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TECHNICAL NOTE

CRIMINALISTICS

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Rapid Separation and Characterization of Cocaine and Cocaine Cutting Agents by Differential Mobility Spectrometry–Mass Spectrometry

ABSTRACT: Forensic drug laboratories are inundated with cases requiring time-consuming GC- or LC-based chromatographic separations of submitted samples. High-throughput analytical methods would be of great practical utility within forensic drug analysis. Recently developed ion-mobility-based separation methods combined with mass spectrometry can often be used without chromatography, suppress chemical interferents of similar mass, and operate in seconds. We have evaluated differential mobility spectrometry–mass spectrometry (DMS-MS) for performance on adulterated cocaine mixtures. The DMS interface is only a few centimeters in length, operates in seconds, and can be adapted to any MS system using atmospheric pressure ionization. Drug cutting agents, typical targets such as cocaine, and drug metabolites are rapidly separated by the DMS ion prefilter. Tests demonstrated characterization of complex mixtures, such as isolation of levamisole, an adulterant with alarming side effects, from a 13-component mixture. DMS-MS holds great potential for the analysis of drug samples submitted for forensic analysis.

KEYWORDS: forensic science, forensic chemistry, separation science, cocaine, adulterants, DMS, FAIMS, differential mobility spectrometry–mass spectrometry

It is common for street-quality cocaine samples to be "cut" with adulterants and/or diluents because they are typically sold by weight. Adulterants possess biological effects that mimic some of those of the drug of abuse and are often utilized by dealers to increase perceived quality to the end user. An example of this includes the use of caffeine as a cocaine adulterant owing to its stimulatory effects upon the central nervous system. While drug-testing laboratories do not often see "common" adulterants, some adulterants observed include but are not limited to procaine, benzocaine, lidocaine, levamisole, tetramisole, xylazine, hydroxyzine, and caffeine (N. W. Brooks, personal communication, February 19, 2010). Diluents do not mimic the biological effects of the drug of abuse and are simply added to increase the bulk of the product for purposes of distribution and economics. Some diluents include boric acid, mannitol, lactose, sucrose, inositol, creatine, creatinine, and sodium bicarbonate (N. W. Brooks, personal communication, February 19, 2010). Identification of adulterants and/or diluents in forensic drug samples can provide probative investigative leads in an effort to determine whether two samples are similar or may have originated from a common source. Rapid profiling of cocaine samples by differential mobility spectrometry–mass spectrometry (DMS-MS) could serve as an important analytical technique in forensic drug investigations.

Reports of the current impasse faced by drug analysts and laboratory managers at often underfunded and inundated forensic laboratories are constantly appearing in both the professional and the popular press (http://www.boston.com/news/nation/articles/2008/11/11/coakley_forensics_testimony_a_burden/ [accessed January 8, 2011], http://homelandsecuritynewswire.com/backlog-baltimore-crime-lab-concern [accessed March 22, 2010], and http://www.mass.gov/?pageID=eohhs2terminal&L=4&L0=Home&L1=Provider&L2=Reporting+to+the+State&L3=State+Laboratory&sid=Eeohhs2&b=terminalcontent&f=dph_laboratory_sciences_p_drug_analysis&csid=Eeohhs2 [accessed January 8, 2011]). Case backlogs, often numbering in the thousands, support the urgent need for new technologies and approaches to improve sample throughput. The problem is likely to be further exacerbated in view of the decision in response to the *Melendez-Diaz v. Massachusetts* case, which will require analysts to appear in court on a regular basis to provide testimony to chemical drug test reports, thus taking them away from the laboratory (http://www.boston.com/news/nation/articles/2008/11/11/coakley_forensics_testimony_a_burden/ [accessed January 8, 2011]). Enhancements to the current analysis schemes utilizing lengthy gas chromatography (GC)- and liquid chromatography (LC)- based chromatographic runs with MS detection would be expected to improve the operating efficiency of forensic drug laboratories nationwide.

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Ion Mobility Separation Methods

In recent years, ion selection methods based on electric-field ion mobility have been combined with MS. The selectivity and specificity of these approaches to the detection of analytes of interest with higher throughput than GC and LC methods make them desirable options. Ion mobility separations occur at atmospheric pressure and are based on the movement of ions in an electric field. The ion speed, or drift velocity, v, is proportional to the applied electric field, E, related by a coefficient that may itself be a function of field: the ion mobility coefficient, $K(E) = v/E$, as described in standard texts on ion mobility (1–3). There are two general operational principles used in ion mobility systems. First to be developed were time-of-flight techniques based on the measurement of the velocity of ions drifting under the effect of low electric field (DC), known as ion mobility spectrometry (IMS) (2,3). An ion's identification in this method occurs through the absolute value of the ion mobility coefficient. More recently, a new technique has been developed in which an ion's identification is based on the measurement of the difference between ion mobility in high and low electric fields. Therefore, this technique is called DMS (it is also known as field-asymmetry IMS [FAIMS]), which is used in this work.

Differential Mobility Spectrometry

DMS and the use of DMS as an ion prefilter for MS were developed for applications in the early 1990s in a series of articles from the former Soviet Union (4–6), which built on inventions made within their military establishment a decade before. This interesting history, properties of different differential mobility device configurations, theory of operation, and current developments in the technology are presented in a recent monograph (7). DMS is similar to conventional ion mobility in that the ions are separated in a bath or drift gas at atmospheric pressure; however, they differ in how they exploit the analytical properties of the ion species. IMS separates ions on the basis of the absolute value of the mobility coefficient, whereas DMS separates ions on the basis of the electric field's effect on the mobility coefficient. The configuration used in the DMS portion of our instrument is illustrated in Fig. 1.

An asymmetric electric field waveform, the RF field or separation voltage (SV), is applied to two parallel electrode plates between which the ions pass through in a continuous, not pulsed, manner. The asymmetric waveform electrical field consists of a short period of high field strength application of one polarity and then a longer period of low field of opposite polarity. The average field over one cycle of the separation field is zero. The separation field is combined with a smaller quasi-static field called the compensation voltage (CV). The compensation field is adjusted so that selected ions pass through the DMS analytical region without contacting the walls and being neutralized.

An initial approach, commonly utilized with the Sionex micro-DMx™ sensor (Bedford, MA), to identify the ideal SV and CV settings for the best combination of selectivity and transmission involves scanning the CV at a fixed SV while monitoring ion signal. It should be noted that the separation response is essentially instantaneous, limited only by the millisecond residence time of ions in the analytical region, and can be maintained stably throughout the continuous infusion of an analyte mixture (8).

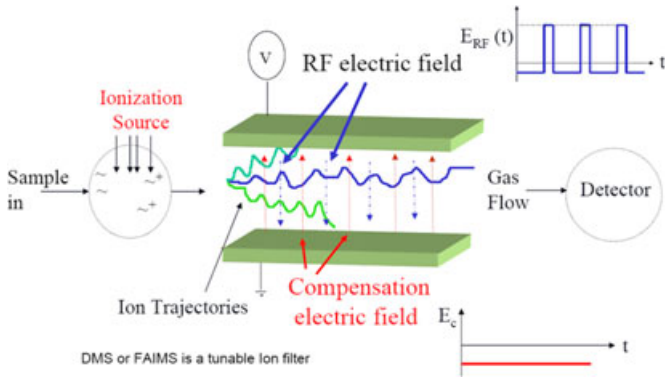

FIG. 1—*Differential mobility spectrometry principle of operation. Ions from an ionization source are entrained in a carrier gas that passes between parallel plate electrodes. An intense asymmetric RF electric field, ERF(t), is applied, which causes the net ion motion per cycle to depend on the difference between the ion mobility in high field and in low field. A compensation field, EC, is adjusted to select specific ion species for detection. EC is also referred to as compensation voltage, symbols CV or Vc.*

DMS in Forensic Applications

Drug analysis units currently employ presumptive, colorimetric spot tests, microcrystalline tests, thin-layer chromatography, UV–Vis spectroscopy, and/or GC-flame ionization detection (nitrogen/phosphorus detection) as screening techniques followed by GC-MS and Fourier transform infrared spectroscopy as confirmatory methods of analysis. Current analytical methods utilize GC and LC because they are able to isolate target compounds in the presence of a wide range of contaminants and adulterants. If chromatography is not used, the presence of other compounds and the chemical noise generated in ion sources can interfere with reliable identification and quantitative measurement. GC-MS and LC-MS identifications are recognized as the most reliable and accurate methods available, because they provide a separation, which is complementary to mass analysis.

In general, a major goal of DMS is to eliminate the necessity for extensive sample preparation and time-consuming chromatographic separations prior to mass analysis. In previous work carried out in our laboratories, we demonstrated that it is possible to replace the necessity for chromatographic-based separations for targeted applications (9–11). Here, we have utilized a miniature differential ion mobility filter, placed in front of the entrance of the mass spectrometer for selective introduction of ions created by a nano-electrospray ionization (ESI) source (Fig. 2). Rapid separation of analytes contained within complex mixtures and reduction in background chemical noise can be achieved. Separation profiles can be generated in less than a minute by simple adjustment of the CV characteristic of the individual mixture constituents' ion mobilities at a fixed SV. Structural characterization is accomplished by using an ion trap in MS/MS mode.

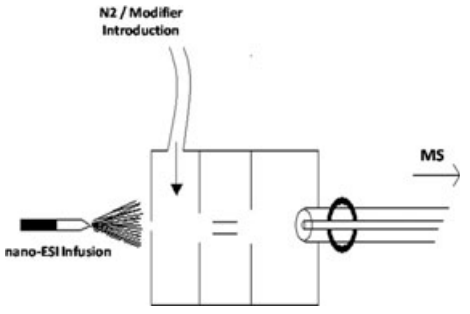

FIG. 2—*Differential mobility spectrometry–mass spectrometry inlet schematic showing N2 drying gas and modifier introduction.*

DMS-MS holds great potential as a new technique in forensic analysis. The rapid nature of the separations offers potential advantages over currently employed techniques traditionally employing GC or LC prior to mass spectral analysis. In an effort to demonstrate the advantages that DMS-MS offers for the analysis of drugs of abuse as standards and in contrived street samples, we show rapid separations of cocaine and cocaine cutting agents utilizing a miniaturized differential mobility spectrometer in tandem with an ion trap mass spectrometer.

Materials and Methods

Optima LC/MS methanol and water and Optima ethyl acetate were obtained from Fisher Scientific (Pittsburgh, PA), and formic acid was obtained from Acros Organics (Morris Plains, NJ). Methanol, water, and formic acid were prepared as a 70:30:0.1 v/v solution, and all samples were prepared in this mobile phase for nano-ESI-DMS-MS analysis. The following standards were obtained from Cerilliant Corporation (Round Rock, TX) and diluted to appropriate concentrations: cocaine, diltiazem, and acetaminophen. Tetramisole HCl, levamisole HCl, lidocaine, xylazine, hydroxyzine, and procaine were obtained from MP Biomedicals (Solon, OH). Theophylline, diphenhydramine HCl, thiamine, creatine, and creatinine were obtained from Acros Organics. Benzocaine was obtained from Chem Service (West Chester, PA), and caffeine was obtained from Sigma-Aldrich (St. Louis, MO). All of the drug, adulterant, and diluent standards were obtained and prepared as 1 mg/mL solutions in methanol prior to dilution in the 70:30:0.1 v/v mobile phase. The standards obtained from Cerilliant Corporation were sold as 1 mg/mL solutions in methanol. Unless otherwise noted, all samples were prepared as 10 ng/uL solutions. UHP nitrogen was obtained from Medical-Technical Gases, Inc. (Medford, MA) and was further purified using an in-line RMSN-2 nitrogen filter (Agilent Technologies, Santa Clara, CA).

The DMS prefilter utilized in this work was developed by Sionex Corporation. The analytical region of the DMS ion filter is 0.5 mm high × 3.0 mm wide × 10.0 mm long, with these dimensions based on balancing resolution requirements and diffusion losses for the measured inlet flow of 0.6 L/min. Sionex electronics provided separation and compensation fields of the flyback type as described in Krylov et al. (12).

Sample mixtures were introduced via infusion using a Harvard Apparatus 22 pump (Holliston, MA) at a flow rate of 300 nL/min. Nano-electrospray was accomplished at 2 kV using a coated, 10 μm PicoTip emitter from New Objective (Woburn, MA). A 50-V bias voltage was applied across the desolvation region to attract ions to the DMS inlet. Ions leaving the DMS filter are carried by gas dynamics/vacuum drag into the inlet capillary of the mass spectrometer. In the desolvation region just before the DMS filter, heated UHP nitrogen gas line was introduced at a flow rate of *c.* 100 mL/min (Fig. 2), while the total MS inlet flow (including vacuum drag) was 600 mL/min. The nitrogen gas was heated to a temperature of *c.* 50°C via electrical heating of a copper desolvation gas line (Fig. 2).

Unless otherwise noted, ethyl acetate vapor was added to the heated nitrogen flow as a modifier, resulting in a concentration of about 1.5% v/v in the DMS analytical region determined by weight loss measurements. The SV was typically set at the maximum value of 1500 V (mean to peak) while scanning the CV across its maximum range from −43 to +15 V in 100 steps. A Thermo Scientific (West Palm Beach, FL), LCQ Classic Ion Trap served as the mass spectrometer for detection of the DMS-separated species.

Results and Discussion

Initial screening of mixtures was accomplished by scanning the CV at a fixed SV. Scanning the full CV range (−43 to +15V) was accomplished within 10 min. Scanning the CV constitutes the method development stage of the procedure and can be viewed in the same way as the development of separation conditions in a GC- or LC-based analysis. Once a useful combination of SV and CV conditions are established, the rapid nature of separations via DMS-MS can be appreciated. The Expert software (Sionex Corp.) controlling the DMS functionality can be configured to visit discrete (SV and CV) values that select a sequence of target ions. The time required per selected ion would typically be in the range of 100 msec to a few seconds depending on the sample concentration and the characteristics of the mass spectrometer. In addition, DMS filtration causes only about 20% loss in signal intensity compared to an instrument without the device mounted, separates targets from interferents, and reduces chemical noise by a factor of 10–50 (typically). These properties of DMS-prefiltered MS systems have been established in detail in recent publications from several different groups. Especially useful background references on differential mobility systems include an overview of DMS-MS by Schneider et al. (8) and the Shvartsburg (7) monograph on differential mobility methods. When ion mobility selectivity is sufficient, separations designed to screen mixtures can usually be completed in rapid fashion, typically under 1 min.

The feasibility of DMS to function as a selective prefilter for the rapid analysis of controlled substances is presented here using cocaine as a target analyte in samples of progressively higher complexity. The infused samples, each containing all of the species within the mixture (Figs 3–7), were introduced via nano-electrospray into the DMS without pretreatment.

An integral feature in improving separations by DMS involves the use of modifiers. The use of gas-stream modifiers to enhance resolution in mobility separations is demonstrated in Levin et al. (10,11) and more recently discussed in Schneider et al. (13,14), and is also used in our tests. For these samples, ethyl acetate is utilized and shown to result in the baseline separation of cocaine and cutting agents in the experiments conducted. For the specific analyses conducted for this study, ethyl acetate was a key modifier and provided the basis for the investigation of more complex mixtures. In an effort to demonstrate the utility of ethyl acetate as a modifier, initially a two-component mixture containing cocaine and its primary metabolite, benzoylecgonine, was created. These compounds share common structural features and represent analytes of interest to the forensic science community. In the absence of ethyl acetate vapor within the desolvation gas, no separation is achieved. However, upon the addition of ethyl acetate as a modifier, we observed baseline resolution of the two species from an infused mixture (Fig. 3). It should be noted that in comparison with a GC-based chromatographic separation, there was no need to derivatize the benzoylecgonine prior to analysis by nano-ESI-DMS-MS.

To further demonstrate the separation capabilities of DMS with the use of ethyl acetate as a modifier, a mixture containing cocaine and five common adulterants was created. The total ion chromatogram for the six-component mixture appears in the top left pane of Fig. 4 as a series of five prominent peaks. The top right pane shows the corresponding full-scan mass spectral data of the mixture, determined by summing over the compensation voltage range of −43V to +15V. The mass data provide an approximation of the data that would be obtained without DMS filtration; however, it does not include the additional interfering chemical noise contributions that would be present with the DMS demounted or in transparent mode.

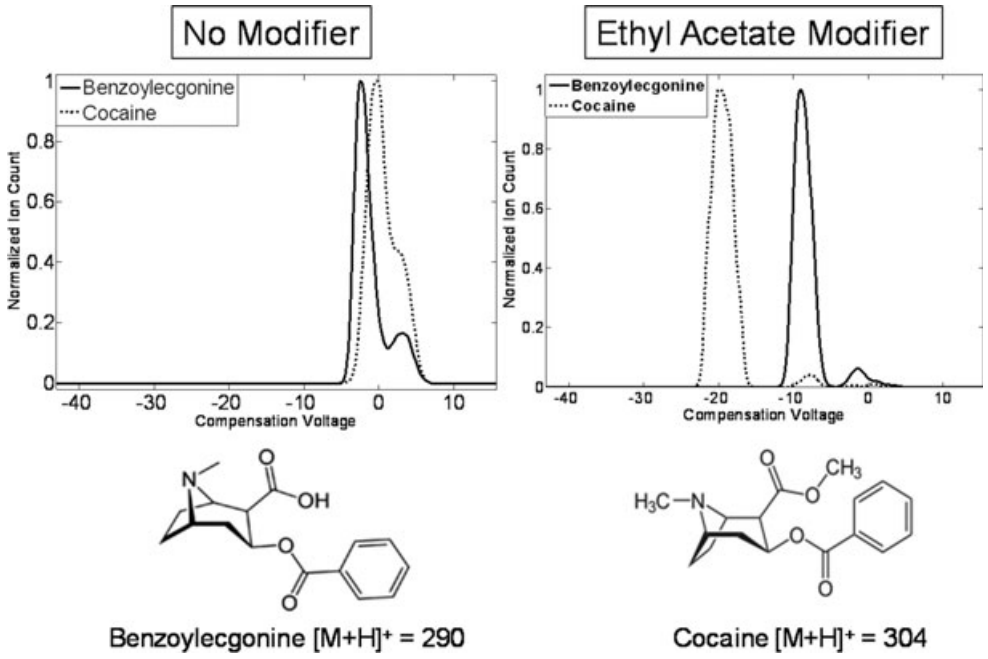

FIG. 3—*Differential mobility spectrometry data demonstrating the effect of ethyl acetate as a modifier on the separation of cocaine and benzoylecgonine, a primary metabolite of cocaine. Selected ion intensities (based on ion current) are separately normalized to 1.*

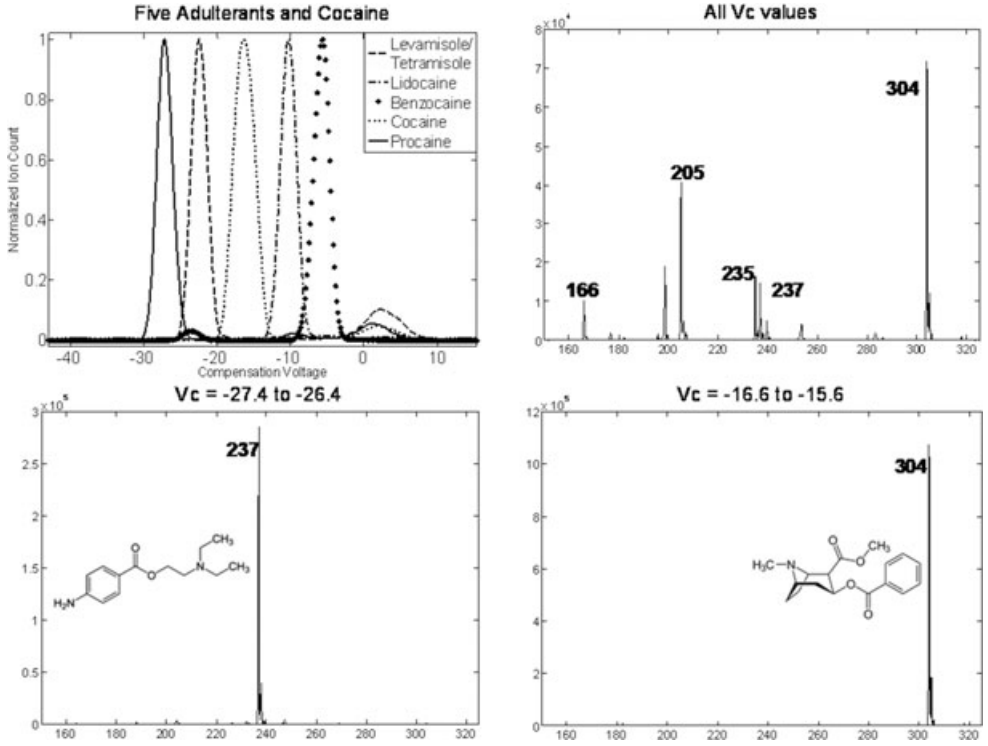

FIG. 4—*Differential mobility spectrometry–mass spectrometry separation showing extracted ion plots (top left) and corresponding mass data for the full compensation voltage range (top right). The figures on the bottom display specific compensation voltages for procaine (237) and cocaine (304). Selected ion intensities (based on ion current) are separately normalized to 1.*

The positive-ion mass spectrum of the nano-electrosprayed sample containing cocaine and five common adulterants in methanol/water/formic acid solution resulted in the presence of five distinct baseline-resolved peaks and is functionally equivalent to an extracted ion plot. While the enantiomers levamisole and tetramisole were not readily separated by this method, good separation was achieved for the three other adulterants relative to the determined CV for cocaine. Mass spectral data for selected CV ranges are represented in the bottom of Fig. 4. Cocaine is very well separated from all the adulterants present within this mixture. The −27.4 to −26.4 range (1 V) is specific for procaine, a commonly observed cocaine adulterant, and its

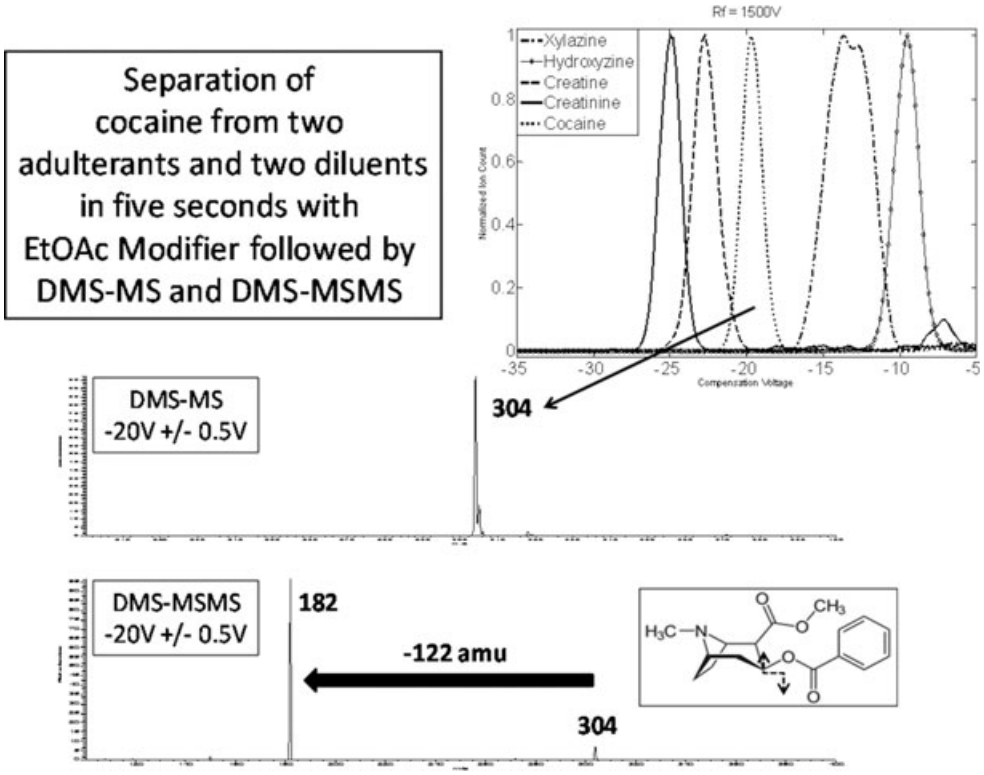

FIG. 5—*Extracted ion plots (top right) of two adulterants and two diluents with cocaine across the compensation voltage (CV) range of −35 to −5 V. The figures on the bottom display differential mobility spectrometry–mass spectrometry (DMS-MS) data at a fixed CV of −20 V for the selected transmission of the cocaine analyte and DMS-MS/MS data (CV = −20 V) showing structural characterization. Selected ion intensities (based on ion current) are separately normalized to 1.*

mass spectrum is shown in the lower left pane. For each of the given compounds, the CV stepping feature was programmed to sit on each respective CV for a period of 5 sec. As a result, separation of the five compounds was demonstrated in 25 sec. It should be noted that the stepping feature of the Expert software is capable of sampling for periods of time as low as about 10 msec per step.

In an effort to test additional mixtures containing both adulterants and diluents for the purposes of rapid separation and characterization, a second five-component mixture was created comprised of xylazine, hydroxyzine, creatine, creatinine, and cocaine. Figure 5 shows the separation of these five compounds followed by DMS-MS and DMS-MS/MS characterization and structural confirmation of the cocaine analyte of interest. It should be noted that separation and structural characterization of cocaine from this mixture was accomplished in 5 sec by DMS prefiltration prior to mass analysis.

To assess the general capability of DMS to suppress chemical noise and to serve as an effective ion filter prior to mass analysis, a more complex 13-component mixture was created to represent an extreme case of cocaine cut with numerous cutting agents. The 13 components including cocaine were caffeine, benzocaine, theophylline, xylazine, levamisole, thiamine, diltiazem, lidocaine, diphenhydramine, tetramisole, acetaminophen, and procaine. Figure 6 represents the full MS scan for the mixture with the DMS transparent (Off) versus On. In the lower portion of the figure, the CV was fixed for 5 sec at −22 V for the selected transmission and characterization of the analyte levamisole. Thus, this system holds the potential for rapid screening of cocaine samples for the presence of levamisole, a common cocaine adulterant with alarming side effects.

Matrix interferences pose a serious problem in chemical analysis, especially when targeted analytes are present at trace levels and/or low concentration relative to matrix components. In accordance with this consideration, a 5000:1 adulterant mixture to analyte sample (10 ng of each adulterant [50 ng total] and 0.01 ng of cocaine) was created in an effort to evaluate the ability of DMS to perform targeted analysis of cocaine in the presence of a large excess of adulterants. The adulterant mixture consisted of benzocaine, lidocaine, procaine, levamisole, and tetramisole, each at a concentration of 10 ng/uL in solution. Cocaine was spiked into this mixture at a concentration of 0.01 ng/uL. A five-point calibration curve for cocaine was prepared in the 50 ng adulterant mixture from 0.01 to 10 ng/uL. Each of the five samples were prepared and analyzed in triplicate, and the curve showed good linearity with an R^2 value of 0.991. The mass spectral data on the right of Fig. 7 represent the 5000:1 adulterant matrix/cocaine sample showing the DMS Off (transparent) versus On (SV = 1500 V, CV = −43 to +15 V). In the bottom spectrum, the 304 ion $[M+H]^+$ for cocaine is apparent whereas in the top spectrum it is absent. While a definitive limit of detection was not established (future work), our results demonstrate the precision of the analytical method and were reproducible based on the preparation and analysis (in triplicate) of the five-point calibration curve in matrix (Fig. 7).

Conclusions

The data presented earlier demonstrate that DMS-MS could serve as a rapid, ambient ion separation and screening/confirmatory technique for forensic drug (cocaine) samples suspected to have

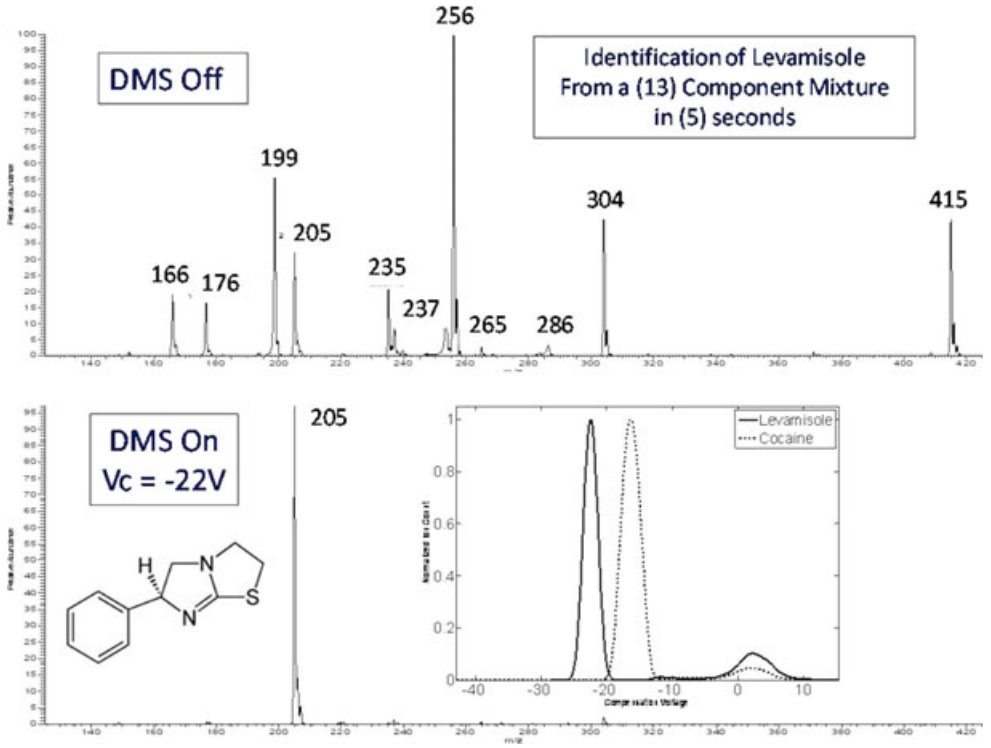

FIG. 6—*Differential mobility spectrometry–mass spectrometry separation showing a cocaine sample adulterated with 12 adulterants including levamisole, a common cocaine adulterant with dangerous side effects. Selected ion intensities (based on ion current) are separately normalized to 1.*

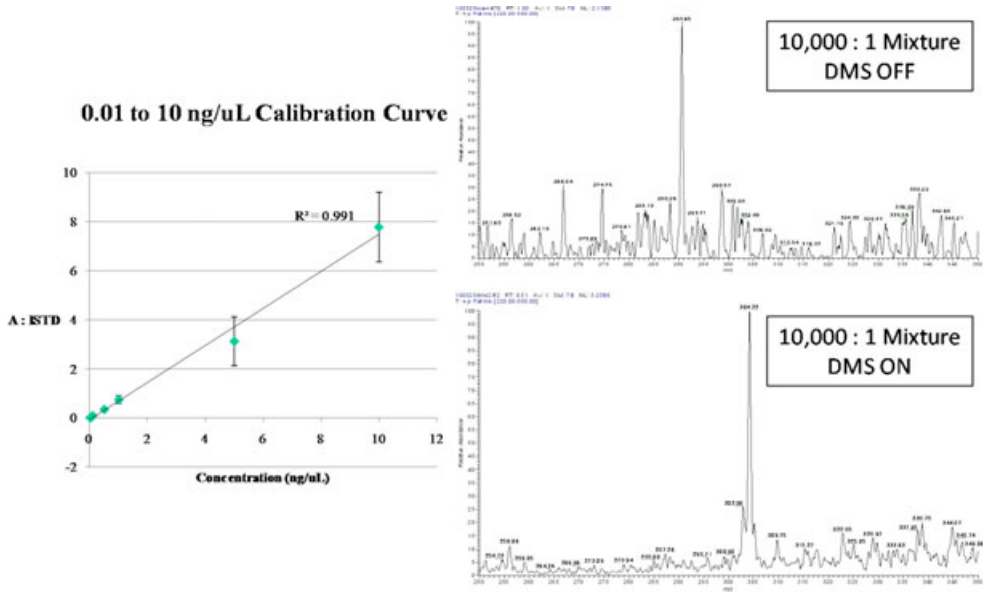

FIG. 7—*(Left) Five-point calibration curve showing the range of 0.01–10 ng/uL of cocaine spiked into 50 ng of an adulterant matrix (10 ng each of: benzocaine, lidocaine, procaine, levamisole, and tetramisole). (Right) 5000:1 adulterant matrix/cocaine sample (0.01 ng cocaine in 50 ng adulterant matrix) showing the differential mobility spectrometry Off (transparent) versus On (separation voltage = 1500 V, compensation voltage = −43 V to +15 V). In the bottom spectrum, the 304 ion [M+H]+ for cocaine is apparent whereas in the top spectrum, it is absent.*

been adulterated with caffeine, benzocaine, theophylline, xylazine, levamisole, thiamine, diltiazem, lidocaine, diphenhydramine, tetramisole, acetaminophen, procaine, creatine, and/or creatinine. Based on the presented results, ethyl acetate showed good selectivity as a desolvation gas modifier for the separated species. After separation has been achieved by DMS, confirmatory analysis by MS/MS can elucidate characteristic structural features of the DMS-separated species. The development of appropriate SV and CV conditions for a DMS-based separation process can be viewed as analogous to the development of a gradient for a GC- or LC-based separation and is accomplished by a 10-min scan of the CV at a fixed SV. However, following the establishment of the DMS

separation conditions, targeted analytes can be selectively transmitted into a mass spectrometer by rapid stepping of the CV for characterization by MS or MS/MS.

In comparison with current chromatographic techniques, ranging from 10 to 15 min for a GC-based separation or 30–45 min for an LC-based separation, here, DMS has been shown to separate and characterize mixtures commonly encountered in forensic laboratories in under 30 sec. As a result, *c*. 20 samples could be analyzed by DMS-MS in the amount of time that it would take to perform a 10-min GC-based chromatographic separation of one sample.

Because of the rapidity of the analysis, we propose that DMS-MS could serve as a viable platform for reducing case backlogs for the targeted analysis of analytes of interest within forensic drug samples. Based on currently accepted SWGDRUG guidelines (15), IMS is an accepted analytical technique in the field of forensic drug analysis. As a variant of IMS, DMS could also prove to be an accepted separation methodology prior to mass spectral characterization.

Differential mobility systems have been successfully interfaced to a wide variety of mass spectrometers including ion trap, single quadrupole, and triple quadrupole mass analyzers. The level of difficulty involved in interfacing DMS to MS varies from one type of mass spectrometer to another. Commercial DMS-MS systems of these types are currently under development.

Additional research should be conducted to evaluate the ability of DMS-MS to serve as a viable analytical technique in drug profiling applications where there may be an interest in determining whether or not two samples could have originated from a common source based on the quantitative determination of the presence/absence of adulterants and/or diluents in cocaine samples. Further work could extend the current capabilities of DMS-MS to other commonly submitted drugs of abuse including heroin and methamphetamine.

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