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A Free Zone Capillary Electrophoresis Method for the Quantitation of Common Illicit Drug Samples*

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ABSTRACT: This paper presents a simple quantitative method using capillary electrophoresis (CE) with liquid cooling to analyze commonly seized illicit substances. Fourteen common basic drugs were screened using a 200mM sodium phosphate run buffer. Linearity and reproducibility are shown for cocaine, heroin, methamphetamine, lysergic acid diethylamide (LSD), and phencyclidine (PCP). Known adulterants and impurities did not interfere with these drug compounds. Comparisons of CE quantitations with results from other laboratory techniques demonstrate the reliable adaptation of CE to the forensic laboratory.

KEYWORDS: forensic science, street drugs, chemistry, capillary electrophoresis, quantitation, cocaine, heroin, methamphetamine lysergic acid diethylamide, phencyclidine

The separative capabilities of capillary electrophoresis (CE) have been documented in the biological (1,2), clinical (3,4), environmental (5–8), pharmaceutical (9–14), and forensic sciences. Forensic analyses include illicit drug seizures (15–20) explosives (21–23), gunshot residue (24,25), DNA (26–28), and toxicology (29–32). Achieving traditionally difficult separations is one of CE's numerous advantages. The technique will become more routine once its practicality and reliability have been proven.

Several papers address this concern and discuss the quantitative utility of CE. For example, sodium dodecyl sulfate (SDS) micellar methods have been used for the quantitation of heroin, amphetamine, and anabolic steroids (33–35). Similarly, reproducible quantitations of heroin and cocaine using a cetyltrimethylammonium bromide (CTAB) micellar system have been accomplished (36,37). Free zone electrophoresis (FZE), the most basic mode of CE, has been used to analyze benzodiazapines, phenethylamines, opiates, cocaine, barbiturates, and antidepressants (38–42) in a variety of biological media.

Traditionally, micelles have been incorporated into the run buffer to separate neutral species that have no electrophoretic mobility. Partitioning into an electrophoresing micelle imparts a net mobility on the solute. However, many common drugs of forensic interest are ionic in nature and can be charged imparting different electrophoretic mobilities to each solute. Basic drugs, in general, are neutral at high pH and positively charged at low pH. Conversely, acidic drugs are negatively charged at high pH. Therefore, the run buffer pH and solute pKa become critical elements creating complications with micellar systems because of ionic interactions with the micelle (43,44). A free zone system eliminates solute-micelle ionic interactions, enabling charge-based separations without adding complexity to the run buffer.

Micellar systems are further complicated because they incorporate surfactants and often organic modifiers into the run buffer. As a result of the multiple components, reproducibility problems can arise. Through buffer depletion and organic modifier evaporation, the micelle concentration can change affecting the phase ratio and the capacity factor (45–47). More importantly, organic modifier evaporation dramatically changes the partition coefficient and other critical system variables such as the phase ratio, the critical micelle concentration, the dielectric constant, and the viscosity (48,49). Changing the dielectric constant and viscosity influences the zeta potential that in turn affects the endoosmotic flow (50,51). Furthermore, the solute's intrinsic mobility may change because of the pKa dependence on the amount of organic modifier (52–55). The majority of illicit drugs received in the laboratory have basic properties. These include cocaine, heroin, methamphetamine, lysergic acid diethylamide (LSD), and phencyclidine (PCP). A FZE method is presented that can screen and quantitate these samples. Using a 200mM sodium phosphate run buffer at pH 4.5, the solutes of interest are positively charged. Separations are achieved through differences in each solute's electrophoretic mobility. Fourteen basic drugs were separated in 20 min with a 67-cm capillary column. For the five common drugs mentioned previously, an internal standard was introduced and the column was shortened, producing run times comparable with other laboratory techniques. In each case, common adulterants, diluents, and impurities were shown not to interfere. Reproducibility and linearity were established.

The simplicity of this method allows for practical adaptation to everyday use in the laboratory. The run buffer has one component and samples are simply diluted. Additionally, this system can be used to quantitate the vast majority of samples received in the laboratory. As will be shown, the method is elementary and very reliable.

Materials and Methods

Chemicals and Reagents

Drug standards (99% + purity), related drug impurities, and adulterants found in Figs. 1 and 2 were obtained from the Drug Enforcement Administration (DEA Special Testing and Research Laboratory, McLean, VA), Mallinckrodt, Aldrich, Sigma, P&B, K&K and Supro. Naphazoline, the internal standard, was purchased

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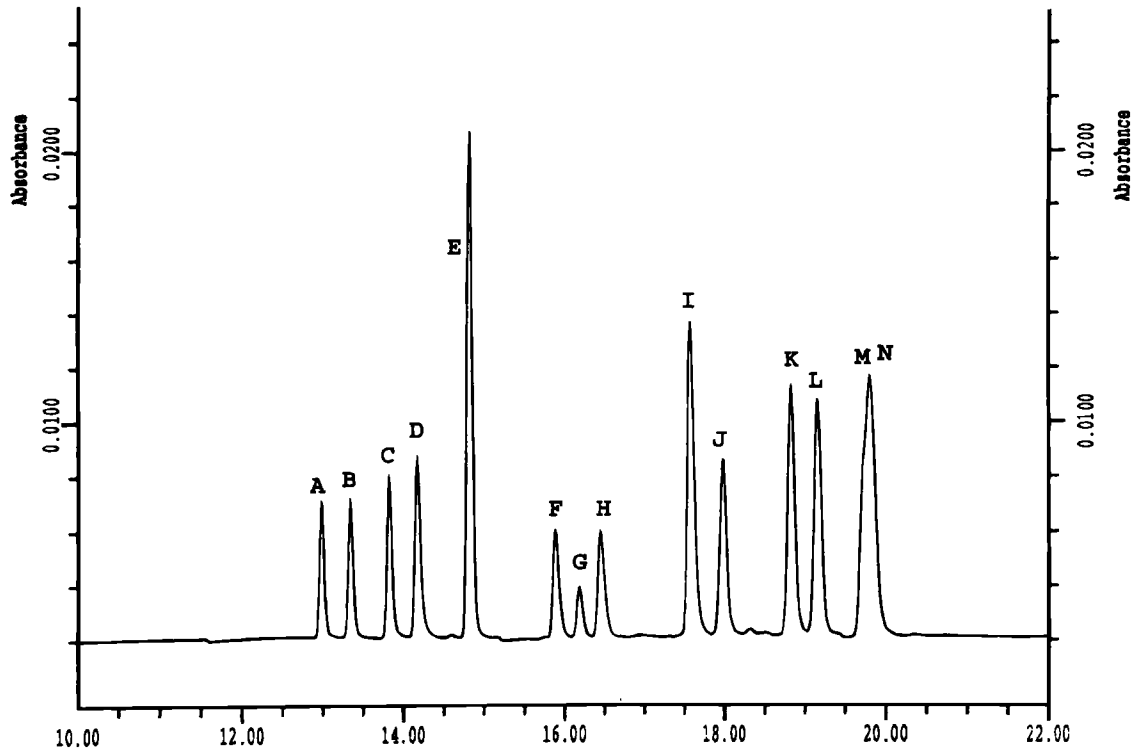

FIG. 1—*Electropherogram demonstrating the separations achieved for fourteen common illicit drugs. A: amphetamine, B: methamphetamine, C: methylenedioxyamphetamine, D: methylenedioxymethamphetamine, E: psilocyn, F: cocaine, G: PCP, H: PCPy, I: methadone, J: codeine, K: morphine, L: acetylcodeine, M: heroin, N: LSD.*

from Sigma Chemical. The run buffer contained sodium phosphate (Sigma Chemical) dissolved in HPLC grade water.

Capillary Electrophoresis Procedure

CE was performed using a Beckman P/ACE System 5500 capillary electropherometer equipped with liquid cooling, a deuterium lamp, and a diode array detector operating at either 230 or 210 nm. Either a 37-cm or a 67-cm length of uncoated fused silica capillary column (50 μm internal diameter) was used. The column outlet was placed a distance of 7.0 cm from the detector window. The temperature was held at a constant 30°C with an applied voltage of 20 kV. All data were processed using Beckman System Gold software, Version 7.1.

The run buffer consisted of 200mM sodium phosphate at pH 4.5. For stacking purposes (56–58), samples and standards were diluted with 100mM sodium phosphate containing either 0.1 or 0.3 mg/mL naphazoline. Filtered samples were introduced by a 2-s high pressure injection. A 2-min run buffer rinse was performed between multiple sample analyses.

Gas Chromatography (GC) Procedure

GC was performed on a 12-m Hewlett-Packard (HP)-1 column using an HP-5890 gas chromatograph with helium as the carrier gas. Depending on the compound, the oven temperature varied from 150 to 270°C. The injector temperature was 270°C, and the flame ionization detector temperature was held constant at 280°C. Samples and standards were diluted with chloroform containing an internal standard.

High Performance Liquid Chromatography (HPLC) Procedure

The HPLC system used a 25-cm C-18 column on an HP-1090 Series II liquid chromatograph. The mobile phase contained acetonitrile and phosphate buffer running at 1.0 mL per minute. Using a diode array, UV absorbance was gathered at 210 nm. Samples and standards were diluted with mobile phase.

Results and Discussion

The presented model is a simple system for the everyday quantitation of commonly encountered illicit drugs. The efficiency of the system is comparable to a relatively complicated micellar system consisting of four components (18). Theoretical plates in the order of 700,000 are routinely achieved allowing for excellent separations. In FZE, resolution is determined by the simple equation:

$$Rs = \frac{1}{4} N^{1/2} \left(\frac{\mu ap}{\mu eof + \mu ef} \right) \quad (1)$$

where N is the number of theoretical plates, μap is the apparent mobility, μeof is the endoosmotic flow (EOF) mobility which is slow under the run conditions (mesityl oxide elutes around 50 min), and μef is the solutes mean electrophoretic mobility defined as:

$$\mu ef = \frac{QV}{4Bnr} \quad (2)$$

where Q is the charge on the solute, V is the applied voltage, n is the run buffer viscosity, and r is the solute's drag coefficient.

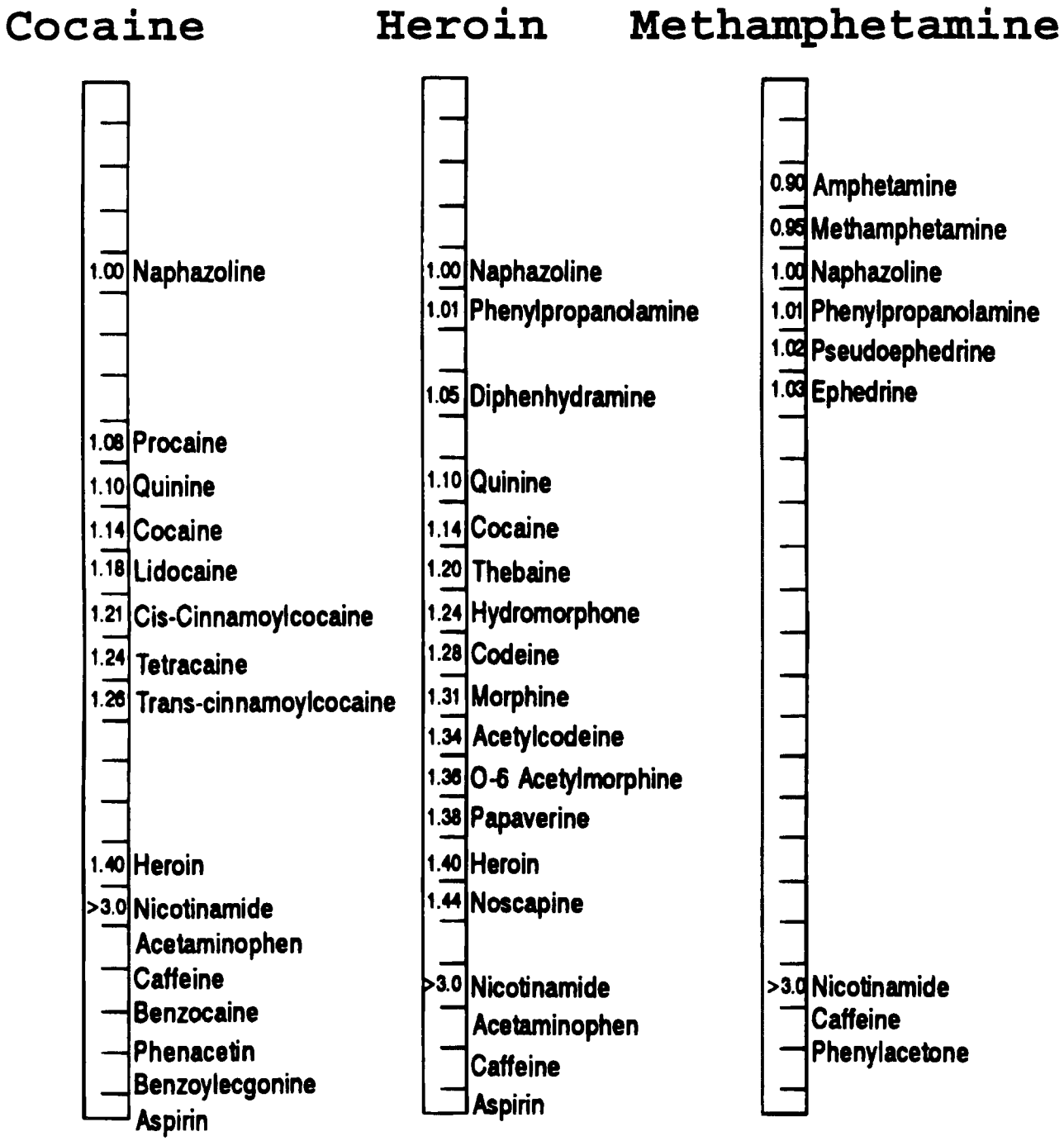

FIG. 2—*Relative migration times against naphazoline for common adulterants and related drug impurities found in cocaine, heroin, and methamphetamine samples.*

Therefore, the size, shape, and charge (dependent on solute pKa and run buffer pH) determine the separability of the method. Figure 1 demonstrates the effective separation based on differences in electrophoretic mobilities of fourteen basic drugs. Only heroin and LSD coelute, however, can easily be distinguished through their ultraviolet absorption. Over nine injections, the relative migration times for each compound against cocaine was less than 0.3%. The FZE method is most reliable for compounds that are positively charged at pH 4.5 in contrast to a micelle system capable of simultaneously screening basic, acidic, and neutral species.

To be used everyday as a quantitative technique, a CE method must compete with the ease and quickness offered by other laboratory techniques. Using a 37-cm capillary column, cocaine, heroin, methamphetamine, LSD, and PCP elute in less than five minutes. Linearity ranges were established for the following common basic drugs and their salt forms; cocaine hydrochloride (HCl) and base; heroin HCl, base and tartrate; methamphetamine HCl; LSD tartrate; PCP HCl; and naphazoline HCl. Cocaine HCl and base samples were prepared from 0.025 to 2.0 mg/mL with 0.3 mg/mL of naphazoline. The other standards were diluted from 0.025 to 1.0 mg/mL using 0.1 mg/mL of naphazoline. The corrected peak area of PCP was linear through 1.0 mg/mL. The upper concentration for

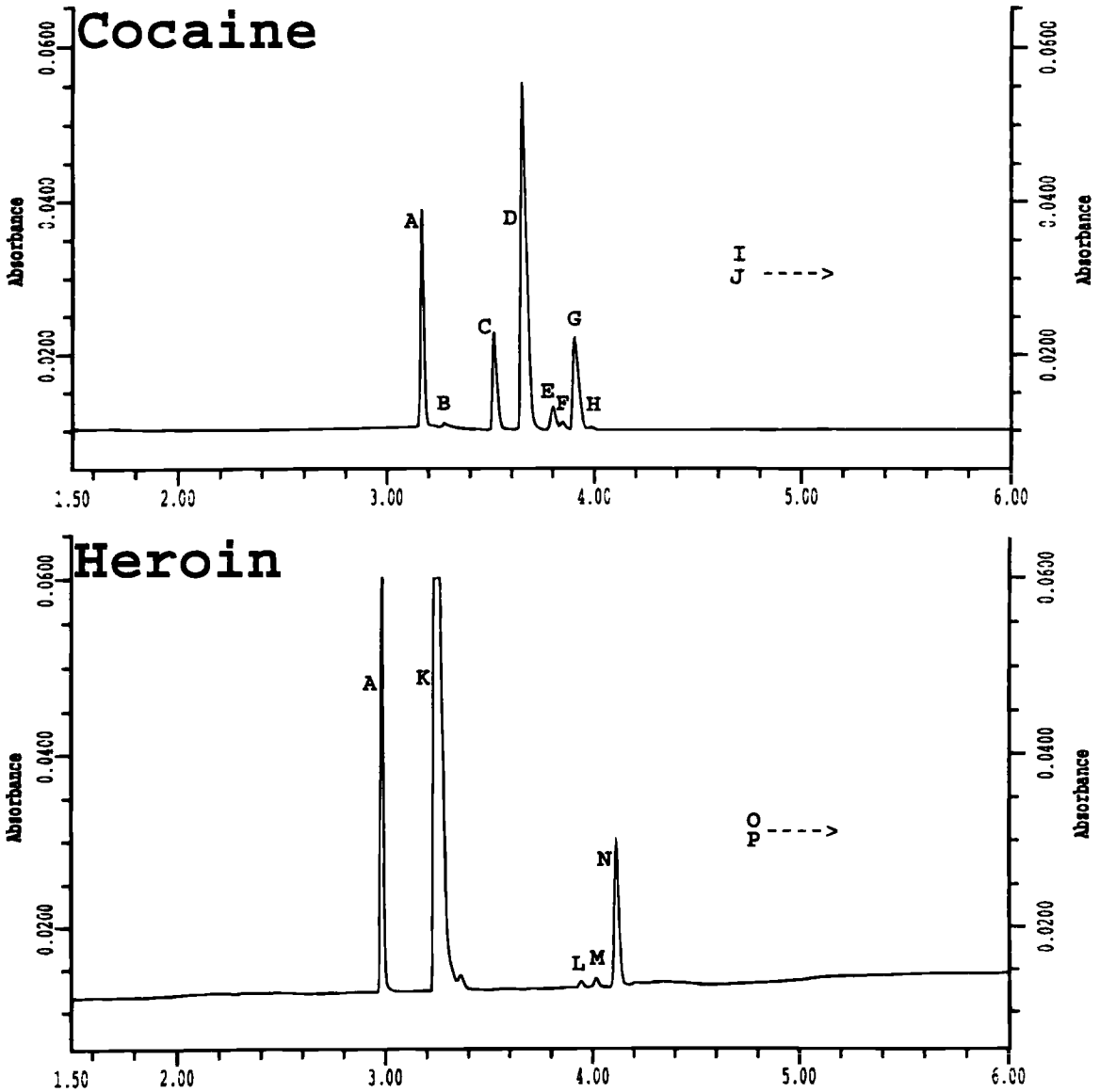

FIG. 3—*Electropherograms of adulterated street samples of cocaine and heroin. Samples were diluted to a concentration of 0.3 mg/mL. A: naphazoline, B: ephedrine, C: procaine, D: cocaine, E: lidocaine, F: cis-cinnamoylcocaine, G: tetracaine, H: trans-cinnamoylcocaine, I: benzocaine, J: caffeine, K: quinine, L: acetylcodeine, M: acetylmorphine, N: heroin, O: acetaminophen, P: aspirin.*

the other drugs was 0.6 mg/mL. Examination of relative peak height resulted in linearity up to concentrations of 0.4 mg/mL for each compound. Correlation coefficients for each range were greater than 0.999. The differences in the peak area and peak height linearity correspond with efficiency data. Above 0.4 mg/mL, theoretical plates drop by as much as 75%.

The run buffer's high ionic strength aides in shielding the wall to reduce peak tailing; however, it generates a much higher current that produces increased Joule heating, causing the system to operate outside of Ohm's law. Thus, the temperature inside the column is not equal to the wall temperature nor the exterior cooling temperature. The Joule heating generates turbulence and convection currents dispersing the bands. Using Burgi's formula (59), the internal temperature was calculated to be approximately 60°C and no signs of thermal breakdown were observed.

As mentioned previously, the EOF is slow but not negligible. The flow produced at pH 4.5 pumps fresh run buffer existing at room temperature through the capillary assisting the external column coolant. A 200mM phosphate run buffer at lower pH produces a slower flow, diminishing this cooling and possibly lowering the linear range. Even though this method runs "hot," the reproducibility and reliability of the method is not compromised. A longer column and different ionic strength would alter the separation efficiency and resolution of the system as well as the linearity limits (60–64).

Reproducibility was established for LSD tartrate and the other drugs in their HCl salt form at concentrations of 0.025, 0.10, 0.30, 0.50, and 1.0 mg/mL with naphazoline. Reproducibility over nine injections was excellent for migration times, relative corrected peak areas, and relative peak heights. For all samples, the relative standard deviation for each category was less than 2%.

Figure 2 illustrates relative migration times against naphazoline for common adulterants and related drug impurities found in cocaine, heroin, and methamphetamine samples. At pH 4.5, only

basic compounds with pKa values greater than 3.0 will elute before the EOF. If soluble, all other neutral and acidic compounds will elute with or after the EOF effectively removing any chance to coelute with the drugs of interest. Because of their lack of electrophoretic mobility, run buffer rinses between injections is necessary to remove them from the column. Figure 3 demonstrates typical electropherograms of adulterated samples of cocaine and heroin. Caffeine, benzocaine, acetaminophen, and aspirin have no forward mobility and do not elute within the six minute run. To illustrate this point, quantitation of street samples with impurities was performed using a one-level calibration from standards diluted to 0.3 mg/mL. Twenty-one illicit samples of cocaine hydrochloride and cocaine base ranging from 26.8 to 94.4% were analyzed, as were eight heroin hydrochloride and five methamphetamine hydrochloride samples. The calculated purities were compared to results obtained by GC analysis. Both techniques resulted in similar quantitations for cocaine, heroin, and methamphetamine. The difference for individual samples was never greater than 3.7%, and the average difference for each drug was less than 1.7%.

A comparison of a run buffer extraction versus chloroform dilution of two liquid PCP samples (33.0 and 99.0 mg/mL of PCP base in organic solvent) was done. For the CE analysis, 1 mL aliquots of each sample were added to the 100-mL run buffer. Each was shaken for three minutes followed by one minute of vortexing. The resulting mixture was centrifuged for one minute, accelerating the separation of the organic and aqueous layers. Further analysis of the samples by GC mass spectrometry indicated the presence of the following components: piperidine, cyclohexanone, bromobenzene, phenol, 1-phenylethanol, 3,5-dimethylpiperidine, 1-cyclohexylpiperidine, 1-piperidinocyclohexane (thermal breakdown), biphenyl, 1-phenylcyclohexene, 1-phenylcyclohexanol, 2-(1-cyclohexenyl) cyclohexanone, and 1-piperidinocyclohexylcarbonitrile. Similar to the earlier discussion, these compounds were either insoluble in the run buffer or eluted with or after the EOF, preventing them from interfering with PCP or the internal standard. The average percent difference between the samples was 1.4%.

Three samples of PCP on marijuana were analyzed by CE and GC. Portions of each were sonicated in run buffer (CE) or chloroform (GC) for 2 h. An average of 11% difference was obtained for the quantitative results. The difference was due to the time and efficiency of the extractions. The plant material matrix did not interfere with the CE analysis. As found with liquid PCP, the sample electropherogram was similar to that of the standard.

Two illicit samples of LSD (30 μg/blotter) on different colored paper were extracted (65) with run buffer and analyzed by CE and HPLC. The difference between the two techniques for both samples was 2.4%. The dyes and whiteners extracted from the paper, which can be problematic with HPLC analyses, did not interfere with the LSD or IS. Iso-LSD was found to separate from LSD with this method; however, lysergic acid methylpropylamide (LAMPA) was found to coelute. Therefore, identification of the drug before quantitation is required. This demonstrates the importance of molecular shape in the drag coefficient in Eq 2. LSD and LAMPA have similar spacial orientations. Their difference is the amine chain length. The chiral center of iso-LSD moves the amine chain orientation, creating a slightly different shape and a different electrophoretic mobility.

Many of the street samples contained unidentified diluents that did not appear to interfere with the analyses. To ensure further the method's practicality for all samples, standard solutions of each drug were prepared with 0.3 mg/mL of the following common diluents; sodium bicarbonate, mannitol, inositol, starch, sucrose, dextrose, fructose, sucrose, lactose, and boric acid. For each drug, the migration times, corrected peak areas, and corrected peak heights were reproducible over nine injections and similar to the pure standards.

To demonstrate the method's ruggedness, 40 analyses were done for each drug from a single run buffer via holding approximately 4.5 mL. The data show a general trend towards increased migration times. The greatest change occurred with LSD that moved from 4.5 to 4.9 min. However, examination of the relative migration times when compared with the internal standard proved steadfast. Relative standard deviations of migration times for all drugs were less than 0.4%. Refreshing the run buffer every ten analyses will keep the daily migration time shift to a minimum.

Conclusion

The presented free zone electrophoresis method can be used as a daily quantitative technique for the majority of illicit drug samples received in the laboratory. The combination of aqueous solubility, ionic properties, and system efficiency allow for complete separation of common adulterants, impurities, and diluents that can be problematic with other laboratory instruments. The simplicity of run buffer and sample preparation offer a rugged, reproducible alternative. Also, the diode array detector can be use to generate UV-Vis spectral data. The combination of migration time and UV-Vis data could be used as an effective screening tool.

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