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Mini Review

Application of Capillary Electrophoresis for Ephedrine and Pseudoephedrine Detection: a Review

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Commonly utilized for drug discovery and pharmaceutical production, ephedrine (EP) and pseudoephedrine (PEP) are forms of epinephrine, and novel and current separation and characterization techniques are essential for determining the presence of these compounds. CE methods used to analyse natural products published during 2000–2018 were covered in this review. The major process advances over the review period focused on derivatization, chiral analysis, detection methods, stacking or online concentration of samples, and sample preparation (mainly using extraction methods). Herbal goods, plants, water, and biological samples were the sample matrices analysed. Developments have also taken place in the fields of quality control, toxicology evaluation and testing for enzyme inhibitors. This review also provides a short description of CE theory and perspectives on CE's potential use for EP and PEP detection.

Keywords: Capillary electrophoresis (CE); Ephedrine; Pseudoephedrine; UV detection; Laser-induced fluorescence detection

1. INTRODUCTION

Ephedrine (EP) and pseudoephedrine (PEP) are epinephrines that relax smooth muscle, constrict blood vessels and excite the central nervous system. In clinical practice, they are often used together with antipyrolystic drugs to treat colds [1–4]. They are also commonly abused as stimulants in competitive sports and have been listed as banned substances by the international Olympic committee. EP product safety concerns led to the development of various analytical approach for alkaloid detection. The method of quantifying these molecules is crucial for determining the labelling and quality of products (including the declaration of "ephedrine-free" products). Due to the different product formulations, the products have different EP alkaloid content. Various detection approaches have been used for EP/PEP quantification, including spectroscopy [5], GC [6], HPLC [7], electrochemical methods [8–11] and capillary electrophoresis (CE) [12–20].

CE is a advanced separation and analysis method with a capillary as a separation channel and a high voltage DC electric field as a driving force. When implemented for analyte separation, CE mainly includes capillary zone electrophoresis (CGE) [21–23], micellar electrokinetic capillary chromatography (MEKC) [24–27], capillary gel electrophoresis (CGE) [28–31], capillary isoelectric focusing (CIEF) [32–36], capillary isotachophoresis (CITP) [37,38], capillary electrochromatography (CEC) [39–42], capillary array electrophoresis (CAE) [43–46], affinity capillary electrophoresis (ACE) [47–49] and non-aqueous CE (NACE) [50–52]. CZE was separated by electrophoresis according to the difference between the net charge and its mass ratio of each sample to be tested. Electrophoresis is relatively simple to operate and is the most widely used of all CE modes. MEKC and CEC are also widely used and studied separation modes. The selection of electrophoretic patterns depends on the nature of the sample to be analysed, as well as several other principles, such as simplicity, universality, selectivity, and sample specificity.

The separation efficiency and precision of CE experiments are affected by different injection methods. The requirement of successful CE separation is to not cause significant zone expansion, and the sample size should be appropriate to avoid overloading [53–57]. Generally, the appropriate injection zone width is 1-2% of the capillary length. If the width of the injection is larger than that, the column effect will be lower. At present, CE adopts direct cylinder injection, including electrodynamic injection, flow mechanics injection, diffusion injection and flow injection.

CE is a powerful separation technique, but it is only a means of separation. With the rapid development of technology and the continuous expansion of the application field, the development of high sensitivity detection technology has been one of the important areas of CE research. Due to the small injection amount of CE, a high voltage electric field needs to be applied during the separation process. Therefore, in invasive detection mode, it is necessary to pay attention to the separation of the capillary from the detector due to high pressure. Therefore, researchers have been paying close attention to the improvement of CE detection technology but also continue to carry out in-depth research on related aspects. To date, many detection techniques have been successfully applied, such as UV-vis [58–61], laser-induced fluorescence [62], electrochemical detection [63–65], mass spectrometry [66–69], nuclear magnetic resonance [70–73], chemiluminescence [74] and electrochemical luminescence [75–77].

In this review, we summarized the recent development of CE-based methods for EP and PEP determination.

2. CE- UV DETECTION

Phinney and colleagues demonstrated three alternatively CE techniques for determining the EP and PEP [78]. Monocyclodextrin or bicyclodextrin chiral selection systems has been used for the separation. These three approaches were successfully used for determining five products containing ephedra. Using a highly sensitive UV detection unit, the determination of the analyte can be achieved at a wide concentration range. Specifically, these methods can determining (-)-EP and (+)-PEP from 0.31 to 76.43 mg/g, and 0.049 to9.23 mg/g, respectively. The results of the three approaches were consistent

with each other and were in well agreement with the results of other analytical methods. The enantiomeric identity of the analyte is determined by the introduction of a certain amount of this molecule. The contents of EP alkaloids in the five products were assigned using the results of the three CE methods.

A simple, accurate and rapid approach for separating and determination of EP by CZE was developed [79]. The pH value and concentration of the buffer, the applied voltage and additives are important factors in the analysis. The optimum conditions were as follows: a 20 mM sodium tetraborate buffer solution at pH 8.50 was used for separation within 10 min. Carrier electrolytes provide baseline separation with good resolution, reproducibility, and accuracy. The calibration block is in a linear analyte concentration range of 0.42~1.33 g ml/L. EP was detected using an ultraviolet spectrophotometer at wavelengths of 205 and 250 nm. According to the reaction of the new external standard solution, the quantity of each component in the sample was calculated. The approach was validated to meet the safety control regulation.

Pan et al. reported [80] another basic and fast constant division technique by mixing flow infusion with CE intended for the examination of essential customary medications. The instrument was designed utilizing commercial capillaries and parts readily accessible in systematic research facilities. Utilizing the double-T configuration, consistent presentation of a progression of tests was accomplished. The scans for EP and PEP were acquired utilizing a borate support in a 25 μm partition channel [81]. Using a 2 M NaOH solution, the linear calibration range for both analytes was 50 to 1000 μg/mL (r = 0.9996), and the recoveries were 91.2–108.2% for EP and 92.6–107.3% for pseudoephedrine. The relative normal peak area deviation was 1.6% for EP and 1.3% for PEP at 500 μg/mL. This method showed excellent performance when repeatedly injected samples into system. Therefore, it can be used for EP and PEP detection in the medical plant samples.Table 1 shows the reports of the CE-UV for EP/PEP determination.

Table 1. Recently developed CE-UV methods for EP/PEP determination.

Assistive technology	Year	Reference
Carboxymethyl-β-cyclodextrin as a chiral selector	2001	[82]
-	2008	[83]
Poly (methacrylic acid-co-ethylene glycol dimethacrylate) monolith microextraction and on-line pre-concentration	2007	[84]
Field-amplified sample injection	2015	[85]
L-leucine as a chiral selector	2002	[86]

3. CE- LASER-INDUCED FLUORESCENCE (LIF) DETECTION

Zhang et al. [87] reported an enhanced CE-LIF approach for separating and detecting the EP and PEP. They studied the separation conditions with optimization in detail. Under the optimized experimental conditions, an excellent linear relationship between the peak height and the analyte concentration (0.7-140 μ m) was obtained. The detection limit was 0.16 μM and 0.17 μM for EP and pseudoephedrine, respectively. It showed that the sensitivity was increased tenfold compared to that

reported in the literature. The method has been successfully used for analysing the EP and PEP in Ephedra.

After derivatization in non-aqueous media, the content of the EP and PEP were detected using CE with laser-induced fluorescence [88]. The derivatization was carried out in offline mode. In the range of 1.23–19.60 mg/L (with correlation coefficients of 0.9970 for EP and 0.9994 for PEP). The linear detection range of the EP and PEP were 0.014 and 0.011 mg/L, respectively. Table 2 outlines the reports of the implementation of CE-LIF for EP/PEP determination.

Table 2. Recently developed CE-LIF methods for EP/PEP determination.

Assistive technology	Year	Reference
Micellar electrokinetic chromatography	2008	[89]
Dynamic SDS coating	2004	[90]
30 mM triethylamine as buffer solution	2005	[91]
7-chloro-4-nitrobenzo-2-oxa-1,3-diazole (NBD-Cl) as a doping agent	2006	[92]
4-chloro-7-nitrobenzo-2-oxa-1, -3-diazole as a doping agent	2004	[93]

4. CE-NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (NMRS) DETECTION

Under CE condition, the PEP and EP exhibited different migration behaviours [94] when utilizing β-cyclodextrin heptane, (2,3-o-diacetyl)-cyclodextrin, and (2,3-o-diacetyl-6-sulfonamide)-cyclodextrin (HDAS). To elucidate the mechanism of chiral recognition, UV, MS, and other spectroscopic techniques were used, especially in laboratory experiments utilizing rotating frames. In neutral cadmium sulfide, EP and methylephedrine form a 1:1 complex, which is characterized by the presence of benzene rings in the cavity, with side chains pointing to the wide edges. Instead, many complexes are formed in HDAS, typically characterized by inverted benzene rings in cavities and side chains pointing to the narrow sides. The complex geometry can be stabilized by ion-ion interactions between the positively charged nitrogen atoms of EP derivatives and the negatively charged HDAS. In addition, ligands can bind to HDAS and other complex chemometrics.

The CE technique was applied for determining caffeine, EP and PEP in foods [95]. The samples were extracted with 0.2 M hydrochloric acid prior to CE analysis and were analysed with a background electrolyte. At pH 2.5 and 7.6, each Cd molecule (sulfate 7-11 group) contained 7.5% H_2SO_4-cyclodextrin. The pH of EP and PEP was 2.5, the anode was on the capillary side, the pH of caffeine was 7.6, and the polarity pattern of electrophoresis was normal. The EOF was reversed by adding triethanolamine to a buffer with a pH of 2.5, thus accelerating the separation of EP from pseudoephedrine. Table 3 shows the reports of the CE-NMRS for EP/PEP determination.

Table 3. Recently developed CE-NMRS methods for EP/PEP determination.

Assistive technology	Year	Reference
α- and β-CD and heptakis(2,3-di-*O*-acetyl-6-*O*-sulfo)-β-CD (HDAS-β-CD) for chiral recognition	2011	[96]
Sulfated β- CD derivatives for chiral recognition	2012	[97]
Four β-CD derivatives for chiral recognition	2012	[98]
Sulfated β- CD derivatives for chiral recognition	2015	[99]

5. CE-MASS SPECTROMETRY (MS) DETECTION

Matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry and nuclear magnetic resonance spectroscopy have been used to describe the properties of two different kinds of sulfuric acid rings and alcohols [100]. The results showed that the Cd detected had a wide degree of sulfation. The average sulfate content of each cadmium-containing molecule was between 6 and 8. In addition, half of the sugars that are detected with Cd were at the 2nd and 6th or 3rd positions of sulfuric acid and not only at the 3rd position. Enantiomeric separation of EP by CZE requires the use of Cd detection as a chiral selector, indicating that Cd-containing molecules have similar chiral selectivity and can be used to separate EP enantiomers. One of these molecules was used to evaluate the enantiomeric purity of (1R, 2S)-EP (or (-)-EP) separated via CE. Quantitative analysis was performed by comparing the corrected peak area of the small enantiomers with that of (-)-ephedrine. A similar work has been used for separating and determining the PE and PEP by the assistance of field-amplified sample injection (FASI) [101]. An approximate 1,000-fold enhancement in sensitivity was achieved with FASI without any loss of separation efficiency. Under optimized conditions, a baseline separation between the two analytes was achieved in a short time. The detection limits of PE and PEP were 0.7 and 0.6 μg/L, respectively. No expensive instruments or compound labelling were required, and the detection limits for PE and PEP obtained by the proposed method were equivalent to those obtained by LIF, LC-MS and GC-MS-CE. The procedure was tested for determining two alkaloids in *Ephedra* herbs were successfully calculated. Table 4 shows the reports utilizing CE-MS methods for EP/PEP determination.

Table 4. Recently developed CE-MS methods for EP/PEP determination.

Assistive technology	Year	Reference
β-CD modified capillary electrophoresis	2003	[102]
Also assisted by UV	2003	[103]
Injection-electrospray ionization-high field asymmetric waveform ion mobility spectrometry	2003	[104]
Direct ionization	2016	[105]
Diode-array detection	2004	[106]

6. PERFORMANCE AND CONCLUSION

Due to the small sample and electrolyte requirement, short analytical time, high performance, ease of operation and automation compared to those of conventional gel electrophoresis, CE is a very attractive separation process. CE is also a versatile method of separation because, due to the different modes that can be used, it can be used for a wide range of analytes. The complexity of test matrices, however, contributes to immense high-resolution needs. The main classical strategies that induce modification of peak efficiency, selectivity and therefore resolution can be applied in this context. Table 5 shows the performance of CE-based methods for PE and PEP detection.

Table 5. Determination of the performance of CE-based methods for PE and PEP detection.

PE (linear detection range)	PE (limit of detection)	PEP (linear detection range)	PEP (limit of detection)	Reference
0.31 to 76.43 mg/g	-	0.049 to 9.23 mg/g	-	[107]
0.7–140 µM	0.16 µM	0.7–140 µM	0.17 µM	[108]
20–5000 ng/mL	3 ng/mL	20–5000 ng/mL	5 ng/ml	[109]
0.20 to 0.00096 µg/mL	-	0.12 to 0.0011 µg/mL	-	[110]
50–1500 µg/mL	2.65 µg/mL	50–1500 µg/mL	2.92 µg/mL	[111]
50-1000 µg/mL	-	50-1000 µg/mL	-	[112]
-	0.7 µg/L	-	0.6 µg/L,	[113]
0.15-101.0 µg/mL	65 ng/mL	-	-	[114]
1.23–19.60 mg/L	0.014 mg/L	1.23–19.60 mg/L	0.011 mg/L	[115]

This review highlights the use of CE as a PE/PEP detection technique. The sensitivity achieved, the relatively simple instrumentation and the possibility of miniaturization make this technique particularly suitable as an analysis system for PE/PEP. In recent years, instrumental advances have slowly been replaced by contributions to the design of analytical applications using nanotechnology and new materials, reagents and solvents, offering a low detection limit, excellent selectivity and the possibility of multi-analyte determination in complex matrices. Important applications have been documented in this review, especially in the biomedical and pharmaceutical fields.

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