at their optimal desorption temperatures, as shown in Fig. 5. Wipe-based organic explosives and refractory nitrate, chlorate, and perchlorate salts were demonstrated. Bezemer *et al.* recently used IRTD-DART-MS to screen wipe samples of seized packages containing illicit pyrotechnics, demonstrating the detection of potassium perchlorate from flash powder and potassium nitrate and sulfur from black powder[80].

A range of homemade explosives have been detected by DART-MS and associated variants. In addition to the peroxide-based explosives and fuel-oxidizer mixture discussed above, Sisco and Forbes completed a series of studies investigating novel nitrate ester explosives [76,81,82]. These studies used an off-axis DART-MS configuration to examine signatures of nitrate ester explosives in the presence of confounding sugar alcohol precursors and partially-nitrated or dimerized by-products, representing impure HMEs. Sisco and Forbes considered detection from a range of substrate surfaces and dopant chemistries, concluding the nitrate ester explosives were preferentially ionized relative to several

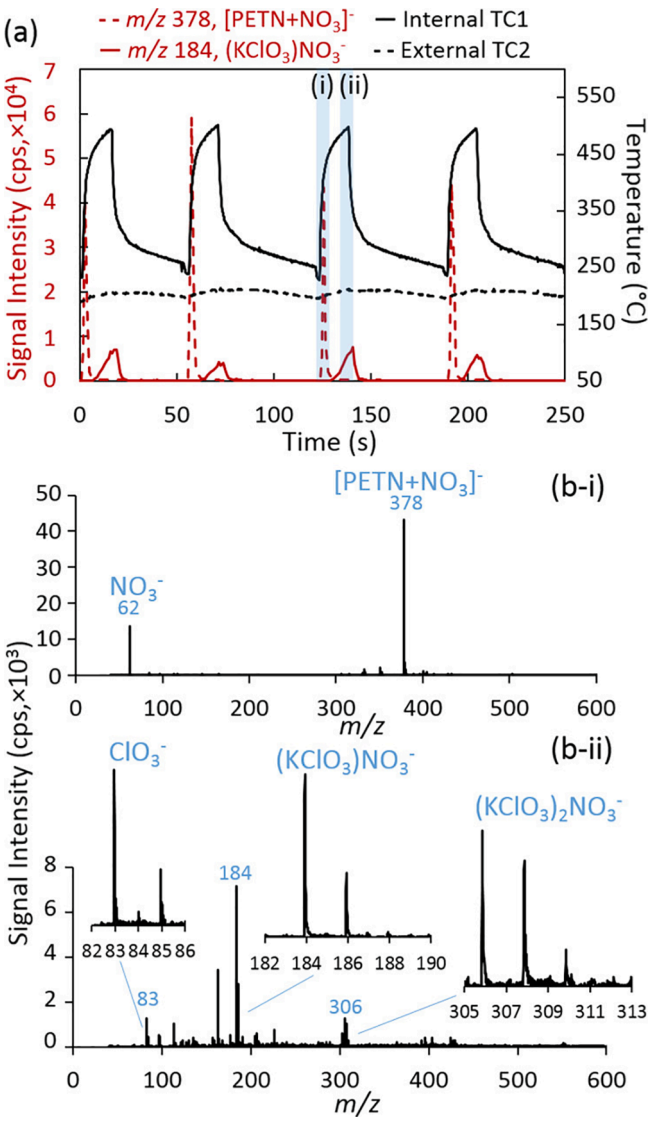

Fig. 5. Demonstration of how IRTD-DART-MS can provide discrete desorption of the more volatile organic and less volatile inorganic compounds. The extracted ion chronograms (EICs) for PETN and potassium chlorate on the same wipe are provided in (a). Mass spectra from beginning (b-i) and end (b-ii) of the desorption profile are also shown, further highlighting the temporal separation of the organic and inorganic explosives. Reprinted with permission from (T.P. Forbes, E. Sisco, M. Staymates, Detection of non-volatile inorganic oxidizer-based explosives from wipe collections by infrared thermal desorption - direct analysis in real time mass spectrometry, Anal Chem. 90 (2018) 6419–6425.). Copyright (2018). American Chemical Society.

orders of magnitude more sugar alcohol[76,81]. Though, signal suppression matrix effects from competitive ionization was observed as the extent of nitration increased (*i.e.,* partially-nitrated by-products)[82].

DART-MS has also been combined with Raman spectroscopy to provide orthogonal signatures from a series of munitions (*e.g.*, mines, grenades, and rockets). Bridoux *et al.* employed both wipe sampling and vacuum impaction to collect residues and particles from these samples, followed by micro-Raman spectroscopy and then DART-MS[83]. The analysis provided unique differentiation capabilities from the orthogonal signatures of explosives, binders, plasticizers, and additives. Recently, Liu *et al.* employed DART-MS and isotope pattern matching to enhance compound identification using 2,4,6-trinitrotoluene as a test case[84].

3.3.2. Gunshot residue and propellants

Similar to explosives and related munitions, DART-MS has been used to detect and characterize a number of associated analytes predominantly used in propellants, ammunitions, or resulting residues, as well as fillers for improvised explosives devices. These compounds generally include smokeless powders, black powders, and black powder substitutes, and may represent trace evidence as unburned, partially burned, and burned residue. Black *et al.* took the detection of gunpowder components one step further and identified polymer compounds from 3D printed firearms[85]. In this study, the authors test fired a series of gun barrels and 3D printed cylinders made from common materials, including acrylonitrile butadiene styrene (ABS), polylactic acid (PLA), polyethylene terephthalate (PETG), chlorinated polyethylene (CPE), and nylon. DART-MS and SEM analysis of samples collected from spent cartridge cases, bullets, and gunshot residue (GSR) stubs exhibited components from the polymer firearm devices, as well as the smokeless powders.

Lennert *et al.* demonstrated traditional screening analysis of smokeless powders by liquid extraction and glass capillary insertion, as well as by direct insertion with forceps[86]. A comparison between GC–MS and DART-MS was conducted on 34 single and double base smokeless powders, including both HCA and PCA discriminatory analyses. Similar class groupings were observed between both techniques confirming DART-MS utility as a rapid screening technique. Lennert *et al.* expanded on this preliminary study to include thermal desorption (TD) of wipe-based sample collections. The hybrid TD-DART-MS platform utilized PTFE-coated fiberglass weave wipes and created a more confined geometry between DART and mass spectrometer inlet, giving a higher classification accuracy than traditional DART-MS[87].

A number of studies have targeted the more volatile components of smokeless powders by incorporating various vapor collection and concentration techniques. Similar to the hybrid techniques introduced for explosives detection, these platforms use novel sampling modalities prior to thermal desorption from the DART gas stream. Li *et al.* utilized a sorbent-coated wire mesh for dynamic headspace concentration from smokeless powder components[88,89]. The graphitized carbon sorbent material was aimed to improve upon swabbing or vacuum collection. When coupled with DART-MS, the method demonstrated chemical signatures of a test smokeless powder with similar capabilities to GC–MS in significantly less time[88]. Li expanded this, completing a chemometric analysis of burned residues from three smokeless powders [89]. In a similar hybrid technique, Williamson *et al.* coupled a capillary microextraction of volatiles (CMV) dynamic air sampling device with DART-MS[90]. The CMV-DART-MS platform was used to investigate 11 organic species common to smokeless powders and resulting burned gunshot residues (*i.e.,* degradation products). Results were directly compared to prior CMV-GC–MS data using a vapor source representing direct air sampling from air around a person's hand. The CMV vapor collection scheme enabled sequential analysis by DART-MS and then GC–MS providing both rapid presumptive and confirmatory analyses.

As with many of the explosives just considered, these propellants may contain both organic and inorganic components. While smokeless powders are predominantly of more volatile organic composition, black powders and black powder substitutes are mostly inorganic in nature with a range of potential organic additives. Forbes and Verkouteren employed the previously discussed IRTD-DART-MS platform for the differentiation of seven black powders and black powder substitutes from wipe-based collections[20]. The discrete temperature ramp and elevated temperatures achieved by the infrared thermal desorption allowed for organic and more volatile components to be desorbed early in the profile, while less volatile inorganic oxidizers to be desorbed later in the profile. PCA of spectra from these two distinct time points in the temperature ramp was completed enabling differentiation of black powders and each of the black powder substitutes.

3.3.3. Fire debris and ignitable liquids

In the final class of related compounds, the analysis of fire debris and ignitable liquids is considered. Given their volatility, these species have traditionally been sampled by SPME or similar vapor collection schemes prior to lengthy GC–MS analysis. DART-MS provides a rapid alternative to screen ignitable liquids and contaminated debris. Davis used DART-MS to screen a series of five gasolines by DART-MS, demonstrating differentiation by visual inspection and chemometric analysis[91]. DART-MS also enabled observation of high-mass ions not found in the GC–MS spectra, providing improved differentiation.

Barnett and Zhang completed a similar study incorporating the QuickStrip high-throughput sampling configuration with DART-MS [92]. Analysis of variance-principal component analysis (ANOVA-PCA) and PLS-DA were used for differentiation. Clear distinctions were observed based on the polymeric components of the fuel additives. In addition to differentiation of the neat fuels, differences in weathered samples (*i.e.,* portions evaporated) were identified. Barnett *et al.* expanded on this study considering not only neat ignitable liquids, but five contaminated substrates, including carpet, wood, cloth, sand, and paper[93]. The authors compared the QuickStrip module with tweezer holders to the ionRocket thermal desorption platform for DART-MS sampling. The QuickStrip DART-MS configuration suffered from background interferences and instrument contamination. However, the thermal desorption system operating at 100 °C/s from room temperature to 600 °C minimized interferences from the different substrates and exhibited reproducible classification[22,93].

3.4. Inks and documents, and paint

Analysis of inks and paints have been an active areas of research for DART-MS for many years and target similar types of compounds for detection. In both applications, the goal of the examination is typically driven by the need to compare a questioned to a known – in instances of hit and run (paints) or document forgery (inks). DART-MS has been leveraged for these samples for its ability to detect not only organic pigments but also other organic compounds within these matrices.

Two studies, completed by Williamson *et al.* and Trejos *et al.* investigated the use of DART-MS to classify and differentiate different types of printer ink samples[94,95]. Both studies utilized the same set of samples that encompassed the different type of printer inks (inkjet, toner, offset, and intaglio). Using positive ion spectra produced by direct analysis of filter paper on which the ink was deposited, discrimination ranging from 54% (for intaglio) to 96% (for toners) was achieved[94]. It was noted that some inks, namely toners and offset inks, were subject to melting in the DART gas stream. Detection of cyan, magenta, and yellow pigments was not possible as the pigment compounds are not well ionized. The data presented in the Williamson study was incorporated in the Trejos study, which looked to create an ink database containing data from Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), laser ablation inductively coupled plasma (LA-ICP)-MS, DART-MS, and pyrolysis (py)-GC–MS[95]. A comparison of techniques found that while LA-ICP-MS provided the greatest discriminating power, DART-MS and SEM performed the next best. Fusion of DART-MS and FTIR data provided increased discrimination capabilities using the organic constituents.

Another study, by Drury *et al.*, compared the analytical capabilities of DART-MS to direct sample analysis (DSA)-MS[96]. DSA-MS is a similar technique to DART-MS but instead of having an open-air sampling region, DSA-MS uses an enclosed sample chamber along with heated nitrogen, and a corona discharge for sample desorption and ionization. Using ballpoint inks as their comparison samples, it was found that both techniques provided similar results, but DART-MS provided increased sampling flexibility as well as lower limits of detection (defined as the smallest ink stroke that could be detected). Pigments and other organic constituents were identified in this study.

In terms of paint analysis, Chen *et al.* investigated the use of DART

coupled to a hybrid quadrupole-Orbitrap (Q-Orbitrap) for comparison of known to questioned samples[97]. As was the case for ink analysis, the benefit of fusing DART-MS data with FTIR was noted with DART-MS excelling at pigment detection and FTIR working well in identifying binders and extenders. In addition to the creation of an organic pigment database, two case samples were analyzed and, in both instances, DART-MS was able to correlate pigments in the questioned and the known samples.

Another recent study from Marić *et al.* compared DART-MS to py-GC–MS for the comparison of clear coat analysis in automotive paints [98]. The clear coat is the outermost layer of paint applied to vehicles to provide protection of the pigment layers and as a UV-protectant coat. Analysis by DART-MS produced signatures attributable to styrene, acrolein, and methylacrylates among other compounds. Although only a small set of four samples was used, similar discriminating power to py-GC–MS was obtained. Marić also investigated the utilization of the ionRocket to complete py-DART-MS of paint chips (containing all layers of paint, not just clear coat) and found the approach allowed for detection of compounds such as hydroxyphenylbenzotriazole, which are not seen by other techniques.

3.5. Lubricants

One unique area where DART-MS is increasingly employed is in the analysis of sexual lubricants. Analysis of these lubricants can be critical in sexual assault cases where there is no DNA evidence – providing a potential mechanism for correlating known and questioned samples. While the first instance of lubricant analysis by DART-MS was reported in 2012[99], there has been a number of recent studies, focused mainly on classification and correlation of different lubricant classes.

Much of the literature surrounding lubricant analysis by DART-MS splits lubricants into three distinct types – water-based, silicone-based, and condom-based. Marić *et al.* investigated 33 different water-based lubricants to determine if lubricant type could be determined if no known comparison sample exists[100]. Through direct analysis of the lubricants (no solvent extraction or other preparation), six groupings were obtained when the positive ionization mode spectra were subjected to principal component analysis (PCA). Of the six groups, four were individual lubricants, with the other 29 lubricants clustering into two groups. Several compounds drove the grouping of the lubricants and included glycerol, ethoxydiglycol, phenoxyethanol, and benzocaine. A similar study was completed by Baumgarten *et al.* for silicone-based lubricants[101]. In this study 37 silicone-based lubricants and condom lubricants were investigated, again with no sample preparation. Using HCA, 11 groups were determined from analysis of the positive and negative mass spectra. Compounds providing differentiation in this study included spermicidal compounds (*e.g.*, nonoxynol-9) that are commonly found in condom lubricants as well as 1,3-dicapryloylglycerol, BHT, octylamine, and pulegone. Baumgarten also demonstrated identification of the PDMS type (*e.g.*, hydroxy-terminated, cyclic, etc.) through a combination of analyses in both ionization modes and utilization of Kendrick mass defect. While an 11-group classification scheme was developed through the study, it was noted that a broader sample set was required to build a better model. In both studies, flavored-based lubricants were found to present unique chemical signatures.

Perhaps the most in-depth study of lubricants in the last five years was completed by Coon *et al.* who utilized chemometrics for the analysis and discrimination of condom lubricants and condom lubricant residues [102]. Utilizing 110 condom types spanning 16 brands the ability to identify the brand of condom was investigated. The effect of aging, contamination with dust, and transference of residue was also investigated. Brand accuracy predictions were found to range from 93% to 100% using a PLS-DA approach with an overall accuracy exceeding 97%. Aging and analysis of a transferred residue were the two most common factors resulting in misclassifications. Their study also revealed 14 *m/z* values present in all samples – providing the potential for universal identifiers for condom lubricants.

Marić *et al.* followed their water-based lubricant study with a more comprehensive study that investigated 90 different lubricants spanning the three types[103]. Using HCA on the mass spectra produced 12 groupings – half of which were attributed to water-based lubricants. Silicone lubricants were grouped together, and 5 groupings of condom lubricants were also identified. A cross-validation of the data using linear discriminant analysis (LDA) presented 12 misclassifications out of 900 classifications, with 9 of those being attributed to a misclassification of a silicone lubricant as a silicone-lubricated condom. Compounds responsible for the groupings were similar to other studies and included glycerol, lidocaine, ethoxydiglycol, triethanolamine, benzocaine, butylene glycol, PDMS, PEG, Isonox, capric triglycerides, octylamine, nonoxynol-9, propylene glycol, phenoxyethanol, acetone anil, and *N,N*-dibutyl formamide.

While lubricants have many chemicals that can be detected, Moustafa *et al.* investigated how similar lubricant signatures were to personal hygiene products (PHPs)[104]. Using a subset of lubricants, condom lubricants, and PHPs, extractions of the samples were analyzed by DART-MS and subjected to HCA. Dichloromethane was found to be the best solvent for extraction (compared to methanol and hexane) and an optimal DART temperature of 300 °C was identified – slightly lower than the temperature used in almost every other study on lubricants (350 °C). HCA led to 11 groupings, two of which uniquely contained PHPs and 3 of which contained both PHPs and lubricants – suggesting that similar spectral signatures may exist for some lubricants and PHPs.

While most studies on lubricant analysis by DART-MS have looked at neat material, or extracts of neat material, this likely does not represent how samples would be submitted to a laboratory. If a sexual assault evidence sample is submitted for analysis, it is likely to be a post-coital swab. As biological material will be present, investigation into the effects of biological material on lubricant analysis is critical. Proni *et al.* investigated this question through the comparison of pre- and post-coital swabs for the detection of condom lubricants[105]. This study targeted detection of the spermicidal compound nonoxynol as a marker and utilized swab extraction for analysis. Detection of nonoxynol on swabs collected up to 8-hours post-coitus was demonstrated, and it was found that freeze drying of samples minimized decomposition.

A unique approach for lubricant analysis was recently demonstrated by Bridge *et al.* and involved the utilization of multiple DART temperatures and the ionRocket to obtain temperature gradient profiling[23]. Looking at water-based lubricants, this study investigated the added benefits of analysis at lower DART temperatures (to obtain information on volatile additives) as well as employment of a temperature programmed desorption (the ionRocket). Using a number of statistical tools, low temperature analysis of lubricants demonstrated differentiation based on additives as opposed to glycerol, which drove differentiation at the traditional, higher, temperature setting. Extraction of base peak chronographs and total ion signals from the temperature programmed desorption data (Fig. 6) provided higher discriminating capabilities, and the fusion of the two datasets provided the highest discriminating power. Combining Pearson correlation coefficients with likelihood ratios was proposed as an optimal approach for the comparison of knowns to unknowns.

3.6. Other applications

In addition to these frequently demonstrated forensic analyses, DART-MS has been applied to the identification and classification of regulated species (*e.g.*, wood and rhinoceros horn), entomology, polymers, beverage adulterants, and a number of other applications. The ability to directly and rapidly analyze unique samples without extensive sample preparation provides appealing capabilities for screening of regulated species of timber. In collaboration with a number of universities, institutions, and agencies, the U.S. National Fish and Wildlife Forensic Laboratory has employed DART-MS and multivariate statistics

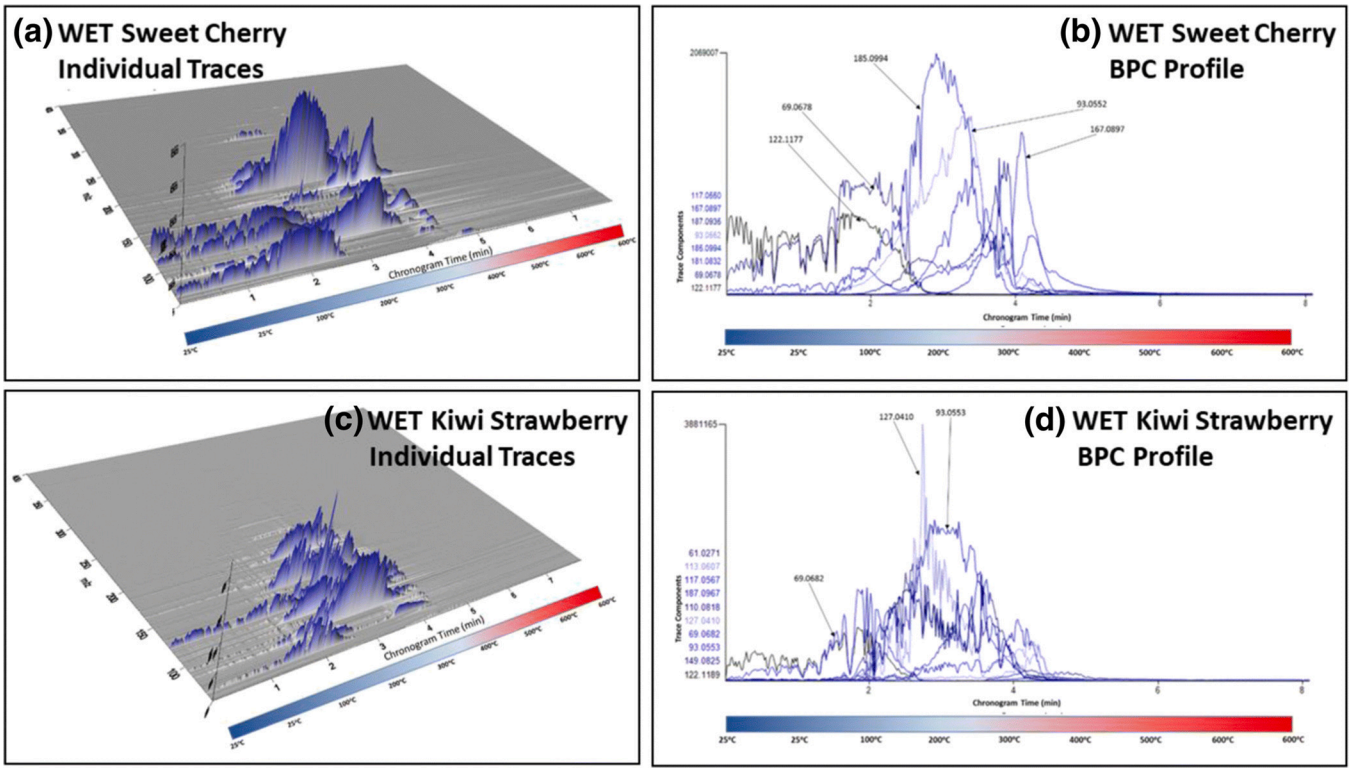

Fig. 6. An example of three-dimensional temperature programmed desorption data obtained using the ionRocket (a and c) for the analysis of representative lubricants as well as an example of base peak chronographs that can be extracted from the data and used to aid in discrimination (b and d). Reprinted with permission from (C. Bridge, M. Marić, Temperature-Dependent DART-MS Analysis of Sexual Lubricants to Increase Accurate Associations, J. Am. Soc. Mass Spectrom. 30 (2019) 1343–1358.). Copyright (2019). American Chemical Society.

for the determination and differentiation of timber species[106–109]. Traditionally, wood anatomy is used to identify endangered or banned species, regulated by CITES – Convention for the International Trade of Endangered Flora and Fauna treaty, however many species often have indistinguishable characteristics. Evans *et al.* and Espinoza *et al.* employed DART-MS in the direct analysis of timber slivers in positive mode MS[107,109]. In combination with both supervised (*i.e.,* kernel discriminant analysis (KDA) on selected diagnostic ions) and unsupervised (*i.e.,* HCA) statistics, species of *Dalbergia* and *Araucaria* were successfully classified and differentiated from look-alike species.

Deklerck *et al.* expanded on these capabilities through automated species analysis of metabolome profiles using a random forest machine learning algorithm[106]. The study demonstrated the significant affect pre-processing parameter settings (*i.e.,* mass tolerance for binning and abundance cut-off threshold) have on classification accuracy. The automated parameter screening and random forest algorithm enabled the identification of illegal timber. Musah *et al.* also combined DART-MS with chemometric methods for the determination of regulated timber, biodiesel feedstock, insect species (from puparial casings), psychoactive plant products, and Eucalyptus species[108]. The use of HCA and heat maps enabled differentiation based on the full chemical profile, without the biases associated with supervised methods, as well as provided details on genetic relationships.

In addition to regulated plant products, classification and differentiation of illicitly traded rhinoceros horn and pangolin scales has been demonstrated. Price *et al.* classified keratin from four taxonomic groups, including rhinoceros (horn), bovid (horn), domestic horse (hoof), and pangolin (scale) samples[110]. Preliminarily, Fisher ratio analysis was used to identify characteristic ions, followed by supervised KDA on a training set of spectra. The rhinoceros horn samples were accurately identified among the look-alike keratin samples. Similarly, Jacobs *et al.* examined the chemotypes of scales from over 100 individual pangolins. These scales have been widely trafficked due to reports of analgesic tramadol content. However, this study directly examined all extant pangolin species and found no presence of tramadol in any[111].

Similar to classification for regulated species, Beyramysoltan *et al.* demonstrated species identification of entomological samples (*e.g.,* carrion insects) using a method that combined DART-MS measurements of ethanol extracted suspensions with supervised Kohonen self-organizing maps (SOM)[112]. These artificial neural networks were used to classify and identify carrion flies from larva, pupa, and adult life stages with accuracies of 100%, 96% and 93%. Similar to other machine learning classifiers, as the model incorporates more species it has potential for aiding rapid identification of carrion insect species. Beyramysoltan *et al.* followed this study by expanding to identification from multispecies mixtures of two to six individual species[113]. In this study, an aggregated hierarchical conformal predictor was applied to a top-down hierarchical classification tree for multispecies discrimination.

The analysis of polymers has also found utility in both traditional DART-MS and a couple hybrid platforms, including combination with hot-stage microscopy and thermal desorption/pyrolysis (*i.e.,* the commercial ionRocket). Zughaibi *et al.* used traditional DART-MS to directly analyze seven closely related nylon standards[114]. Differentiation was achieved through simple manipulation of the DART gas temperature, is-CID, and observation of monomers, dimers, and trimers. Though polymers can be directly analyzed in a traditional configuration, the mass spectra are highly dependent on the DART gas temperature. Hybrid platforms provide more specific control over the heating process. For example, Ashton *et al.* developed a platform that incorporated a miniature hot-stage, optical microscopy, custom DART source, and ion trap mass spectrometry[115]. Synchronization of optical images with positive and negative mode mass spectra provided physical and chemical information as a function of temperature for the analysis of polymer

heating. The developed platform enabled observation of volatile oligomers releasing from medical and domestic grade silicone. The authors also used the system to detect and identify polyethylene and polystyrene microplastics from beach sand samples.

A couple recent works have also employed the commercially available ionRocket for thermal desorption and pyrolysis of polymer-based samples. Cody *et al.* used this system to characterize polymers and additives[116]. Kendrick mass analysis was applied to the mass spectra collected from fluorinated polymers heated up to 600 °C. The precise control over heating allowed for separation and analysis of polymer additives, short polymer chains, and fragments. Liang *et al.* completed a similar analysis of polymeric fibers from forty textile samples[117]. In combination with PCA and Pearson product moment correlation (PPMC), classification of fibers based on mass spectral profiles was achieved. The authors demonstrated the simplicity of sample analysis and interpretation of results, presenting an approach applicable to forensic identification of fiber evidence.

In addition to regulated species identification and polymer differentiation, DART-MS has also recently been used for the analysis of beverages, fabric stains, hair, latent fingerprints, and DNA extracts. Sisco and Drake employed traditional DART-MS for the analysis of low molecular weight adulterants from a range of common beverages, including juices, sodas, energy drinks, and liquors[118]. The rapid technique enabled adulterant detection from the complex liquids at comparable levels to confirmatory headspace GC–MS. Later, Sisco and Robinson expanded on this analysis by demonstrating ethanol quantification from alcoholic beverages using a confined geometry DART-MS configuration[119]. Here, a headspace vial is directly coupled to DART-MS through an enclosed T-junction for analysis in seconds.

Kern *et al.* incorporated DART-MS into a forensic workflow for rapid screening of fabric stains[120]. The presumptive identification of theobromine and caffeine, known components of chocolate, were matched to a control sample of chocolate ice cream using LC-MS. In another hybrid technique, Fowble and Musah coupled laser ablation with DART-MS for chemical imaging of latent fingerprints[121]. The platform was able to spatially resolve both endogenous and exogenous components from latent fingerprints from lift tape. DART-MS has also been used to evaluate mass analyzers for forensic work. Duvivier *et al.* used DART-MS to compare an Orbitrap, quadrupole Orbitrap, triple quadrupole, and quadrupole time-of-flight mass analyzers for the forensic analysis of THC from intact hair samples[122]. As might be expected, the hybrid quadrupole Orbitrap and quadrupole time-of-flight demonstrated the mass resolution necessary to distinguish THC from endogenous isobaric interferences. Finally, Moreno *et al.* employed DART-MS as a screening tool to evaluate the quality of DNA extracts [123]. Specifically, DART-MS was used to analyze the level of polymerase chain reaction (PCR) inhibitors remaining following various extraction methods. The study demonstrated the wide utility of DART-MS as a rapid screening tool for many applications. These studies highlight that DART-MS can be applied to nearly all evidence types of relevance to forensic chemistry, not just common applications of drugs and explosives detection.

4. DART-MS related resources for forensic chemists

For laboratories that have implemented or are considering implementing DART-MS into their laboratory, there are a number of additional resources that are available beyond the large body of peer-reviewed publications. Laboratories such as the Virginia Department of Forensic Science and Harris County Institute of Forensic Science have made their validation, training, and operating manuals publicly available[124]. A few workshops that have been given on DART-MS are also publicly available and provide a more in-depth look into the fundamentals of the technique[125]. Textbooks have been published specifically on DART-MS[126] and on ambient ionization mass spectrometry in general[127,128] as well as textbooks where forensic applications of DART-MS are discussed[129]. For drug analysis, NIST hosts a DART-MS spectral database that is freely available[130]. A number of software tools, such as MassMountaineer, TSS Unity, AnalyzerPro, and PIMISA exist to help with data analysis, searching, deconvoluting, and statistical processing. As the implementation of DART-MS in forensic science and other fields continues to increase, the list of available resources will undoubtably continue to grow.

5. Research needs and the potential future for DART-MS analysis

Though a large research base for forensic applications of DART-MS exists, there is still a number of areas that require increased attention and development. One of the biggest questions that remains relatively unanswered, outside of drug screening, is how well the technique performs with real casework. Many applications lack large-scale studies and comparisons that utilize real world samples. This is true even in drug analysis for applications other than drug screening. Increased collaborations between researchers and forensic chemists would help address this need which is critical for aiding practicing forensic laboratories in their decisions on whether or not DART-MS is a suitable tool. With the increasing use of statistics and chemometrics, the need for large datasets is also becoming more apparent. Much of the work that describes classification models for sample differentiation does so using relatively small and non-diverse sample sets. In these cases, test samples are not always from different sources than the samples used to build the models (*i.e.,* training data). While obtaining samples, or spectra, for sufficiently large datasets is often difficult, it is necessary to truly understand the strengths and limitations of proposed chemometric applications.

As laboratories contemplate moving from helium to nitrogen for the DART source gas, it is critical to understand the consequences of doing so. While initial research has shown that spectra are largely similar, and, depending on the configuration, sensitivity may not suffer, this has not been exhaustively studied for all types of samples. Addressing questions such as whether comparison spectra generated using helium can be used for nitrogen comparison also needs to be established. The utility of dopant addition, which has been demonstrated for argon DART, should be investigated to identify if similar benefits for nitrogen DART analysis can be realized. Fully understanding any differences in analytical metrics (limits of detection, reproducibility, etc.) between helium and nitrogen DART also needs to be established. The same is true for the recently released pulsed helium DART configuration.

Additional research incorporating the time dimension for data interpretation may prove extremely valuable in moving DART-MS from a purely screening tool to a confirmatory technique. The use of mass spectrometry platforms that incorporate DMS or IMS, to allow for rapid separation of compounds, should also be further explored since initial results have shown promise for increasing confidence in an identification. Temperature programmed desorption, especially for complex mixture analysis, presents another promising tool where the time dimension could be incorporated and leveraged for enhanced confidence. Even approaches as simple as spectral deconvolution to observe differences in desorption order may, along with timed sample introduction, aid in compound confirmation. This approach may prove valuable in automated mass spectral background subtraction, and has been recently demonstrated on ambient ionization mass spectrometry data[131].

One hurdle to widespread implementation of the technique is the access to adequate data processing and data extraction tools along with availability of appropriate databases. Many of the mass spectrometry systems that DART is coupled to are not designed for non-chromatographic analyses.

Therefore, the extraction and processing of data, as well as post analysis is often cumbersome – especially when simple peak list searching is not sufficient. Some manufacturers have begun to move towards automated data extraction and analysis, but much still needs to be done. Tools that will provide automated mass spectral extraction

from the total ion chronograph would be a great asset to the DART-MS user. Advances in spectral searching, to aid in identification of compounds within complex mixtures, would also help increase usability of the technique. Similarly, incorporating data from multiple is-CID fragmentation spectra would also aid in increasing the confidence of identification and, possibly, provide increased isomer differentiation capabilities. This ability, however, would require access to adequate spectral libraries, of which few currently exist. Since laboratories use a wide range of mass spectrometers (single quadrupole, triple quadrupole (QQQ), TOF, Orbitrap, ion trap, and Q-TOF), the comparison of the utility of a single library across MS platforms would be a fruitful study. Likewise, an in-depth round robin to understand mass spectral reproducibility across systems would aid in a better understanding of the utility of databases. An extensive resource base that provides forensic chemists with access to training materials, validation examples, operating procedures, and documentary standards, would also further aid in increasing adoption of the technique by the field.

Increased adoption of the technique will likely open a range of potential opportunities and applications that currently do not exist. Unlike many analytical instruments, the rapid analysis and simple operation of DART-MS make it well positioned to be used in a joint-user configuration where multiple disciplines have access to the same instrument. Such an approach may lower the barrier of entry for laboratories and provide increased justification for procurement. Moving the DART-MS system out of the laboratory space and into the evidence receiving area is another potential future application of the technique. The ability to detect trace residues from wipes of evidence could prove valuable in triaging evidence that is submitted or providing preliminary analysis to submitting agencies without waiting for a full analytical workup. The correlation of the residue to the contents would need to be well understood for this to occur – similar to published efforts for drug evidence [67]. This type of rapid, near-complete chemical profile will prove valuable for forensic intelligence efforts as well. Implementing DART-MS as a single technique, or part of a suite of techniques, for building databases and processes to link samples will likely be more frequently demonstrated in the near future. With the increased use of novel sample introduction or sample preparation approaches, the ability to confidently and reproducibly analyze a wide range of samples will continue to grow. Increased toxicology applications will be realized, especially as sampling approaches that increase reproducibility and sensitivity are demonstrated. Combining the speed of DART with reproducible sample introduction methods will provide a means to quickly create databases and complete studies into the uniqueness of compounds or variations in chemical makeup or a wide range of materials in a fraction of the time of traditional chromatographic techniques.

DART-MS has been demonstrated to successfully analyze an array of samples including drugs, explosives, gunshot residues, inks, plants, insects, and beverages. Advances in sample preparation, sample introduction, and chemometric approaches have shown that the technique can be used for more than screening of samples. A number of barriers to widespread adoption still exist, including development of better data analysis tools, increased access to reference data, and increased availability of relevant training and validation documentation. A clear need for increased collaboration between researchers and forensic chemists, to better understand the strengths and weaknesses in analyzing real case samples and to unlock novel implementations to address analytical challenges also exists. While the widespread adoption of the technique is still gaining traction, recent research highlights the widespread potential it has for nearly all forensic chemistry disciplines.

6. Disclaimer

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Certain commercial products are identified in order to adequately specify the procedure; this does not imply endorsement or recommendation by NIST, nor does it imply that such products are necessarily the best available for the purpose.

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.

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