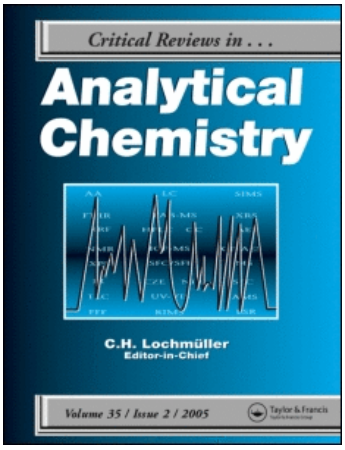

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A Review on the Hyphenation of Solid Phase Microextraction with Capillary Electrophoresis and Mass Spectrometry

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Hyphenation of analytical techniques is a promising trend due to their wide applicability. This article explains the hyphenation of solid phase micro-extraction to capillary electrophoresis. Different modes of solid phase microextraction (SPME) are reported to increase sensitivity of the methods. Various advantages and problems that occurred during the hyphenation are highlighted. Besides using this as a tool of separation, solid phase microextraction capillary electrophoresis (SPME-CE) is considered with special emphasis on applications utilizing its hyphenation to mass spectrometry. As SPME offers a high preconcentration factor, its hyphenation with capillary electrophoresis mass spectrometry (CE-MS) is very promising.

Keywords Solid phase microextraction, capillary electrophoresis, mass spectrometry, hyphenation techniques

INTRODUCTION

Capillary electrophoresis (CE) is a versatile analytical technique used to determine all types of analytes ranging from small inorganic anions to large molecules, including different food contaminants (1–3). CE was described in 1930 by Arne Tiselius (4), where he used it for the separation of proteins in an open quartz U-tube (5, 6). This method was optimized by Hjertén (7) in 1967 to reduce thermal effects. Further progress was made by the introduction of polyacrylamide-gel-filled glass tubes together with detection by staining and audioradiography for analysis of small amounts of proteins (8, 9). In the late 1970s (10) and early 1980s (11, 12), free zone electrophoresis was rediscovered. Mikkers et al. (10) used Teflon^{TM} tubing with 200 mm ID to reduce heat convection problems. However, due to the poor detector sensitivity, large injection volumes had to be applied, resulting in sample overloading leading to low efficiency of separation. Efficient electrophoretic separation was demonstrated by Jorgenson and Lukacs (11, 12) by using capillaries with an ID of 100 mm. However, uncharged substances were not separated. This was modified in 1984 by Terabe et al. (13), who added surfactants to the electrophoretic buffer and developed micellar electrokinetic chromatography (MEKC), which allows separation of both neutral and charged analytes. Variation in capillary design and development of different operation modes, such as capillary isoelectric focusing (CIEF) (14), gel-filled capillaries (CGE (15)) and gel-coated capillaries (e.g. polyimide coating) (16) led to high-resolution separation (Fig. 1). The introduction of commercial CE instruments in late 1988 further fueled new developments and applications. CE in capillaries with nanometer ID (e.g., 770 nm) requires very sensitive and low-volume detectors, which allow the analysis of extremely small samples, such as the contents of single cells (17). Historically, CE gained the technical development of different separation modes in combination with various detection methods. Despite its great resolution power, the popularity of CE is hampered by its sensitivity, which is inherent in the small path length (path length is equal to ID) when on-line absorbance detectors are used. Attempts have been made to alleviate this limitation by using commercially available bubble cell capillaries (18, 19) and Z-shape high sensitivity optical cells, giving rise to four- to five-fold improvement in sensitivity. For fluorescent compounds, sensitivity could also be significantly improved with UV/visible laser-induced fluorescence detection (20), but laser stability (e.g., He Cd laser) and the exorbitant cost of UV lasers still represents a major hurdle. If non-fluorescent compounds are of interest, they must undergo tedious and complicated derivatization procedures that are difficult to perform in small volumes or at low concentrations (20).

Analytical capability for the extraction and pre-concentration of trace organic contaminants from aqueous, gaseous and solid samples has become extremely important with increasing environmental and health awareness. Various types of extraction

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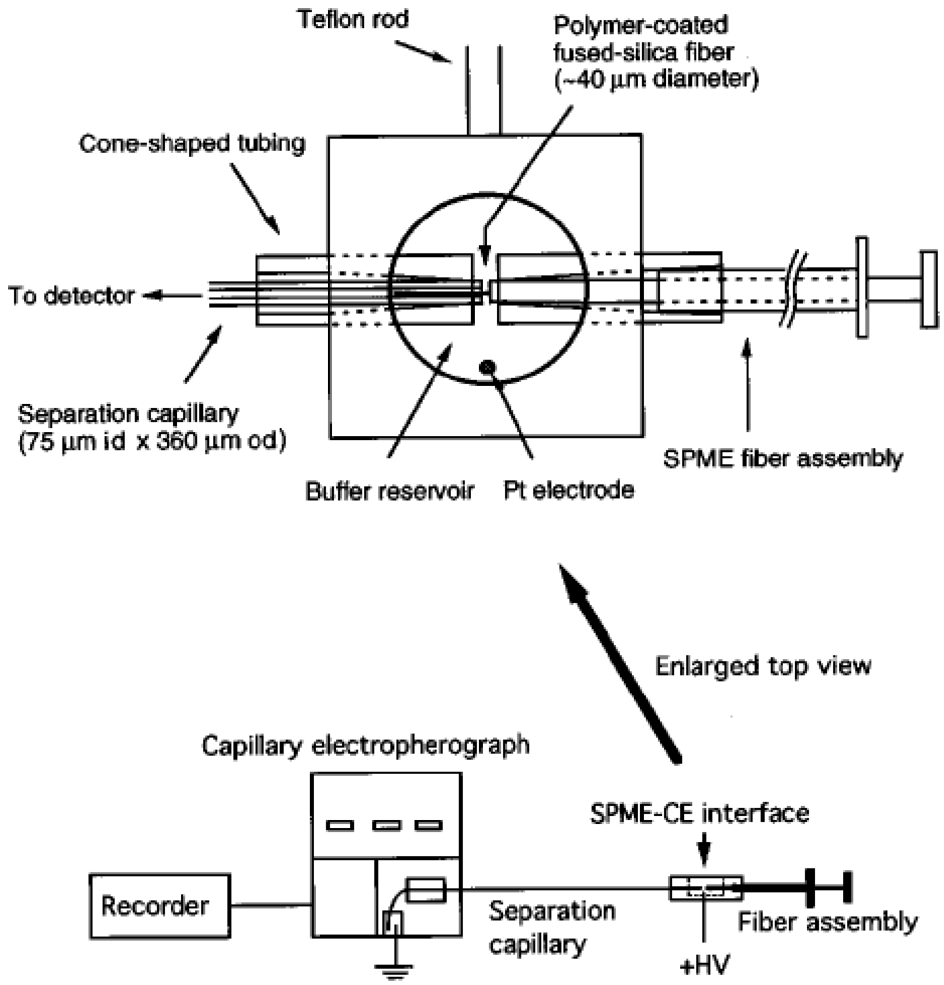

FIG. 1. Schematic of the SPME-CE system. Figure is not to scale (reproduced with permission from (27)).

methods like soxhlet extraction, liquid-liquid extraction, accelerated solvent extraction, microwave-assisted solvent extraction, solid-phase extraction, supercritical fluid extraction, purge and trap extraction, and other methods are traditionally used for this purpose. Some of these methods are time consuming and/or expensive while others employ a large volume of hazardous organic solvents.

Solid phase micro-extraction (SPME) developed by Pawliszyn et al. in 1989 effectively overcame these difficulties (21–23). SPME was developed to address the need for a fast, solvent-free and field compatible sample preparation method (23–25). SPME is a universal sampling and extraction method which can be used to sample air, water, and the headspace above solids. Once sampling is complete, the SPME fiber containing the analytes of interest can be directly introduced into analytical instruments. SPME methods are still in the initial stages of the development, but the results are very promising. Initial interest in SPME has been driven by the promise of a solvent-free environment, fast extraction, convenient automation and easy hyphenation with analytical instruments. So far, methods have been developed primarily for the quantitative analysis of the target analytes in the relatively clean matrices. The capability for the direct field measurements and the investigation of the multi-phase equilibrium processes should follow the development of technology. So far application work has been devoted primarily to environmental analysis, with a focus on aqueous matrices. However, application to air, sludge and soil have also been developed, so that better approaches are emerging for the analysis of all types of matrices, including gases, liquids and solids. The range of analytes that can be analyzed by SPME includes volatile, semi-volatile and even non-volatile organic and inorganic species. Results on priority pollutants indicate that SPME can meet method requirements defined by the environmental protection agency, as performance is similar to the more traditional techniques of static headspace analysis, purge-and-trap, liquid-liquid extraction and solid-phase extraction. SPME can be tuned to a given application by the choice of the appropriate coating or device design. SPME has been most broadly accepted by the food industry, particularly in the flavor and fragrance areas. SPME simplifies not only the monitoring of

freshness and purity of such products, but also characterization of the optimum time of harvest. In clinical applications, SPME has been used to monitor drug residues in blood, urine and other body fluids. In forensic applications, SPME has been used to monitor traces of accelerates in fire debris.

SPME has several important advantages compared to the traditional sample preparation techniques:

- It is a rapid, simple, solvent-free and sensitive method for the extraction of analytes,
- It is a simple and effective adsorption/desorption technique,
- It is compatible with analyte separation and detection by HPLC–UV system,
- It provides linear results for wide concentration of analytes,
- It has small size, which is convenient for designing portable devices for field sampling, and
- It gives highly consistent, quantifiable results from very low concentration of analytes.

Design of SPME

There are two different techniques for the SPME method: fiber SPME and in-tube SPME. Fiber SPME is a modified syringe-like instrument, which consists of a fiber holder and fiber assembly with built-in fiber inside the needle. The fused silica fiber is coated with a relatively thin film of several polymeric phases. Due to its small physical diameter, cylindrical geometry and stability at higher temperatures, it can be incorporated into a syringe-like holder. The SPME holder provides protection to fiber and allows piercing of the rubber septum of the GC injector. The fused silica fiber is retracted within the needle of the SPME holder when it is not in use. During operation, the silica fiber is exposed to the sample in its matrix. In-tube SPME (26) is an automated version of SPME that can be easily coupled to a conventional HPLC autosampler for on-line sample preparation, separation and quantitation. It has been termed "in-tube" SPME because the extraction phase is coated inside a section of fused-silica tubing rather than coated on the surface of a fused-silica rod as in the conventional syringe-like SPME device. The new in-tube SPME technique has been demonstrated as a very efficient extraction method for the analysis of polar and thermally labile analytes.

APPARATUS FOR SPME-CE

The SPME-CE coupling is difficult to perform, as it is on-line to CE, compared with LC. The main problem for on-line SPME-CE coupling is related to the low injection volume (a few nanoliters) typically used in CE. This low volume makes it difficult to develop an interface with a zero-dead-volume connection. In order to avoid this problem, Wang and Pawliszyn (27) propose the use of laboratory-made 40-mm o.d. fibers, which can be inserted directly into a separation capillary of 75 mm i.d. Although this interface greatly facilitates the direct insertion of SPME fiber into the capillary end, permitting the complete desorption of analytes inside the capillary, its implementation is limited by the use of laboratory-made special fibers and by the use of an interface that introduces the fiber inside the capillary with high precision. The SPME-CE system proposed by Wang and Pawliszyn (27) is shown in Fig. 1. This system consists of three parts: SPME fiber assembly, interface, and CE system. Custom-made SPME fibers are used in this study. SPME-CE interface is made of a Teflon block and some space is provided to accommodate the buffer solution, SPME fiber and the capillary tubing. Two tunnels with a diameter of 2.0 mm each are drilled through opposing sides of the buffer reservoir, ensuring that the two tunnels were precisely aligned. An Inner-Lok^{TM}capillary connector is cut into two halves and two pieces of inner conical tubes are created. The cut face of one conical tube is carefully polished until a 360 μm OD. capillary could barely extrude from it. This piece of conical tube is used as a CE capillary guide in the interface. The second conical tube is prepared from half of a different Inner-Lok connector. The two conical guide tubes (with 2.0 mm OD) are pressed into the two tunnels, respectively, from both sides of the interface block until a $\sim$1 mm gap was left between them in the center of the buffer reservoir. The alignment is checked by inserting a short piece of 245 mm OD capillary through the guide tubes. Epoxy glue was applied to further secure the guide tubes in position. A piece of 0.5 mm diameter platinum wire is sealed to the bottom of the buffer reservoir to serve as an anode for CE. The interface block is clamped to a stand during the experiment. To facilitate fiber insertion, the inlet end of the CE capillary is etched to a conical shape by HF before use, following the procedure described by Sloss and Ewing (28). The detection end of the capillary is connected to a glass bottle containing helium flowing through the capillary, and the inlet end of the capillary is etched with 50% aqueous HF solution for 20 minutes. After etching, the capillary tip is placed in a 1 M sodium carbonate solution to neutralize the acid, and finally washed with deionized water. CE separations are carried out on a capillary electropherograph. The separation capillary is 75 mm ID, 360 mm OD and 40 cm total length (32 cm to the detector). Each new capillary is pretreated with 0.1 M NaOH for 10 minutes. Before each run, the capillary is rinsed with buffer for 3 minutes under pressure. Detection is carried out at a selected wavelength. Electropherograms are recorded using either a strip-chart recorder or an integrator.

HYPHENATION OF SPME WITH CE-MS

In principle, SPME procedures should be compatible and easy to couple with CE, which can be considered as a micro-separation technique. However, such a coupling is difficult to perform on-line to CE, due to the low injection volume (a few nanoliters) used in CE. This low volume makes it difficult to develop an interface with a zero-dead-volume connection. A new on-line interface that permits the use of commercial SPME fibers is developed by Santos et al. (29). The system consists of a simple SPME-CE interface made of a methacrylate material.

The interface, which can be considered as a modification of a vertical split-flow interface, has an additional channel closed with a septum that permits the introduction of the fiber in the interface, right at the end of the capillary and the electrode (Fig. 2). In order to couple the interface to the commercial capillary electrophoresis electron spray ionization mass spectrometry (CE-ESI-MS) system, it was necessary to perform a slight modification in the hardware of the instrument, as the instrument needs to detect a vial in the sample position that is lifted by an elevator to immerse the capillary end together with the

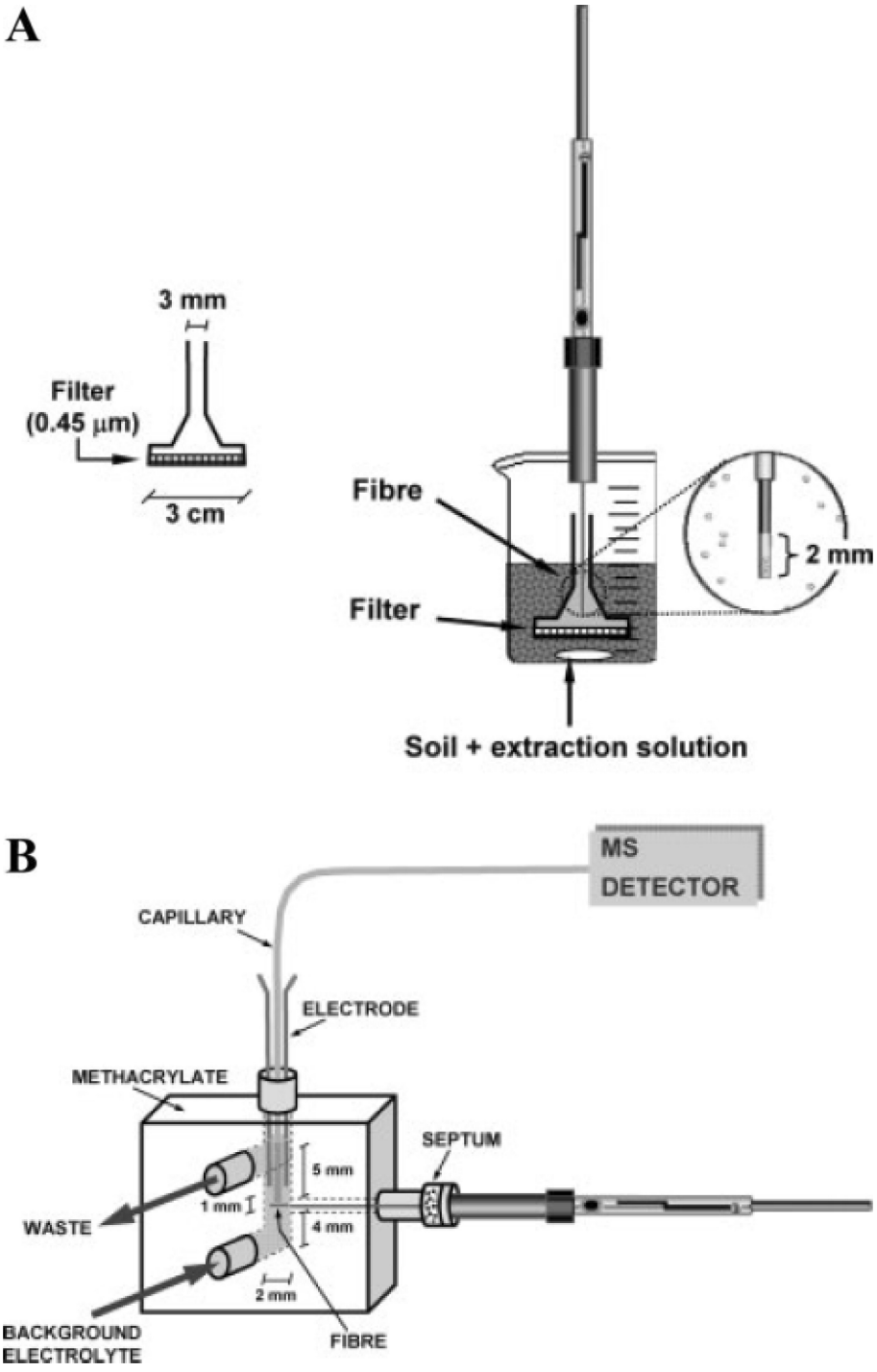

FIG. 2. (A) Filter arrangement for filtration and analyte extractionby SPME. (B) Interface for SPME-CE-MS coupling (reproduced with permission from (29)).

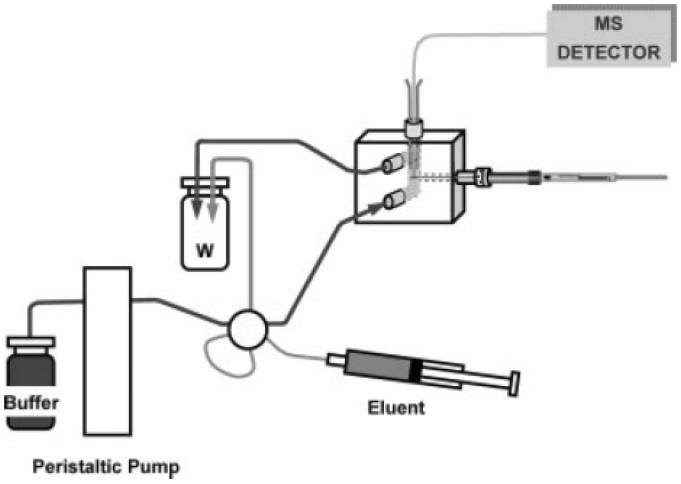

FIG. 3. Manifold use of the on-line coupling of SPME to CE-MS (reproduced with permission from (29)).

surrounding electrode into the inlet vial. To avoid the collision of the elevator with the interface, the cabling of the inlet and outlet elevators must be interchanged following the recommendations (30). As a consequence, Chem Station detects a vial in the inlet position, which is in fact located at the other position. Thus, the collision of the elevator with the flow CE interface is avoided and a high voltage can be applied to the CE-ESI-MS system. Finally, the flow system described in Fig. 3 was connected to the interface. As can be seen, the flow system consists of a stream with an electrophoretic separation buffer and an injection valve that permits the introduction of an acetonitrile plug in the stream to elute the analytes.

APPLICATIONS

In recent years, SPME combined with CE has been used for the separation and determination of pesticides, ephedrine derivatives, polycyclic aromatic hydrocarbons, phenols, barbiturates, amphetamine derivatives, proteins, iodophenols, drugs and enantiomers, etc.

SPME-CE with UV Detection

Poor sensitivity of capillary electrophoresis ultraviolet (CE-UV) precluded the direct use of this technique for the direct analysis, obtaining LODs above their MRL values. On-line CE pre-concentration protocols combined with SPME could provide a simple (and inexpensive) methodology to overcome the poor sensitivity of CE-UV. Moreover, this combined strategy can be applied to a broad number of compounds. Thus, to improve the sensitivity as much as possible for the compounds of interest, different on-line pre-concentration methods using normal and reverse polarity can be investigated in order to combine them

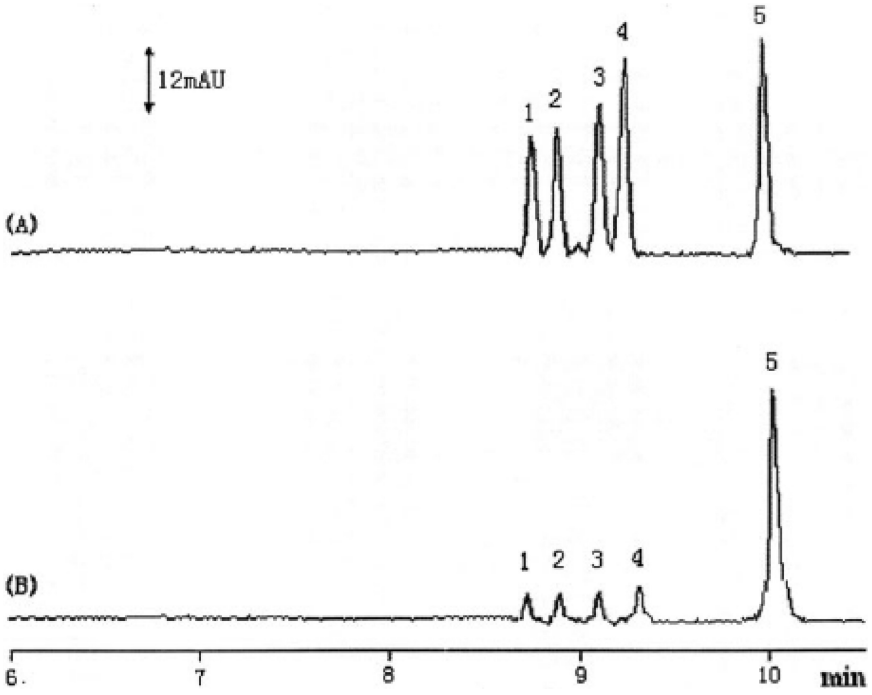

FIG. 4. Electropherograms of the amphetamine standard samples obtained by (A) in-tube SPME-CE and (B) direct CE analysis. Peaks: (1) Amphetamine, (2) Methamphetamine, (3) 3,4-methylenedioxyamphetamine, (4) 3,4-methylenedioxymethylamphetamine, (5) berberine. Amphetamine standard sample was 0.5 mg/L, berberine (IS) was added to the eluate (A) after SPME or (B) directly in the standard sample at 5 mg/L. In-tube SPME conditions: flow rate, 0.04 mL/min; extraction time, 10 min. Electrokinetic injections, 10 kV, 10 s.

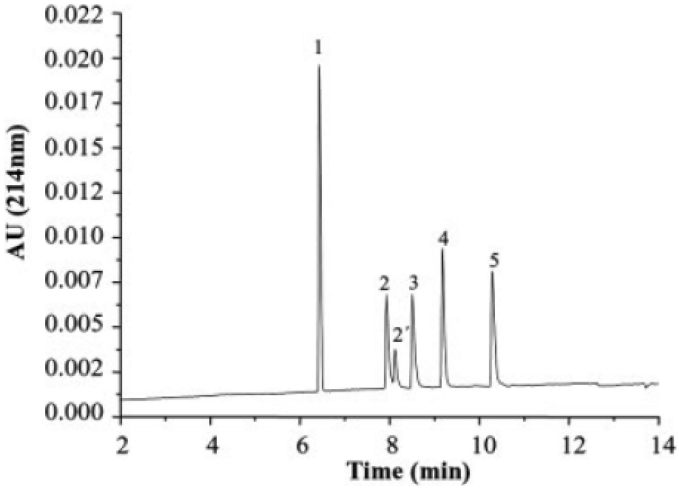

FIG. 5. Electropherogram of the separation of the selected pesticides. Buffer, 0.4 M acetic acid, pH 4; total length of the capillary, 57 cm (50 cm effective length); voltage, 25 kV; temperature, 257°C; UV detection at 214 nm; hydrodynamic injection at the anode for 12 seconds at 0.5 psi; sample, 25 mg/mL of (1) cyromazine; 2 (2, 2′) pyrifenox, Z and E isomers; (3) pirimicarb; (4) cyprodinil; (5) pyrimethanil in methanol.

with SPME and CE-UV. Borges et al. describe the combined use of SPME and CE-ultra violet (SPME-CE-UV) for the investigation of pesticides in foods (31). Li and Weber mentioned a method for the determination of barbiturates by SPME-CE-UV (32). Fang et al. (33) developed a sensitive method for the determination of ephedrine derivatives, using headspace SPME, with a novel fiber followed by CE. Nguyen et al. described a method for the separation and determination of polycyclic aromatic hydrocarbons by SPME coupled with cyclodextrin-modified CE-UV detection (34). Wang and Pawliszyn described an on-column interface for coupling SPME sampling technique with CE-UV for the analysis of the priority pollutant phenols (27). Wei et al. (35) proposed a method based on in-tube SPME with capillary zone electrophoresis (CZE) and it was used for simultaneous determination of four amphetamines in urine (Fig. 4).

SPME-CE with Mass Spectrometry

CE with MS detection overcomes the poor sensitivity and selectivity of on column UV detection. Rodriguez et al. described an off-line SPME method coupled with CE-MS for the simultaneous determination of five acidic pesticides (36). Borges et al. presented a highly sensitive procedure for the detection of multiple pesticides at trace level in foods by combining SPME with CE-MS (Fig. 5) (37). Tong et al. developed a method for identification of proteins in complexes by SPME coupling with CE-tanden mass spectrometry (38). Kannamkumarath et al. described a fast speciation analysis of iodophenol compounds in river waters by CE-inductively coupled plasma-MS with off-line SPME (39). A new interface for the on-line coupling of a fiber for SPME with a CE system with an electrospray interface for MS detector was developed by Santos et al. and was tested for the analysis of tetracycline antibiotic residues in soils (Fig. 6) (29).

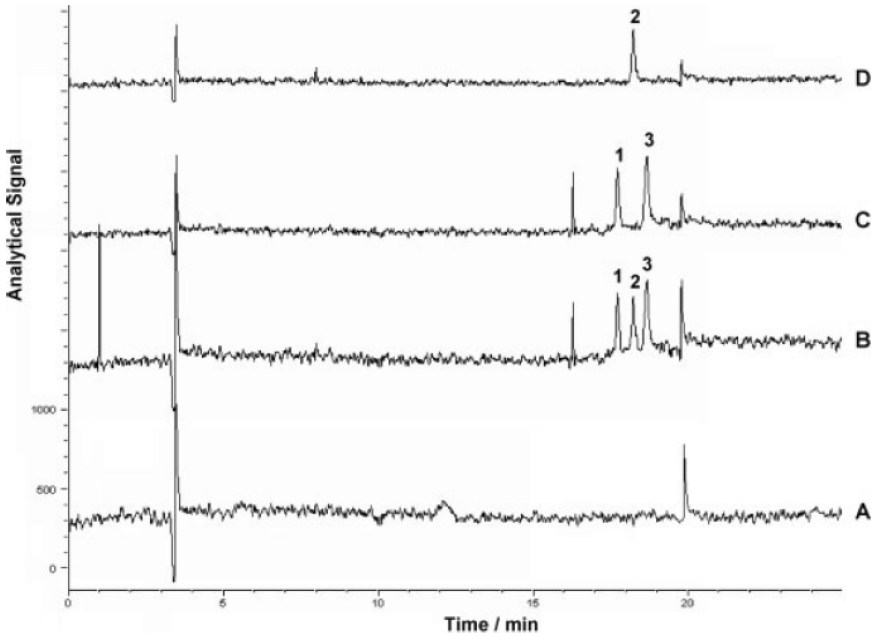

FIG. 6. Electropherogram of a soil sample: (A) blank sample, (B) spiked with 12 mg/kg. (C) Extracted ion electropherogram at m/z 445 and (D) extracted ion electropherogram at m/z 462. Peaks: (1) tetracycline, (2) oxytetracycline, and (3) doxycycline. Buffer, 30 mM acetic acid, pH 2; voltage, 15 kV; temperature, 20°C.

CONCLUSION

During recent years CE has drawn considerable attention for the analysis of various analytes and is considered to be a powerful tool as compared to GC and HPLC. Various advantages of CE are its high resolution, speed and small sample volume requirements, and the separated substances are directly transferred to the mass spectrometer. Hyphenation of SPME to CE-MS system adds the distinct advantages of a high pre-concentration factor and sensitivity. However, some minor disadvantages like type of the fiber, temperature, time, salt content, etc. exist, which may be minimized by using modified fibers or changing the modes of SPME. However, these disadvantages are over-weighed by the high pre-concentration factor and rapidness, etc. achieved during the sample preparation using SPME. Thus, the future of SPME-CE-MS is very promising and it needs to be widely explored.

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