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Improved detection of drugs of abuse using high-performance ion mobility spectrometry with electrospray ionization (ESI-HPIMS) for urine matrices

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ABSTRACT

High-performance ion mobility spectrometry (HPIMS) with electrospray ionization (ESI) has been used to separate drugs of abuse compounds as a function of drift time (ion mobility), which is based on their size, structural shape, and mass-to-charge. HPIMS has also been used to directly detect and identify a variety of the most commonly encountered illegal drugs, as well as a mixture of opiates in a urine matrix without extra sample pretreatment. HPIMS has shown resolving power greater than 65 comparable to that of high-performance liquid chromatography (HPLC) with only 1 mL of solvent and sample required using air as the IMS separation medium. The HPIMS method can achieve two-order of magnitude linear response, precise drift times, and high peak area precision with percent relative standard deviations (% RSD) less than 3% for sample quantitation. The reduced mobilities measured agree very well with other IMS measurements, allowing a simple "dilute-and-shoot" method to be used to detect a mixture of codeine and morphine in urine matrix.

1. Introduction

A recent review highlights the noticeable changes in drugs of abuse analysis over the past twenty years [1]. While the more well-known classes of illegal drugs dominate the detection targets, newer compounds that mimic their psychotropic effects, but are structurally different enough to evade legislation, are a rapidly growing and evolving sector for drug interdiction [1,2]. In particular, ion mobility spectrometry (IMS) is an analytical technique that has seen a wide adoption for detection of trace amounts of illegal drugs. IMS rapidly and sensitively detects compounds based on differences in structural shape, size, and mass-to-charge (m/z) ratio and can readily be adapted to include new detection targets [3]. Therefore, IMS is now a well-proven technique for the rapid detection of drugs of abuse [4–16], particularly for field detection [17] in both forensic applications [9] and enforcement scenarios such as baggage screening [3,18].

Other detection scenarios could also benefit from the advantages of IMS screening. Modern clinical toxicology involves testing for the specific pharmacological agents responsible for the majority of intoxicated patients presenting to hospital emergency departments. When required, a patient's urine sample is obtained and analyzed by hospital clinical laboratories for drugs of abuse using a set of automated immunoassays that detect a single drug (e.g. cocaine) or a class of drugs (e.g. benzodiazepines). The typical automated immunoassay analyses encompass 7 tests run in parallel to screen urine samples for the 24 drugs and agents that comprise 80% of intoxication cases. While the per-test cost is low, the high annual volume of tests conducted incurs a large aggregate cost [19], and the incubation times required by immunoassays range from 12–30 min at the best.

When an immunoassay does test positive for opiates, it cannot reveal which one or at which concentration. As a result, the physician cannot tell whether the patient has overdosed on heroin, or has simply tested positive from medically prescribed codeine. For drug identification and quantitation, most hospital laboratories send the specimen out for additional testing by gas chromatography–mass spectrometry (GC–MS) [20], a process that takes several days and adds significant cost. However, physicians need to treat intoxicated patients immediately, and so this delay makes drug identification essentially useless except for purposes of counseling the patient about their abuse.

Alternatively, ion mobility spectrometry (IMS) can provide resolving power similar to chromatography as a separation technique [21] and could be developed to provide separation capabilities at lower cost and with greater ease of operation for potential use in typical clinical settings. Previously, drugs such as ephedrine [11], cocaine, and its metabolites cocaethylene and benzoylecgonine [8] have been individually separated and quantitatively

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detected in urine with good sensitivity using IMS. Therefore, the development of more rapid methodologies that detect relevant toxins sensitively, but also provide definitive identification of the toxin with semi-quantitative assessment of the amount of drug present, would dramatically change the diagnostic outlook for toxicology testing. A less costly test bed would also save on health care costs, given the sheer volume of drug tests processed by hospitals annually [19]. Thus, an ion mobility spectrometry platform is an ideal technology for eventual development of a point-of-care device. To address these issues, a high-performance ion mobility spectrometry (HPIMS) platform using electrospray ionization (ESI) has been applied to detection of drugs of abuse in a urine matrix with a simple "dilute-and-shoot" method. ESI is a "soft" ionization technique that produces ions of intact small molecules [22]. ESI is especially useful for drug compounds with higher molecular weights such as active pharmaceutical ingredients (APIs) that either degrade using traditional thermal desorption evaporation with IMS or are non-volatile [23–25]. ESI also provides the option of direct analysis of liquid samples, including urine, after simple dilution and direct analysis with IMS. To that end, a series of the most common illegal drugs of abuse have been analyzed in seconds with ESI and HPIMS. The results show resolving power comparable to HPLC [21] with two-order of magnitude linear response, an improvement over previous thermal desorption IMS instruments, which have half the resolving power [26] of ESI-HPIMS. In addition, ESI-HPIMS has been used for direct detection and identification of an opiate mixture in a simulated urine matrix with no sample pretreatment beyond dilution with ESI solvent.

2. Materials and methods

2.1. Electrospray ionization with high-performance ion mobility spectrometry (ESI-HPIMS)

As in previous research [27–29], a commercial electrospray ionization-high performance ion mobility spectrometry (ESI-HPIMS) system (GA2100, Excellims Corp.) was used to analyze the drug compounds. Generation of gas-phase analyte ions is the first step in ion mobility spectrometry, and the earlier development of ESI with IMS [30] allowed for field detection of non-volatile compounds and biological samples with IMS that traditionally were only analyzed by HPLC in a laboratory environment, leading to a wider adoption of IMS in diverse applications. This ESI-HPIMS system was described in detail elsewhere [29]; thus, only pertinent details are given below.

Fig. 1 shows a schematic of the ESI-HPIMS analyzer. Analyte ions (depicted by the different hued shapes in Fig. 1) were generated by ESI with liquid sample injection rates of 1.5 to 4 μl min^{-1} through an electrospray needle (1) held at 2400 V above the drift potential of 8000 V. For the urine matrix studies, the positive ion mode voltage was much higher at 4300 V. The ionized droplets underwent desolvation in the desolvation region (2) and were subsequently introduced into the drift tube via a pulsed Bradbury–Neilson ion gate (3) with gate pulse widths from 50 to 100 μs. The drift tube and gas pre-heater were held at a constant temperature of 180 °C for the screening performance studies and 160 °C for the urine matrix studies. The upper potential of the desolvation region of the IMS was held at 8000 VDC and the gate reference voltage was held at approximately 4900 VDC, producing a drift field of approximately 470 V cm^{-1} over the 10.5 cm long drift tube. The potentials were positive polarity for cations and negative polarity for anions.

Ions were separated according to the their size, shape, reduced mass, μ, and charge, q, as they moved under the influence of the drift field through the 1.3 L min^{-1} of counter-flowing drift gas in the drift region (4) as discussed below. The mobility spectrum represented a sum over 5 to 10 spectra with a width of 25 ms, which were then sampled at a Faraday plate detector (5) and averaged for a total of 30 to 60 s. Drift times were measured with uncertainties lower than ± 0.02 ms. Data were acquired using Excellims VisIon™ control and acquisition software and were exported for post-processing to Microsoft Excel. Atmospheric pressure in the laboratory was monitored and recorded for all experiments to properly correct the mobilities as shown below.

An ion's mobility through the drift tube determined its separation, defined practically as the ratio of the average ion velocity (v_d) to the applied electric field (E) when operating in the low-field region. Experimentally, an ion's mobility (K) was determined with the following equation:

$$K = \frac{v_d}{E} = \frac{L^2}{t_d V} \quad (1)$$

This equation is for separation over the length of the drift region, L, in cm based on the time in seconds to travel the length of the drift region (drift time, t_d) under the voltage V applied to it [3]. For a given set of experimental parameters, the mobility represented the ion-drift gas collision processes at the molecular level, as shown by the following equation:

$$K \propto z/(\mu^{2/2}\Omega) \quad (2)$$

Ω was the average ion-drift gas collision cross section, z was the number of charges on the ion, and μ $[=mM/(m+M)]$ was the reduced mass of an ion (m) and the neutral drift gas (M). For ions more massive than the drift gas molecule, the reduced mass nearly equaled M and the mobility was only proportional to z and Ω. For a constant charge state, a change in the ion mobility would require a change in the collision cross section, which was determined by the fundamental interaction potential between the ion and the neutral

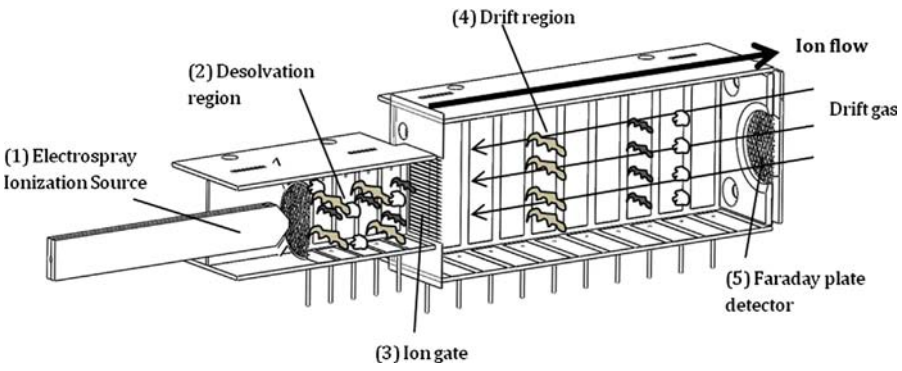

Fig. 1. Diagram of the electrospray ionization-high performance ion mobility spectrometer (ESI-HPIMS) with the different sections labeled. The mobility separation based on size and shape in the drift region (4) after the ion gate (3) is schematically demonstrated by the black, gray, and white shapes.

drift gas molecule, the collision dynamics, and the size and shape of the ion and neutral molecule. Thus, differences in structure size and shape resulted in different mobilities (i.e., drift times). Analogous to chromatography, the drift gas could be thought of as a weak stationary phase for the ion mobility experiment [3].

The mobility measured was relevant only under the given experimental conditions. Therefore, K could be converted to a mobility defined under standard conditions, K_0, known as the reduced mobility in $cm^2\ V^{-1}\ s^{-1}$, illustrated in Eq. (3), where P was the drift tube operating pressure (in Hg) and T_d was the temperature of the drift tube in Kelvin [3].

$$K_0 = K(P/29.92)(273.15/T_d) \quad (3)$$

Converting to a reduced mobility allowed for direct comparison to mobilities measured in other drift time IMS experiments [3,31]. To account for any systematic differences or other instrumental factors, the reduced mobilities for the illegal drug compounds, K_0(drug), were calibrated using Eq. (4) [12,32].

$$K_0(\text{drug}) = (t_d(\text{cal})/t_d(\text{drug}))K_0(\text{cal}) \quad (4)$$

In positive ion mode, K_0(drug) was calibrated against K_0(cal)= 1.86 $cm^2\ V^{-1}\ s^{-1}$ for nicotinamide, which was the internal standard in other commercial drug detection IMS instruments [9,26]. For negative ion mode, the K_0(cal) for 1,2,4,5-benzenetetracarboxylic acid (i.e., pyromellitic acid) of 1.32 $cm^2\ V^{-1}\ s^{-1}$measured by Beauchamp and co-workers [33] using ESI-IMS with MS was used to calibrate those mobilities.

2.2. Chemical standards

All of the chemicals were used as obtained from the manufacturer. The methanol and water electrospray solvents were HPLC grade (Alfa Aesar). For the positive ion mode analysis, acetic acid (Sigma Aldrich, 99.7+%) was added in small amounts by volume to the ESI solvent to provide an additional source of protons, increasing the ionization efficiency. UriSub urine matrix substitute (CST Technologies) was used for the experiments in detecting drugs of abuse in urine samples. Standard solutions of 1 mg mL^{-1} concentration of the illegal drug compounds were purchased from Cerilliant. These stock solutions were diluted with methanol:water electrospray solvent or were spiked into the urine matrix–solvent mixture to the desired concentration. The pyromellitic acid (negative ion mode) and nicotinamide (positive ion mode) calibrant compounds were obtained as pure compounds from Alfa Aesar (96%) and Sigma Aldrich (≥98%), respectively. Standard solutions of these calibrants were prepared at 1 mg mL^{-1} concentration in HPLC-grade methanol, and then diluted in appropriate electrospray solvent to 50 ppm for calibration.

3. Results and discussion

3.1. ESI-HPIMS performance figures for drugs of abuse analysis

Positive ion mode ion mobility spectra for individual 50 ppm (50 ng μL^{-1}) solutions of standards in 90:10 methanol:water with 0.5% (v/v) acetic acid for several of the major illegal drug compounds necessary for screening applications are plotted together in Figs. 2 and 3. The reduced mobilities measured with ESI-HPIMS in the standard ESI solvent given in Table 1 have been calibrated against the known K_0 for nictotinamide [9,26] as discussed in the previous section. The values are in very good agreement with the literature values, also provided in Table 1. As seen in Figs. 2 and 3 and in Table 1, the average IMS resolving power, R, defined as the ratio of the drift time, t_d, to the width at half height, Δt_d [3], is at least 65 for all of the illegal drug

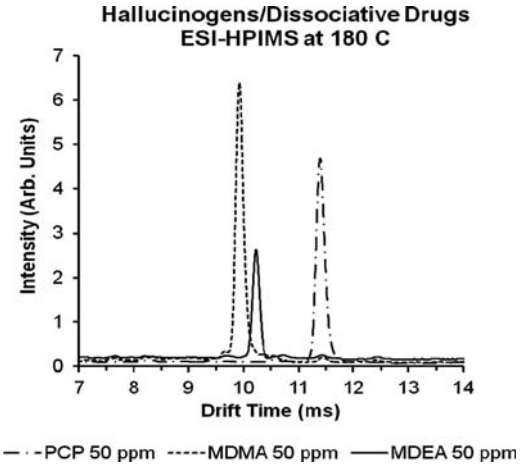

Fig. 2. Ion mobility spectrum using ESI-HPIMS analysis of hallucinogens (PCP) and dissociative drugs (MDMA, MDEA) in air drift gas.

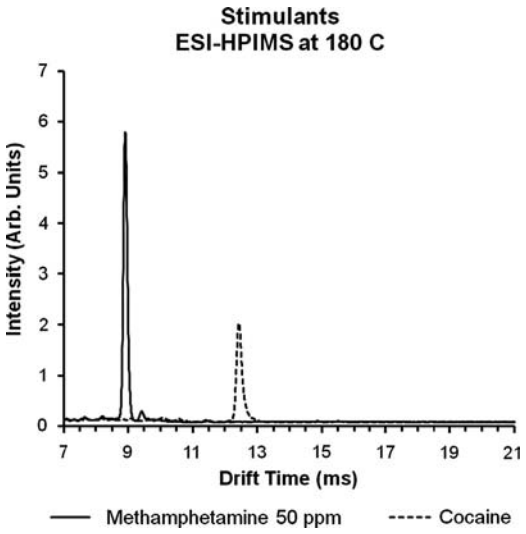

Fig. 3. Ion mobility spectrum using ESI-HPIMS analysis of the stimulants cocaine and methamphetamine in air drift gas.

compounds, and 70 or greater for most of them. Fig. 4a shows a mobility spectrum for cocaine measured in the ESI-HPIMS with R=71 vs. the cocaine mobility spectrum from the other commercial IMS drug trace detector measured by Gabowitcz et al. in Fig. 4b with R of only around 30 [26]. This is over twice the resolving power of the current thermal desorption introduction IMS instruments commerically available for trace detection of illegal drugs [26].

The negative ion mode reduced mobility for phenobarbital determined with ESI-HPIMS (K_0=1.283 $cm^2\ V^{-1}\ s^{-1}$) calibrated against the literature mobility for pyromellitic acid [33] is 12% lower than the phenobarbital K_0 from the literature measured using a GC inlet to volatilize it and ^{63}Ni atmospheric pressure ionization [3,31]. Using pyromellitic acid as a calibrant gives a measured K_0 for citric acid of 1.560 $cm^2\ V^{-1}\ s^{-1}$ using ESI-HPIMS, in exact agreement with the literature value from the same study as the pyromellitic acid [33]. As shown in Eqs. (1) and (3), the drift time is inversely proportional to mobility and proportional to mass. Therefore, the lower phenobarbital K_0 value reported for HPIMS with ESI indicates a longer drift time, and thus, a likely higher mass-to-charge ratio phenobarbital ion, consistent with the "softer" ionization mechanism of ESI. Also, small molecule analyte ions are typically generated as singly charged anions via ESI.

Table 1
Reduced mobilities, K_0, in $cm^2\ V^{-1}\ s^{-1}$ for individual drug standards measured using electrospray ionization-high performance ion mobility spectrometry (ESI-HPIMS) using air drift gas at a drift tube temperature of 180 °C. The average resolving power, R, is defined as the average ratio of drift time to the width of the peak at half-maximum ($t_d/\Delta t_d$).

Compound	ESI-HPIMS K_0 ($cm^2\ V^{-1}\ s^{-1}$)	ESI-HPIMS Avg. R	Literature K_0 ($cm^2\ V^{-1}\ s^{-1}$)	Reference(s)
Positive ion mode[a]				
Methamphetamine	1.658	72	1.63	Refs. [3,5,12,13,62]
			1.62	Ref. [32]
			1.61	Ref. [62]
			1.59	Ref. [5]
MDMA	1.488	68	1.47	Refs. [3,12,60]
			1.42	Ref. [5]
			1.363	Ref. [6]
MDEA	1.445	69	1.42	Ref. [60]
			1.37	Ref. [5]
			1.323	Ref. [6]
PCP	1.296	69	1.27	Ref. [3]
			1.255	Ref. [13]
Cocaine	1.188	71	1.17	Ref. [12]
			1.16	Refs. [3,9]
			1.15	Ref. [13]
			1.063	Ref. [6]
Δ-9-THC	1.074	70	1.06	Ref. [12]
			1.05	Ref. [3]
			1.040	Ref. [13]
Codeine	1.158[c], 1.12	66[c]	1.21, 1.18	Ref. [3]
Morphine	1.194[c], 1.153	65[c]	1.26, 1.22	Ref. [3]
			1.214, 1.164	Ref. [13]
			1.23	Ref. [12]
Negative ion mode[b]				
Phenobarbital	1.283	75	1.44	Ref. [3]

[a] Calibrated using literature K_0 for nicotinamide ($1.86\ cm^2\ V^{-1}\ s^{-1}$). See Refs. [9,26].
[b] Calibrated using literature K_0 for pyromellitic acid ($1.32\ cm^2\ V^{-1}\ s^{-1}$). See Ref. [33]. (See text for details).
[c] Main ion mobility peak in 80:20 methanol:water ESI solvent.

Therefore, the mobility measured with HPIMS likely corresponds to a higher mass analyte ion. Negative mode electrospray ionization of phenobarbital in MS experiments confirm that the main ion generated is the $[M–H]^-$ deprotonated species [34,35], consistent with the mobility peak seen here.

The earlier IMS K_0 determination of Ithakissios [31] for phenobarbital used air as the gas in the ^{63}Ni ionization source region which should result in the main reactant negative ions being O_2^- or $OH^-(H_2O)_n$ clusters at atmospheric pressure [3,31,36]. In principle the ion-molecule source chemistry should result in the same deprotonated phenobarbital anion as seen with ESI [34,35]. However, the higher literature K_0 values in negative ion mode have been measured using a ramped GC sample introduction from 120 to 300 °C with a higher IMS temperature of 230 °C. The GC injector for those measurements has also been held at 310 °C [31]. Thermal decomposition of substituted barbituric acids occurs at temperatures below 250 °C, with loss of the phenobarbital hydrocarbon substituents (i.e., C_2H_5- and C_6H_5-) beginning at around 170 °C [37]. These sample introduction conditions thus could have degraded the phenobarbital prior to its IMS analysis, resulting in lower mass ions that would have correspondingly higher reduced mobilities as seen originally [31], possibly accounting for the differences with the current ESI measurement.

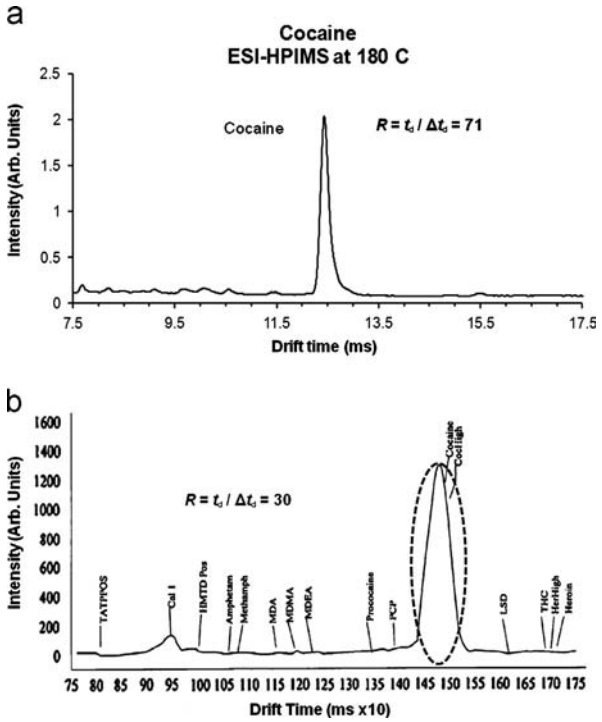

Fig. 4. (a) Ion mobility spectrum of ESI-HPIMS analysis of cocaine with resolving power of 71. (b) Ion mobility spectrum of cocaine by Gabowitcz et al. using a thermal desorber introduction commercial IMS-based illegal drug detector with resolving power of 30. See Ref. [26].

In addition to improved resolving power using HPIMS, the instrument shows a good linear response range. The peak area plotted as a function of sample concentration has a two-order of magnitude range for many of the drug compounds, as illustrated in Fig. 5a and b for codeine and phencyclidine (PCP), respectively, measured using ESI-HPIMS. The drift times can be measured within ± 0.02 ms, leading to very precise mobility measurements of $\pm 0.002\ cm^2\ V^{-1}\ s^{-1}$. Moreover, the peak area measurement using HPIMS has excellent precision, leading to very precise sample quantitation. The percent relative standard deviation (% RSD) for the peak area has been determined for several drugs of abuse and over-the-counter (OTC) active pharmaceutical ingredients (APIs) as shown in Table 2. The %RSD is defined as in Eq. (5) for the ratio of the standard deviation in peak area, σ_A, to the average peak area, ⟨area⟩, from 5 to 8 replicate measurements.

$$\%\mathrm{RSD} = \sigma_{\mathrm{area}}/\langle area\rangle \quad (5)$$

As seen in Table 2, the %RSD is less than 3% for many different types of active drug compounds and often less than 2%. The values prove that the HPIMS instrument can precisely quantitate the amount of drug in a given sample. Having higher precision measurements combined with narrower peak widths in HPIMS allows detection applications with narrower windows for generation of alarm conditions.

3.2. Simplified direct detection of codeine and morphine in urine matrix with ESI-HPIMS

Having demonstrated the capabilities of the ESI-HPIMS system, Fig. 6a and b shows the application of the bench top ESI-HPIMS for detecting illegal drugs in matrices. First, morphine and codeine calibration standards in typical 80:20 methanol:water ESI solvent with 0.5% (v/v) acetic acid have been measured separately. The solid black lines represent the spectra for the blank 80:20 methanol:water ESI solvent. In Fig. 6a, the thick dashed line

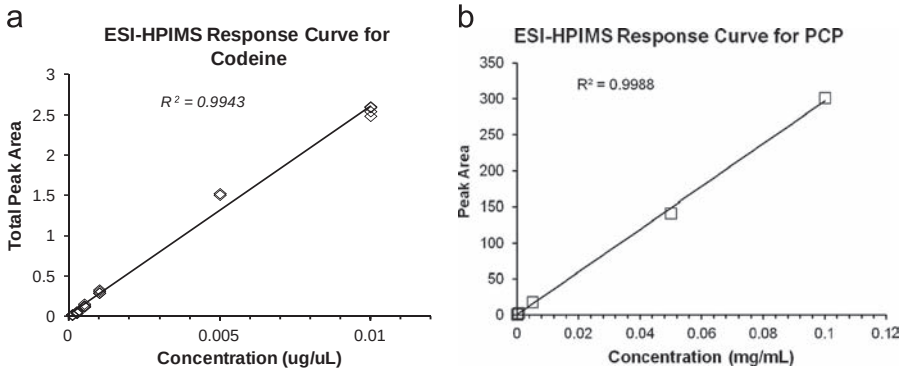

Fig. 5. (a) Response curve for codeine total peak area vs. sample concentration; (b) response curve for PCP peak area vs. sample concentration using ESI-HPIMS.

Table 2
Percent relative standard deviation (%RSD) in the peak area measured using electrospray ionization-high performance ion mobility spectrometry (ESI-HPIMS) detection of illegal and over-the-coutner (OTC) drug compounds in positive ion mode.

Compound name	%RSD
Acetaminophen	0.97
Chlorpheniramine maleate	2.83
Dextromethorphan HBr	2.25
Guiafenesin	1.00
Phencyclidine (PCP)	1.84

represents the spectrum of a 20 ng μL^{-1} (20 ppm) morphine standard (Cerilliant), overlaid with the dotted line representing the spectrum for 20 ng μL^{-1} (20 ppm) of codeine standard (Cerilliant), both in ESI solvent. The mobility peaks of morphine and codeine can be baseline separated and identified, with resolving power, *R*, greater than 60 for both species. In Fig. 6b, an equimolar mixture of morphine and codeine at concentrations of 0.1 μM (~30 ng μL^{-1}, 30 ppm) in ESI solvent can be readily detected. The two peaks are clearly distinguishable in the mixture.

Interestingly, the morphine ion intensity is reduced in the presence of codeine in the mixture in Fig. 6b. It is a known issue with ESI that some constituents may ionize preferentially during the electrospray process, consuming a portion of the finite amount of ion charge in the droplets and decreasing the ability to ionize the other analytes to be monitored in the sample [38]. Nonetheless, the morphine peak can be clearly identified and detected in the mixture. Most drugs of abuse have greater charge affinities than the interferences in the sample mixture. Therefore, the charge suppression effect from urine matrix should be minimal, but possible mitigation steps are discussed later.

To this end, the ESI-HPIMS bench-top system can directly detect drugs of abuse in a urine sample. A commercial synthetic urine matrix has been used (UriSub, CST Technologies, Inc.) that is manufactured with the characteristics of urine such as specific gravity, viscosity and pH for use as a component in preparing standards and controls for in-vitro diagnostic tests in clinical chemistry and for immunological standards and controls. Synthetic urine matrices are commonly used for assessing test methods [39] and this particular product has been proven effective for use with drugs of abuse testing [40]. It has also been used to assess the accuracy of urine detection methods for HPLC with SPE treatment [41] and to determine the dose response curve for immunoassay screening in untreated urine [42].

Fig. 7 shows ion mobility spectra taken using the ESI source at a drift tube temperature of 160 °C with air drift gas in positive ion mode to test if morphine and codeine can be detected in untreated urine samples. The solid black line is the background spectrum for

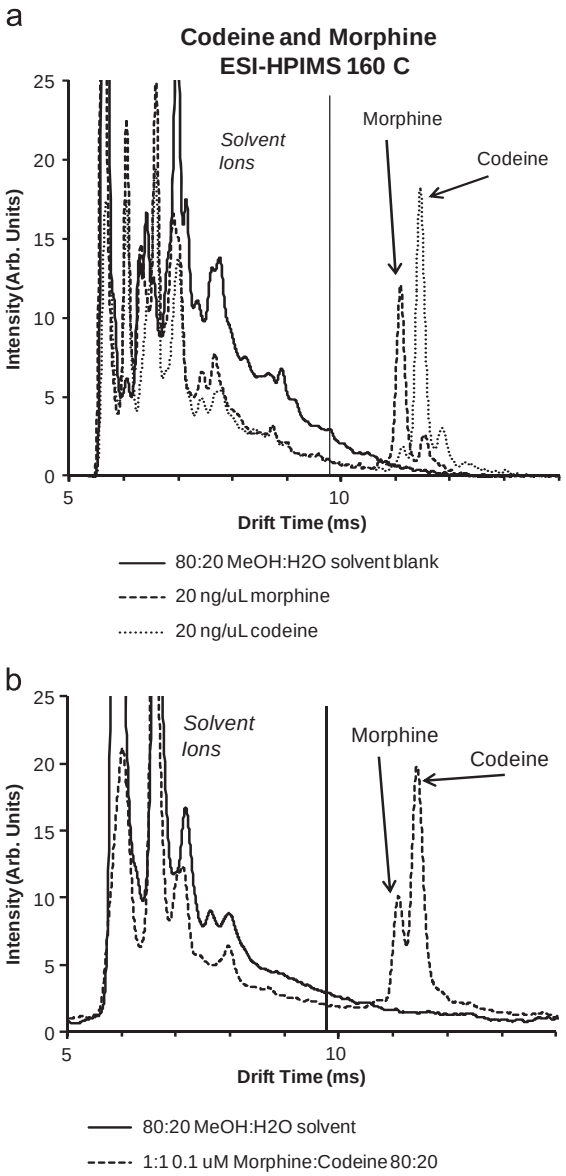

Fig. 6. (a) Ion mobility spectra using ESI-HPIMS for individual morphine and codeine standards; (b) ion mobility spectra using ESI-HPIMS for 0.1 μM equimolar mix of morphine and codeine.

a standard 80:20 methanol:water ESI solvent. To simulate a direct sample analysis, 100 μL of blank UriSub urine matrix was mixed with 900 μL of a 90:10 methanol:water ESI solvent to create 1 mL of an approximately 80:20 methanol:aqeuous ESI solution. This

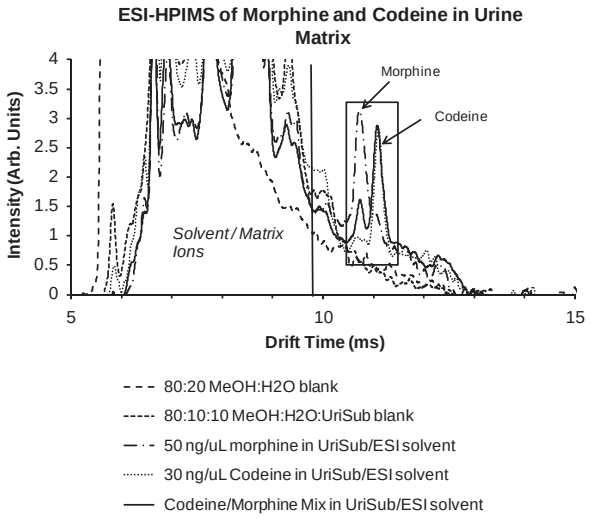

Fig. 7. Ion mobility spectra for direct ESI-HPIMS analysis of codeine and morphine in synthetic urine matrix.

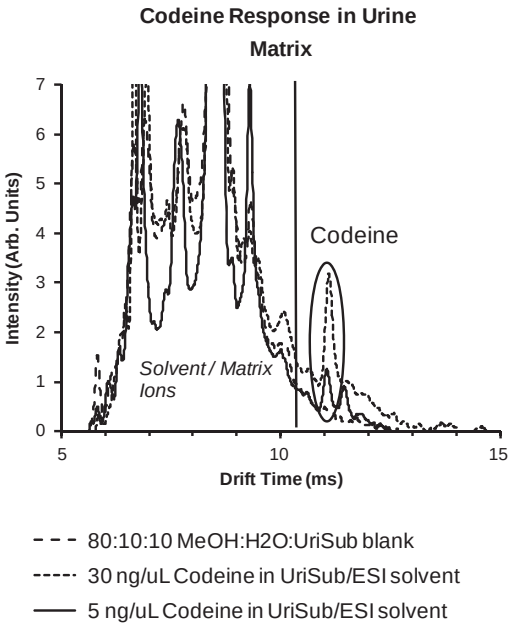

Fig. 8. ESI-HPIMS response for detecting codeine in synthetic urine matrix.

solution was then directly injected into the ESI source of the HPIMS at 3 μL min^{-1}, resulting in the background spectrum given by the dashed black line. Subsequently, a 100 μL sample of UriSub spiked with morphine standard (Cerilliant) was similarly diluted to 1 mL with 900 μL of a 90:10 methanol:water ESI solvent to 50 ng μL^{-1} (50 ppm) of morphine and directly injected at 3 μL min^{-1} to produce the spectrum given by the dotted-dashed line. A higher concentration is used to demonstrate the capabilities because of the weaker ionization response of morphine vs. codeine in a mixture using ESI discussed above. This same experiment has been repeated for UriSub spiked with codeine standard (dotted line) to 30 ng μL^{-1} (30 ppm). More importantly, when codeine standard is injected into the ESI source with morphine, both peaks are detectable in the urine matrix (solid line), as seen with just pure ESI solvent. Similar to those earlier experiments, charge competition arises between morphine and codeine as codeine has a higher charge affinity. Nevertheless, these experiments show that direct sample analysis can be achieved with identification of opiate species even in a matrix.

Preliminary tests of the sensitivity for the direct analysis method without pretreatment have also been done with the ESI-HPIMS and the UriSub urine matrix. Fig. 8 shows the mobility spectra for samples of codeine standard spiked into 100 μL of UriSub and again diluted with 900 μL of 90:10 methanol:water ESI solvent to 30 and 5 ng μL^{-1} (30 and 5 ppm). All of the experimental conditions are identical for both samples and both have been injected at 3 μL min^{-1}. The codeine ion mobility peak is detectable at 5 ng uL^{-1} (5 ppm) without any pretreatment of the spiked sample, and the intensity decreases linearly over this small range of concentrations. At this liquid injection rate with signal summing in the mobility spectrum for 750 ms, under 200 pg can be detected using HPIMS. Consequently, the initial ESI-HPIMS analysis of drugs of abuse in urine has clearly demonstrated good selectivity and promising sensitivity for urine detection, even without any substantial optimization of the sample preparation and minimal solvents or sample required.

Nonetheless, the issues of charge suppression in the presence of drug mixtures or from interfering matrix components should be addressed further through judicious use of additional sample preparation steps as part of the procedure. Future development of an on-site drug screening method using ESI-HPIMS would be best suited to a recently developed direct electrospray source (Directspray) that performs ESI directly from the needle of a sample syringe [43], allowing for higher throughput of multiple samples by eliminating transfer lines that results in carryover and long clear down times. A promising choice amenable for use with Directspray that offers good sample cleanup with minimal sample in as little as a minute is microextraction in packed syringe (MEPS) [44], a technique shown to extract a range of analytes from water, urine, and other biological fluids [45–47] including drugs [48,49] and pesticides [50,51]. MEPS has been described as a short LC column method contained within a sample syringe [45] that uses many of the same packings and solvent mixtures [52]. The packed bed is also a scaled-down version of solid-phase extraction (SPE) beds, making it straightforward to scale previously developed SPE methods as needed [52]. Jafari et al. recently demonstrated MEPS sample preparation with subsequent ESI-IMS analysis of herbicides in water [53]. A MEPS sample method would be useful for removing matrix interferences, but it could possibly be developed using solvent mixtures to isolate codeine and morphine given their different elution times in LC [54–56]. Alternatively, a quick, easy, cheap, effective, rugged, safe (QuEChERS) method [57] might be developed for sample cleanup as done with other drug classes [58,59]. However, the extra steps involved vs. MEPS while effective, might be more suitable to a laboratory-based sample screening assay.

4. Conclusions

Ion mobilities for the most commonly encountered drugs of abuse have been measured using electrospray ionization (ESI) and high-performance ion mobility spectrometry (HPIMS). The reduced mobilities from HPIMS agree very well with previous measurements [3,5,6,9,12,13,60–62], but the HPIMS provides resolving power double that of the currently accepted IMS trace drug detectors with thermal desorber sampling [26], giving performance comparable to high-performance liquid chromatography (HPLC) [21]. The method also provides linear response over two-orders of magnitude in concentration.

ESI-HPIMS offers two key advantages for this application. First, the higher resolving power enables a lower false positive rate when used as a drug screening methods, reducing the instances of false positives, whereby an unrelated chemical with a reduced mobility close to that of the illegal drug target falls within the

detection range. This reduction improves the confidence of detection and identification of the actual presence of an abused substance. Second, using ESI as a source allows direct analysis of liquids such as urine to detect drugs of abuse present. More importantly, ESI can ionize larger, thermally labile or larger, non-volatile drug compounds such as prescription APIs that are increasingly being abused because they are legal to possess, but provide the desired effect. This ability to screen a wide range of drug compounds directly from liquid matrices like urine provides a solid basis for adapting ESI-HPIMS into a clinical use instrument for drug toxicology.

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References

[1] T.A. Brettell, J.M. Butler, J.R. Almirall, Anal. Chem. 83 (2011) 4539–4556.
[2] A. Wohlfarth, W. Weinmann, Bioanalysis 2 (2010) 965–979.
[3] G.A. Eiceman, Z. Karpas, Ion Mobility Spectrometry, 2nd ed., CRC Press, Boca Raton, 2005.
[4] L.M. Matz, H.H. Hill Jr., Anal. Chem. 73 (2001) 1664–1669.
[5] L.M. Matz, H.H. Hill Jr., Anal. Chem. 74 (2002) 420–427.
[6] L.M. Matz, H.H. Hill Jr., L.W. Beegle, I. Kanik, J. Am. Soc. Mass Spectrom. 13 (2002) 300–307.
[7] L.M. Matz, H.H. Hill Jr., Anal. Chim. Acta 457 (2002) 235.
[8] Y. Lu, R.M. O'Donnell, P.B. Harrington, Forensic Sci. Int. 189 (2009) 54–59.
[9] T. Keller, A. Keller, E. Tutsch-Bauer, F. Monticelli, Forensic Sci. Int. 161 (2006) 130–140.
[10] L. Elias, A.H. Lawrence, On-site sampling and detection of drug particulates, in: T.A. Gough (Ed.), Analysis of Drugs of Abuse, Wiley, Chichester, England, 1991pp. 373–400.
[11] J.K. Loknauth, N.H. Snow, Anal. Chem. 77 (2005) 5983.
[12] A.B. Kanu, H.H. Hill Jr., Talanta 73 (2007) 692–699.
[13] C. Wu, W.F. Siems, H.H. Hill Jr., Anal. Chem. 72 (2000) 396–403.
[14] A.B. Kanu, C. Wu, H.H. Hill Jr., Anal. Chim. Acta 610 (2008) 125–134.
[15] A.H. Lawrence, Anal. Chem. 72 (1989) 580–584.
[16] H. Lai, P. Guerra, M. Joshi, J.R. Almirall, J. Sep. Sci. 31 (2008) 402.
[17] V. Lopez-Avila, H.H. Hill, Anal. Chem. 69 (1997) 289R–305R.
[18] H.H. Hill, G. Simpson, Field Anal. Chem. Technol. 1 (1997) 119–134.
[19] G. Lum, B. Mushlin, Lab. Med. 35 (2004) 368–373.
[20] G. McMillin, F. Urry, Drug Testing Guide for Chronic Pain Management Services, Rpt. # 1718.07, ARUP Laboratories, Salt Lake City, 2007.
[21] G.R. Asbury, H.H. Hill Jr., J. Microcolumn Sep. 12 (2000) 172–178.
[22] L. Konermann, E. Ahadi, A.D. Rodriguez, S. Vahidi, Anal. Chem. 85 (2013) 2–9.
[23] M.A. Strege, Anal. Chem. 81 (2009) 4576.
[24] M.A. Strege, J. Kozerski, N. Juarbe, P. Mahoney, Anal. Chem. 80 (2008) 3040.
[25] C. Qi, A. Granger, V. Papov, J. McCaffrey, D.L. Norwood, J. Pharm. Biomed. Anal. 51 (2010) 107.
[26] T. Gabowitcz, D. Ridjosic, S. Nacson, US Patent, App. No. 11/303,012, 2008.
[27] C.A. Krueger, C.K. Hilton, M. Osgood, J. Wu, C. Wu, Int. J. Ion Mobil. Spectrom. 12 (2009) 33–37.
[28] C.A. Krueger, A.J. Midey, T. Kim, M. Osgood, J. Wu, C. Wu, Int. J. Ion Mobil. Spectrom. 14 (2011) 71–79.
[29] C.K. Hilton, C.A. Krueger, A.J. Midey, M. Osgood, J. Wu, C. Wu, Int. J. Mass Spectrom. 298 (2010) 64.
[30] D. Wittmer, Y.H. Chen, B.K. Luckenbill, J.H.H. Hill, Anal. Chem. 66 (1994) 2348–2355.
[31] D.S. Ithakissios, J. Chromatogr. Sci. 18 (1980) 88–92.
[32] E.S. Reese, P.B.D. Harrington, J. Forensic Sci. 44 (1999) 68.
[33] H.I. Kim, P.V. Johnson, L.W. Beegle, J.L. Beauchamp, I. Kanik, J. Phys. Chem. A 109 (2005) 7888.
[34] A.U. Jackson, N. Talaty, R.G. Cooks, G.J. Van Berkel, J. Am. Soc. Mass Spectrom. 18 (2007) 2218–2225.
[35] J.C. Spell, K. Srinivasan, J.T. Stewart, M.G. Bartlett, Rapid Commun. Mass Spectrom. 12 (1998) 890–894.
[36] G.E. Spangler, C.I. Collins, Anal. Chem. 47 (1975) 393–402.
[37] S.C. Moldoveanu, Pyrolysis of Organic Molecules: Applications to Health and Environmental Issues, Elsevier, Oxford, 2010.
[38] P. Kebarle, Y. Ho, On the mechansim of electrospray mass spectrometry: fundamentals, instrumentation, and applications, in: R.B. Cole (Ed.), Electrospray Ionization Mass Spectrometry, Wiley, New York, 1997, pp. 42–50.
[39] N.C. van de Merbel, TrAC Trends Anal. Chem. 27 (2008) 924–934.
[40] K. Faulstich, M. Eberhard, R. Gruler, K. Haberstroh, IVD Technologies, July 2007.
[41] M.J. Silva, E.P.J. Samandar, J.L. Preau, J.A. Reidy, L.L. Needham, A.M. Calafat, J. Chromatogr. B 860 (2007) 106–112.
[42] C. Boehmea, E. Molokovab, F. Minjac, S. Geisa, T. Loschera, L. Mabokod, V. Koulchinb, M. Hoelscher, Trans. R. Soc. Trop. Med. Hyg. 99 (2005) 893–900.
[43] A.J. Midey, A. Camacho, J. Sampathkumaran, C.A. Krueger, M.A. Osgood, C. Wu, Anal. Chem. submitted.
[44] H. Bagheri, Z. Ayazi, Anal. Methods 3 (2011) 2630–2636.
[45] A.R. Chaves, F.Z. Leandro, J.A. Carris, M.E.C. Queiroz, J. Chromatogr. B 878 (2010) 2123–2129.
[46] R. Abdel-Al, J. Chromatogr. B 801 (2004) 317–321.
[47] A. El-Beqqali, A. Kussak, M. Abdel-Rehim, J. Chromatogr. A 1114 (2006) 234–238.
[48] Z. Altun, L.G. Blomberg, E. Jagerdeo, M. Abdel-Rehim, J. Liq. Chromatogr. Relat. Technol. 29 (2006) 829–839.
[49] I. Moreno, B. da Fonseca, D. Oppolzer, A. Martinho, M. Barroso, A. Cruz, J.A. Queiroz, E. Gallardo, Bioanalysis 5 (2013) 661–668.
[50] H. Bagheri, Z. Ayazi, A. Aghakhani, N. Alipour, J. Sep. Sci. 35 (2012) 114–120.
[51] H. Bagheri, Z. Ayazi, A. Es'haghi, A. Aghakhani, J. Chromatogr. A 1222 (2012) 13–21.
[52] M. Abdel-Rehim, Z. Altun, L. Blomberg, J. Mass Spectrom. 39 (2004) 1488–1493.
[53] M.T. Jafari, M. Saraji, S. Yousefi, J. Chromatogr. A 1249 (2012) 41–47.
[54] R. Coles, M.M. Kushnir, G.J. Nelson, G.A. McMillin, F.M. Urry, J. Anal. Toxicol. 31 (2007) 1–14.
[55] A.B. Ruzilawati, W.N. Wan Yusuf, Int. J. Pharm. Sci. Drug Res. 5 (2013) 18–22.
[56] I. Dioumaeva, J.M. Hughes, SAMHSA Compliant LC/MS/MS Analysis of Opiates (Morphine and Codeine) in Urine With Agilent Bond Elut Plexa PCX and Agilent Poroshell 120, Agilent App. Note 5990-9625EN, 2013.
[57] M. Anastassiades, S.J. Lehotay, D. Stajnbaher, F.J. Schenck, J. AOAC Int. 86 (2003) 412–431.
[58] W. Peysson, E. Vulliet, J. Chromatogr. A (2013), in press.
[59] R.P. Lopes, É.E. de Freitas Passos, J.F. de Alkimim Filho, E.A. Vargas, D.V. Augusti, R. Augusti, Food Control 28 (2012) 192–198.
[60] T. Keller, A. Miki, P. Regenscheit, R. Dirnhofer, A. Schneider, H. Tsuchihachi, Forensic Sci. Int. 94 (1998) 55–63.
[61] A. Kanu, J.H.H. Hill, Talanta 73 (2007) 692–699.
[62] A.H. Lawrence, Anal. Chem. 58 (1988) 1269–1272.