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Reliability of ion mobility spectrometry for qualitative analysis of complex, multicomponent illicit drug samples

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ABSTRACT

Ion mobility spectrometry (IMS) has been used for trace analysis of illicit drugs, but it can also provide reliable qualitative analysis of bulk forensic drug items, despite the complexity of these samples. The drug/drug and drug/excipient combinations representing over 80% of the samples reported by state and federal forensic laboratories over the past 7 years were compiled from reports of the National Forensic Laboratory Information System (NFLIS). From this set of materials, IMS detection windows were set for eight controlled substances, including methamphetamine, 3,4-methylenedioxymethamphetamine hydrochloride (MDMA), cocaine, heroin, fentanyl, hydrocodone, oxycodone, and alprazolam. The reduced mobilities of the eight controlled substances were measured over an extended period of time to determine variability with respect to the size of the detection windows. Uncertainties in reduced mobilities smaller than 0.001 $cm^2\ V^{-1}\ s^{-1}$ were obtained, and detection windows were set to between ± 0.003 and $\pm\ 0.005\ cm^2\ V^{-1}\ s^{-1}$. Reduced mobilities are instrument and operating condition dependent, and must be determined for each instrument. Peak overlaps are observed in the drug/drug combinations, but at least one controlled substance can be detected in each mixture. Excipient concentrations must be quite high (>75 wt%) in binary mixtures to interfere with the detection of the controlled substance. IMS can be used to identify many of the excipients, and can detect multiple (for these samples, as many as 4) substances in complex samples. Over-the-counter (OTC) tablet medications for cold, flu, and allergy relief can be distinguished from tablets containing controlled substances. Bulk materials, including tablets, are sampled simply by using a fine probe to restrict the amount of material transferred to the IMS substrate. IMS represents a distinct advantage over color tests for field analysis of illicit drugs, except in the case of cannabis/THC samples.

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1. Introduction

Preliminary identification of illicit drugs is conducted daily by law enforcement in a multitude of venues, primarily through the use of color tests. Color tests utilize reagents in liquid or aerosol form that react with the suspect material, resulting in a color that must be interpreted correctly to identify the class of drug [1,2]. There are practical limitations to these tests, including the ability to correctly mix the reagents in the field and the interpretation of the resulting color(s). Color tests are designed to target the type of compound and functional groups, and multiple tests must be used to cover the range of common illicit drugs. Of course, a wide range of instrumental techniques are available for the analysis of drugs, with gas chromatography–mass spectrometry serving as the primary method. A field-deployable, instrument-based technique that can be used easily by non-technical personnel, and that identifies specific drugs given the broad spectrum of materials expected in illicit trade would be useful. Both ion mobility spectrometry (IMS) and Fourier transform infrared spectroscopy (FT-IR) can be used for drug identification and are field-deployable, and IMS in particular is designed for a non-technical user. FT-IR has the potential to quantify methylamphetamine samples, but results are poor for complex samples containing substances different from calibration samples [3], IMS is used for detecting trace levels of illicit drugs [4–6] but it has not been used for the identification of bulk drug samples. The issues that are most important to address for bulk samples are the ability to sample a small amount to prevent saturation of the system, and the selectivity of IMS given multiple analytes in a sample.

Ion mobility spectrometers saturate, depending on the drug and the operating conditions, at amounts ranging from a few nanograms to hundreds of nanograms. IMS uses atmospheric pressure chemical ionization (APCI), and the reaction chemistry can become unpredictable as the reservoir of charge is depleted at high sample amounts [7]. In addition, excess material can result in the contamination of the instrument, resulting in memory affects and an inability to return quickly to background levels.

Compounds are identified in IMS by the reduced mobilities (K_0) of product ions; for illicit drugs the product ions are typically M^+ or

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$(M+H)^+$. Reduced mobility can be calculated from the drift time given the length of the drift region and the strength of the electric field, and then corrected to standard pressure and temperature. There are considerable practical limitations to this type of measurement [8], and commercial instruments typically use an indirect approach for measuring reduced mobility by referring to an internal calibrant:

$$(K_0)_{\text{unknown}} = \frac{(K_0 * t_d)_{\text{calibrant}}}{(t_d)_{\text{unknown}}} \quad (1)$$

where t_d is the drift time. A limitation with IMS is the absence of reference compounds for reduced mobility that are insensitive to environmental conditions and can be used as absolute standards [8,9]. Although the use of 2,6-di-*t*-butyl pyridine has been proposed [8], the IMS community has not adopted any common reference materials. As a result, there can be a large variability in the values of reduced mobility reported for the same compound. Commercial instruments use detection windows that define the allowable range in reduced mobility for a given drug; these detection windows are smaller than the reported uncertainties, and are based on proprietary information. To our knowledge, the variability in reduced mobility for a given drug during routine operation of a commercial instrument has not been reported.

The detection libraries of commercial IMS instruments may include a number of drugs that are no longer common in illicit trade, and lack a number of drugs that are. The types of samples that are routinely encountered by law enforcement are tabulated by the Drug Enforcement Administration (DEA), which compiles statistics on the results of forensic drug testing [10]. Forensic drug samples are typically complex, containing multiple drugs and excipients. Multicomponent samples not only challenge the selectivity of IMS, but they also present the potential for competitive ionization, with loss of signal of one or more analytes [11]. For APCI, there is a limited reactant ion reservoir and therefore competitive charge transfer among compounds. In the case of illicit drugs, it is known that heroin can be difficult to detect in the presence of cocaine [6,12]. Because IMS has been used in trace screening environments, issues of selectivity and competitive ionization have generally been defined with respect to environmental contaminants [5,6,13]. In this paper, however, we are concerned with the complexity of the sample itself.

This study was designed to test the reliability of IMS to detect the presence of at least one controlled substance in multicomponent illicit drug samples. A sample set that describes the majority of samples analyzed by forensic laboratories in the U.S. was defined and then used for testing. The variability in reduced mobility of each controlled substance in the sample set was determined, from which a systematic choice in the size of the detection window could be made. The potential for false positives and false negatives from the sample set given any binary mixture of controlled substances, or controlled substances and excipients, was evaluated. A simple sampling procedure was developed that allows for the analysis of bulk materials without saturating the instrument. In addition, a suite of over-the-counter pharmaceuticals was tested for their potential to produce false positives.

2. Experimental

2.1. Instrumental parameters

A Smiths Detection Ionscan 400B[1] (Danbury, CT) was used for the majority of the experiments. The ambient air intake was bypassed to allow intake of dry air from a laboratory fitting, thus avoiding the frequent changing of the desiccant otherwise necessary during routine operation. A second instrument, a Smiths Detection Ionscan 500DT, was used for a limited set of experiments. Both instruments are housed within the Advanced Measurement Laboratory at NIST under controlled conditions of temperature (20 ± 0.5 °C) and relative humidity (45 ± 5%). These conditions are better than those expected for instruments operated in the field, and may result in lower variability in the measurements. The default temperature settings recommended by the manufacturer for narcotics detection were used. For the Ionscan 400B, these include a desorber temperature of 288 °C, a drift tube temperature of 233 °C, and an inlet temperature of 287 °C. The same temperature settings for the 500DT are 236, 242, and 265 °C, respectively. Temperatures were controlled and monitored through the instrument firmware, and were not directly measured.

Thirty individual spectra (referred to as segments by the firmware) were collected per analysis over a total analysis time of 12 s. The detection algorithm evaluates each segment for the presence of peaks within the defined detection windows. A Gaussian peak fitting function within the instrument firmware was used to calculate peak positions from the spectrum produced by averaging over the 30 segments. Reduced mobilities were calculated using Eq. (1) in the instrument software with a reference value for the internal calibrant (nicotinamide) of 1.962 $cm^2\ V^{-1}\ s^{-1}$ (Ionscan 400B) or 1.960 $cm^2\ V^{-1}\ s^{-1}$ (Ionscan 500DT). Minimum peak heights of 50 intensity units (i.u.) were used for the detection algorithm, although peaks below that minimum value could be post-processed to determine peak heights.

2.2. Materials

Reference drug solutions were obtained from Sigma Aldrich (St. Louis, MO) and contain 100–1000 μg/mL with a stated uncertainty of ±5% of a single drug in methanol. They include cocaine hydrochloride, heroin hydrochloride, Δ^9-tetrahydrocannabinol (THC), methamphetamine hydrochloride, 3,4-methylenedioxymethamphetamine hydrochloride (MDMA), d-amphetamine sulfate, 3,4-methylenedioxyamphetamine hydrochloride (MDA), caffeine, and alprazolam. Compounds obtained in powder form (Sigma Aldrich, St. Louis, MO) include: mannitol, myo-inositol (minimum 99%), procaine hydrochloride (minimum 97%), acetaminophen, diphenhydramine hydrochloride, dextromethorphan, and (1S, 2R)-(+)-ephedrine hydrochloride (minimum 99%). Fentanyl citrate, hydrocodone bitartrate, oxycodone, chlorpheniramine maleate, pseudoephedrine hydrochloride, loratadine, phenylephrine, guaifenesin, and doxylamine succinate were purchased in powder form from U.S. Pharmacopeia (Rockville, MD). Dilutions of solid materials were made in 95% ethanol. Samples were prepared by solution deposition onto polytetrafluoroethylene (PTFE) substrates sold by Smiths Detection specifically for positive ion mode operation. The solutions are deposited onto the center of the circular (32 mm diameter) substrates and allowed to evaporate to dryness prior to analysis. Small volumes are deposited (<10 μL) in order to prevent wicking of the solution outside the analysis area defined by the circular desorber dimensions (18 mm diameter).

Samples of forensic drug exhibits were obtained from the Montgomery County MD Police Department (MCPD) Crime Laboratory and from the DEA Mid-Atlantic Laboratory. The samples include: 6 cocaine samples, 2 methamphetamine samples, 2 heroin samples, 2 MDMA samples and 2 marijuana/THC samples. The DEA supplied quantitative analyses of drug content for each sample, along with the identification of additional compounds. Pharmaceutical preparations of hydrocodone and oxycodone were obtained by prescription, and include generic Vicodin (hydrocodone:acetaminophen 5 mg:500 mg and 7.5 mg:750 mg) and OxyContin (20 mg oxycodone). The content of these pharmaceuticals, along with purchased, over-the-counter (OTC) tablets, were assumed correct as provided by the manufacturers.

2.3. Analysis of binary pairs

Binary pairs of two controlled substances were tested to determine the ratios at which both substances could be detected in a sample. Samples were prepared by codeposition of solutions, and the range in compositions from 3 to 97 wt% of the second substance was tested. The mass of each compound that produced a peak with a maximum amplitude of at least 100 intensity units (i.u.) was determined, and this amount was used as the lower limit for that substance in forming any of the binary pairs. The boundaries on the range of compositions at which both substances could be detected were located to within ±5 wt%, except where they were identical to the end points (3 or 97 wt%). The boundaries were tested by at least 5 repetitive measurements. Binary pairs of controlled substances with excipients were also tested by codeposition of solutions to determine the amount of excipient needed to interfere with detection of the controlled substance. A survey approach was used to locate the maximum amount of excipient which was then tested by at least 5 repeated measurements.

3. Results and discussion

3.1. Selected representative sample set

The National Forensic Laboratory Information System (NFLIS) operates under the Drug Enforcement Administration (DEA) and compiles information annually in the U.S. from 276 federal, state, and local forensic laboratories. Every year since 2001, when NFLIS became fully operational, cocaine, THC, methamphetamine, and

[1] Certain commercial equipment, instruments, or materials are identified in this document. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the products identified are necessarily the best available for the purpose.

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Table 1
Drug/drug and drug/excipient combinations found in a majority of forensic drug exhibits.

Controlled substance 1	Controlled substance 2
Cocaine[b]	Heroin[a]
	Methamphetamine[b]
	Oxycodone[b]
	THC[a]
Methamphetamine	MDMA[a]
	Amphetamine[b]
	Heroin
	THC
Heroin	Fentanyl[b]
MDMA	MDA[a]

Controlled substance	Excipient
Cocaine	Procaine
	Inositol
	Lactose
Heroin	Procaine
	Mannitol
	Caffeine
	Diphenhydramine
Methamphetamine	Ephedrine/pseudoephedrine[c]
	Caffeine
MDMA	Ephedrine
	Caffeine

[a] DEA schedule 1.
[b] DEA schedule 2.
[c] Restricted under: Combat Methamphetamine Epidemic Act of 2005 (CMEA) contained in Title VII of the USA PATRIOT Improvement and Reauthorization Act of 2005 (H.R. 3199).

heroin have accounted for 80–90% of the forensic drug items analyzed by these laboratories, with the next most common drugs, hydrocodone, alprazolam, oxycodone, and MDMA accounting for an additional 3–6% nationally. All remaining identified drugs represent less than 1% each of the total number of exhibits. The most common drug combinations involving cocaine, heroin, and methamphetamine are also identified in the NFLIS reports, as are the most common excipients. The information from the NFLIS reports dating back to 2001 was used to develop most of the combinations listed in Table 1. Not specifically tabulated in the reports are combinations of MDMA (i.e. Ecstasy) with other drugs. Common additions to MDMA include methamphetamine and MDA, and the excipients ephedrine and caffeine [14]. Some sample combinations are more common in different regions of the country, and a particularly problematic combination is fentanyl mixed with heroin [15,16]. Hydrocodone (e.g. Vicodin), alprazolam (e.g. Xanax), and oxycodone (e.g. OxyContin) are the 3 most common representatives of the growing trend in abuse of diverted pharmaceuticals [17]. Oxycodone and alprazolam are distributed as tablets in which the active ingredient is mixed with inert materials such as starches, cellulose, etc. Oxycodone is also available in tablet form in combination with another analgesic. Hydrocodone is available in tablet form in combination products and also in liquid form with other cold medications. The combinations listed in Tables 1 and 2 comprise our best estimate of a sample set that encompasses the majority of illicit drug samples.

Table 2
Pharmaceutical tablet preparations of top 3 diverted pharmaceuticals.

Controlled substance	Other active ingredients
Alprazolam	None
Hydrocodone	Acetaminophen
	Chlorpheniramine + pseudoephedrine[a]
Oxycodone	Acetaminophen
	Aspirin

[a] Tussend: pseudoephedrine/chlorpheniramine/hydrocodone 4 mg/5 mg/60 mg.

3.2. Reduced mobilities and detection windows

The reduced mobilities of all substances listed in Tables 1 and 2 were measured over an extended period of time, as much as a year in some cases, and the average values and uncertainties are given in Table 3. The values apply to the specific instrument (Ionscan 400B) operated under the conditions outlined earlier, and are not given as general reference values. As a comparison with the literature, reduced mobilities have been reported for cocaine [18,19] (1.15 and 1.16 $cm^2\,V^{-1}\,s^{-1}$ to 1.18 $cm^2\,V^{-1}\,s^{-1}$), heroin [18–20] (1.037 and 1.04 $cm^2\,V^{-1}\,s^{-1}$ to 1.05 $cm^2\,V^{-1}\,s^{-1}$), methamphetamine [18,20] (1.63 $cm^2\,V^{-1}\,s^{-1}$), MDMA [21] (1.42, 1.449, and 1.4733 $cm^2\,V^{-1}\,s^{-1}$), and alprazolam [22] (1.15 $cm^2\,V^{-1}\,s^{-1}$). The variability in the literature values is probably due to differences in instrumental operating parameters that affect the reduced mobility of both the internal calibrant and the target analyte. Three of the controlled substances were measured on a second instrument in our laboratory (Ionscan 500DT) that uses a lower desorber temperature as the default setting; the values of reduced mobility measured on this instrument are lower by 0.004–0.005 $cm^2\,V^{-1}\,s^{-1}$. When the desorber temperature of the Ionscan 400B was lowered from 288 to 150 °C, the reduced mobilities were smaller by 0.003–0.004 $cm^2\,V^{-1}\,s^{-1}$. Reduced mobilities are also dependent on the composition of the drift gas, which can be exploited to improve the selectivity of IMS [23]. Changes in reduced mobility of 30–40% were observed for methamphetamine, MDMA, cocaine, and heroin in drift gasses of pure CO_2 and pure N_2O when compared with air [23]. The concentrations of CO_2 and N_2O in air are so small (385 ppm and 322 ppb, respectively [24]) that we would expect variation in these components to have a negligible effect on reduced mobility. Of more importance in field applications is the ability to restrict water vapor from the drift region, which we were able to control more reliably by direct intake of dry air from a laboratory fitting. This was done simply to avoid continual replacement of dessicant material throughout this experiment; ambient air can be used with dessicant material in the field where dry intake air is not available. Detection windows may shift when the instrument is operating under different environmental conditions, however individual instruments can be calibrated to account for this shift.

The reduced mobilities given in Table 3 were taken as the best available values for the instrument at the stated operating parameters, and were used to replace the existing values in the firmware. Detection windows were set for eight controlled substances, which together represent the most commonly reported drugs, with the exception of THC. THC was not included because of problems with the reliability of detection. Pure THC deposited from solution will generate a characteristic IMS peak [18,20,25], but we have been unsuccessful at detecting the compound from marijuana or by sampling the surface contamination of a used marijuana pipe. While the main psychoactive component in marijuana is THC, the plant contains over 400 notable compounds [26]. Two related cannabinoids, cannabinol and cannabidiol, were studied by Su et al. [27] by solution deposition of pure compounds, and were found to produce IMS responses. In the case of marijuana, IMS does not offer any advantages over existing presumptive tests (the Duquenois–Levine color test and thin layer chromatography with standards), which are considered conclusive for identification of THC [2].

The reduced mobilities of amphetamine and MDA are also included in Table 3, but no detection windows are listed. Amphetamine and MDA were included in this study to evaluate interferences with the targeted drugs. They are present in a small proportion of drug exhibits (national totals in 2006 of 0.23% for

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Table 3
Reduced mobilities and intensities for controlled substances and excipients. Detection windows for 8 selected controlled substances. The uncertainties are given as the standard deviation (SD) of the measurements.

Compound (IMS alarm on)	Intensity at 1 ng, a.u.		K_0, $cm^2 V^{-1} s^{-1}$			Detection window		
	Mean	1 SD	Mean	1 SD	n	μs	K_0	K_0
Meth (1)	496	60	1.6428	0.0009	42	±35	−0.0053	+0.0054
MDMA (2)	352	33	1.4718	0.0004	34	±40	−0.0049	+0.0049
Hydrocodone (3)	138	37	1.1844	0.0004	6	±45	−0.0036	+0.0036
Oxycodone (4)	170	39	1.1709	0.0003	10	±39	−0.0030	+0.0030
Cocaine (5)	151	36	1.1644	0.0006	41	±45	−0.0034	+0.0035
Alprazolam (6)	0[a]		1.1536	0.0003	6	±45	−0.0034	+0.0034
Fentanyl (7)	181	48	1.0550	0.0004	12	±50	−0.0031	+0.0032
Heroin (8)	20	12	1.0463	0.0006	27	±50	−0.0031	+0.0031
Compound (IMS alarm off)	Intensity at 1 ng, a.u.		K_0, $cm^2 V^{-1} s^{-1}$					
	Mean	1 SD	Mean	1 SD				
Amphetamine	89	49	1.6753	0.0004				
MDA	70	34	1.5018	0.0008				
THC	20	9	1.0500	0.0004				
Ephedrine	208	61	1.5824	0.0004				
Pseudoephedrine	106	41	1.5838	0.0002				
Procaine	540	111	1.3117	0.0010				
Diphenhydramine	252	54	1.2339	0.0003				
Chlorpheniramine	446	124	1.2175	0.0006				

[a] Intensity at 10 ng = 95 a.u. (1 SD = 20 a.u.).

amphetamine and <0.08% for MDA), primarily in combination with other controlled substances already targeted for detection. Limiting the number of detection windows to only those compounds that are critical, and likely to be detected, contributes to a lower probability of false positives.

The widths of the detection window are given in units of drift time (μs) in Table 3, which is the input required by the firmware, and as calculated K_0 values (which are not necessarily symmetric). The detection windows are fairly conservative when compared with the uncertainties, ranging from a factor of 5 to a factor of 12. We could have tailored the detection windows with respect to the uncertainties, but chose, for simplicity, to use values from 35 to 50 μs, in steps of ±5 μs. This results in fairly consistent widths for the detection windows in terms of reduced mobility. The detection window for methamphetamine was set slightly larger to account for the larger uncertainty in the value of reduced mobility. The detection window of oxycodone was carefully tailored and deviated from the ±5 μs step size in order to prevent overlap with the detection window of cocaine.

The reduced mobilities of the excipients from Tables 1 and 2 that produce positive ion responses are given in Table 3. Values are given in the literature for ephedrine [21] (1.572, 1.5848, and 1.5843 $cm^2 V^{-1} s^{-1}$), pseudoephedrine [28] (1.59 $cm^2 V^{-1} s^{-1}$), procaine [7] (1.31 $cm^2 V^{-1} s^{-1}$), and chlorpheniramine [28] (1.25 $cm^2 V^{-1} s^{-1}$). The absence of an IMS response for lactose, mannitol, acetaminophen and caffeine has also been reported [6].

3.3. Peak overlap and competitive ionization

A composite spectrum of most of the compounds from Table 3 is given in Fig. 1, and the detection windows for the target drugs are shown. This was done for illustration purposes to demonstrate the breadth of the peaks with respect to the detection windows, and the potential for spectral overlap. In actuality, samples containing the number of compounds represented in Fig. 1 would generate spectra with peaks for only a few of the compounds, depending on their concentrations and ionization affinity. The results from the testing of binary pairs of controlled substances (from Table 1) are given in Fig. 2. The four pairs of compounds on the left have peaks that are well separated, whereas the four pairs on the right have compounds that exhibit spectral overlap. For the pairs on the left, both compounds can be detected over a fairly large range of compositions. The peak intensity of pure heroin is low relative to most of the other compounds, and it must be present at levels of 10 wt% or more in binary mixtures with cocaine and 20 wt% or more with methamphetamine to be detected. [We report intensities in Table 3 at an arbitrarily chosen mass of 1 ng. The uncertainties in the measured intensities are quite large, which is commonly observed for IMS data.]

The results for the four pairs on the right in Fig. 2 are more complicated, although for each pair both compounds can be detected, although over a more limited range. The analysis of a sample containing MDA and MDMA is shown in Fig. 3, comparing 2 spectra (segments) selected from the 30 segments collected during the 12 s analysis time. The spectrum derived from the average of the 30 segments is also shown. Although MDA and MDMA cannot be resolved in the averaged spectrum, they are resolved during the analysis sequence. Early in the analysis (segment 4, 1.2 s) the peak is within the MDA window, whereas later in the analysis (segment 10, 3.0 s) the peak is within the MDMA window. This may be due to differences in desorption characteristics of the two compounds, although a difference in desorption time is not observed for the pure

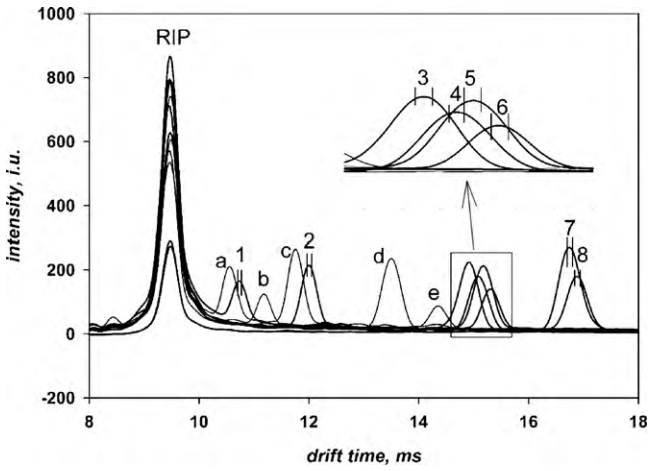

Fig. 1. Composite spectrum with the reactant ion peak (RIP) at a fixed location, showing detection windows (parallel lines) for analytes labeled in Table 3. Peak heights have no significance. Additional peaks labeled (a) amphetamine, (b) ephedrine/pseudoephedrine, (c) MDA, (d) procaine, and (e) diphenhydramine.

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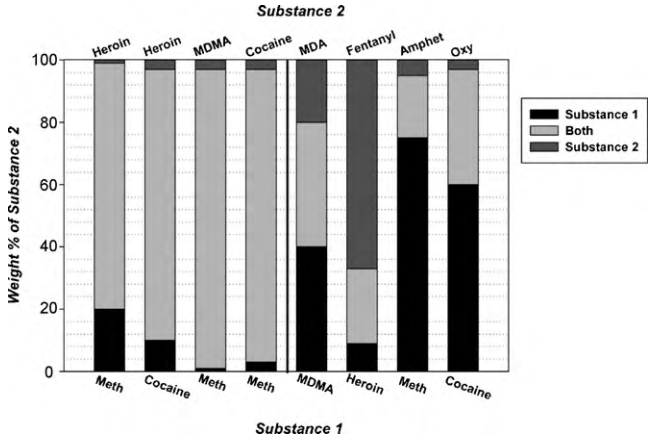

Fig. 2. Binary mixtures with no spectral overlap (left 4 pairs) and spectral overlap (right 4 pairs). Key refers to the detection of one or both of the controlled substances in the mixtures.

compounds. It may be due to changes in the balance of the reaction chemistry with time. The elucidation of the exact mechanisms controlling the ion chemistry is beyond the scope of the current work. However, the pattern is reproducible, and, because the detection algorithm can be set to detect peaks present in a single segment, both compounds can be reliably detected in samples where the peaks are not otherwise resolved. There is more variability in reduced mobility (i.e. peak positions) for cases of spectral overlap when compared with the pure substances. The sizes of the detection windows given in Table 3 are sufficient for the increased uncertainty in reduced mobility, given the pairs tested.

The results from binary mixtures containing excipients and controlled substances are given in Table 4. Pure procaine has a relatively high peak intensity, and 75 wt% will interfere with the detection of heroin; 90 wt% will interfere with the detection of cocaine. Pure diphenhydramine also has a relatively high peak intensity, and 80% by weight or more will interfere with the detection of heroin. For a ternary mixture containing heroin, diphenhydramine, and procaine, the heroin signal is lost when the excipients represent 66 wt% or more of the sample (33 wt% procaine, 33 wt% diphenhydramine). The presence of excipients that do not generate an IMS response (caffeine, lactose, inositol, mannitol, and acetaminophen) have no effect on the detection of the controlled substances, although earlier studies report losses in intensity due to inert materials [5,6]. It is possible that the inert materials interfere with desorption processes, resulting in a lower intensity for the same mass of a compound. However, given that we are sampling bulk amounts, we can increase the amount of sample to adjust for any loss in intensity from inert materials.

Table 4
Detection of controlled substance as a function of wt% excipient.

Controlled substance	No detection of controlled substance	
Cocaine	≥90%	Procaine
Heroin	≥75%	Procaine
Heroin	≥80%	Diphenhydramine
Methamphetamine	≥95%	Ephedrine
Methamphetamine	≥95%	Pseudoephedrine
MDMA	≥95%	Ephedrine

3.4. Bulk materials

A field approach to sampling should allow for direct transfer of solid material to the sampling medium without an intermediate dissolution approach. The requirement for IMS is to transfer as little material as possible, resulting in mass loadings of a few hundred nanograms or less. We found that using a fine needle probe (pin vise with straight needles, 10 μm tip, Ernest F. Fullam Clifton Park, NY) as the sampler provided good results for powders and pharmaceutical tablets. Powdered materials were sampled by touching the powder with the probe and then touching only the tip of the probe to the sampling medium. Tablets were sampled by first breaking the tablet in half to avoid the outer coating, and then sampling the broken surface. Some trial and error is necessary to arrive at the correct amounts. Fig. 4 shows the results of sampling a tablet containing MDMA, comparing the spectrum obtained from transferring too much material to the surface with that obtained from transferring a correct amount. Oversampling is indicated by a dramatic reduction in the reactant ion peak (RIP), and persistence of the compound peaks during attempted clear down cycles. Oversampling also results in the formation of additional peaks as a result of changes in the APCI reactions. These additional peaks may generate false alarms, as their positions are difficult to predict.

The time required to return to a background level can be used as a general guide to determine whether oversampling has occurred, and therefore whether the results might be suspect. The instrument is returned to background levels by initiating a 12 s

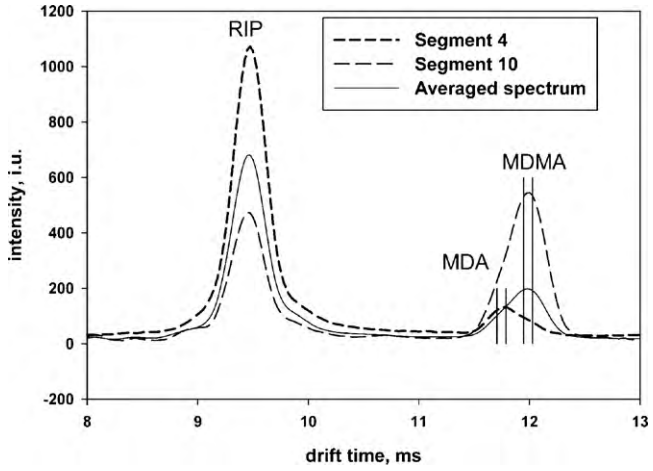

Fig. 3. Change in peak position with analysis time for sample containing 2 ng MDMA and 5 ng of MDA. Detection windows for the two compounds represented by parallel lines.

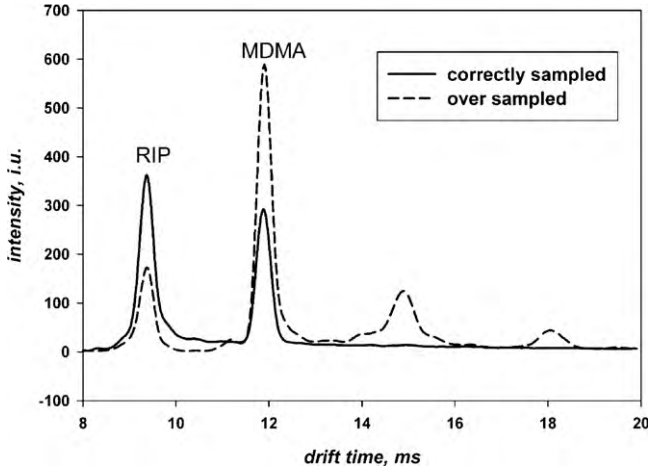

Fig. 4. Averaged spectra obtained by sampling a tablet containing 41% MDMA and caffeine. When correctly sampled, the only peak present in addition to the reactant ion peak (RIP) is MDMA.

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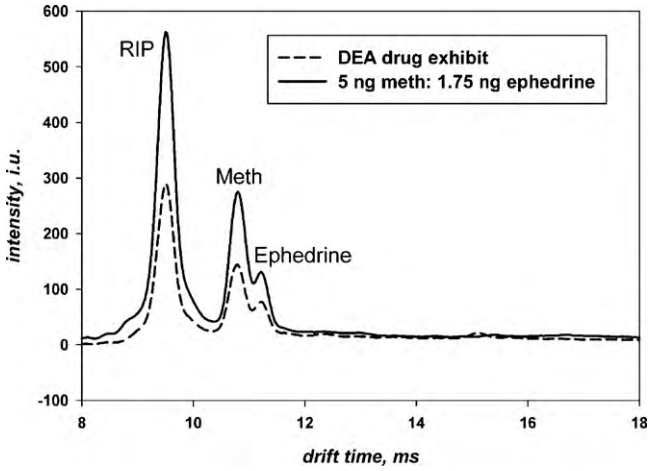

Fig. 5. Averaged spectrum for actual drug exhibit containing 65 wt% methamphetamine and ephedrine compared with averaged spectrum from solution-deposited reagent grade materials.

analysis procedure without a sample in the desorber. For correct sampling amounts, only one or two such cleardown cycles are needed. When correctly sampled, the spectra produced by bulk materials compare quite favorably with those produced from solution deposition of the same components. This is illustrated in Fig. 5 for a bulk powder sample containing 65 wt% methamphetamine and ephedrine. The bulk powder is an authentic material obtained by seizure. Another authentic sample, an Ecstasy tablet containing 6 wt% MDMA and caffeine, procaine, diphenhydramine, and ketamine, was analyzed successfully as shown in Fig. 6.

3.5. Pharmaceutical preparations including OTC products

The tablet preparations listed in Table 2 for alprazolam, hydrocodone, and oxycodone do not present any significant analytical difficulties for IMS. Acetaminophen and aspirin do not produce positive ion IMS responses, nor do the inactive ingredients that are typically present in tablet formulations. A sample prepared with the same ratio of ingredients as the prescription formulation containing hydrocodone, pseudoephedrine, and chlorpheniramine yields IMS responses for hydrocodone and chlorpheniramine.

Twenty-nine OTC cold, flu, and allergy tablets containing one, two, or three active ingredients with or without acetaminophen were evaluated by IMS. The active ingredients include three

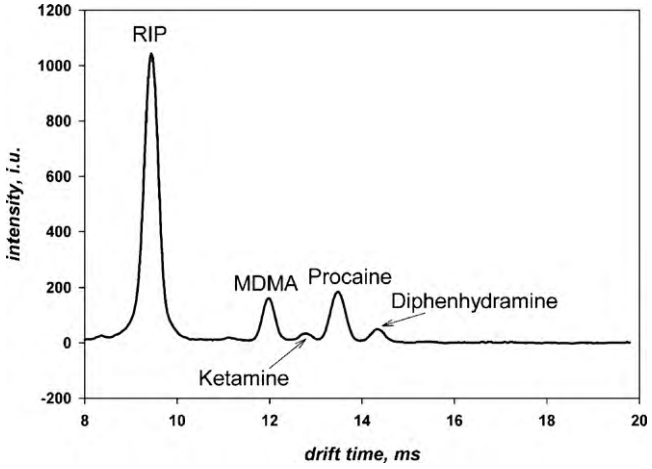

Fig. 6. IMS spectrum averaged over segments 2 through 4 from a tablet containing 6 wt% MDMA, caffeine, procaine, diphenhydramine, and ketamine (K_0 = 1.376 $cm^2\ V^{-1}\ s^{-1}$).

Table 5
Reduced mobilities for active ingredients in OTC cold/flu/allergy tablets.

Compound	Intensity at 1 ng, a.u.		Reduced mobility, K_0, $cm^2\ V^{-1}\ s^{-1}$	
	Mean	1 SD	Mean	1 SD
Phenylephrine	16	26	1.5653	0.0041
Guaifenesin	0[a]		1.5012	0.0003
Doxylamine	501	31	1.2254	0.0003
Dextromethorphan	220	47	1.2042	0.0005
Loratadine	332	34	1.0225	0.0004

[a] Intensity at 50 ng = 85 a.u. (1 SD = 11 a.u.).

compounds in common with illicit drugs – pseudoephedrine, chlorpheniramine, and diphenhydramine – and the compounds listed in Table 5. Detection windows were set for each OTC compound in addition to the eight detection windows for the controlled substances (from Table 3). There are no overlaps with the eight controlled substances, although guaifenesin (an antitussive) has a reduced mobility that is the same, within uncertainty, as that of MDA. The tablets were broken in half and sampled, and the results were repeated at least three times. There were no false positives for controlled substances. In fact, IMS provided a reasonable qualitative analysis of the tablets, with identification of almost all compounds, even in the three-component (plus acetaminophen) tablets. We would not set detection windows for the OTC compounds for analysis of illicit drugs, but report here that IMS may provide a means of qualitative analysis of certain OTC tablets.

The samples that are negative for controlled substances are not described in the NFLIS reports, and may contain compounds that have similar reduced mobilities to the targeted controlled substances. For many drugs, reduced mobility is inversely proportional to molecular weight, but there are exceptions [18] and the proportionality is not sufficiently robust to allow accurate predictions of reduced mobility. A study undertaken by the Federal Bureau of Prisons evaluated 84 pharmaceutical preparations, and identified 4 compounds that generated false positives for controlled substances [29]. Similar types of studies would need to be conducted to more fully understand the potential for false positive results with IMS.

4. Conclusions

IMS can provide a reliable qualitative analysis of the types of samples discussed in this paper, which represent the majority of forensic drug items. Detection windows were set for eight controlled substances, including methamphetamine, MDMA, cocaine, heroin, fentanyl, hydrocodone, oxycodone, and alprazolam. Existing presumptive tests should continue to be used for cannabis/THC, but IMS could replace other presumptive tests. IMS is fast, requires minimal sample preparation, and does not involve any subjective analysis of the results. As with any presumptive test, the uncertainties lie in the potential for false positives. Future developments in IMS technology would be necessary to improve selectivity through enhancements in resolution.

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