CAPILLARY ELECTROMIGRATION METHODS: A REAL ALTERNATIVE IN FOOD SAFETY?

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1. Introduction

Food safety is related to the monitoring of hazards in food to protect the consumer health. The European Union (EU) has one of the highest food safety standards in the world due to the solid set of legislation and the mechanism created in 1979 to ensure the efficient communication when risks to public health are detected in the food chain, the Rapid Alert System for Food and Feed (RASFF) [1]. The European Food Safety Authority (EFSA) was also created in 2002 to assess the risk of hazards to human health when they are ingested via food. It provides high-quality scientific advice based on the expertise of scientists and the quality of its science-based information and methodologies, which are grounded in internationally recognized standards [2]. To guarantee safe and good-quality food and to meet international trade requirements, the development of selective, sensitive, and accurate analytical methods is mandatory for the control of a great number of chemical hazards [3].

In this sense, capillary electrophoresis (CE) has emerged in the last decades as a very well established separation technique, alternative or complementary to chromatography, applied in food analysis. Some of its advantages are the high separation efficiency, short analysis time, low sample and reagent consumption, reduced cost of capillaries and environmentally friendly, in the line of principles of Green Chemistry [4,5,6]. Its versatility, due to the different modes, and the combination with different detection systems, such as laser induced fluorescence (LIF) or mass spectrometry (MS), the applied sample treatments before analysis and the on-line or in-line preconcentration strategies have helped to overcome the main limitation attributed to CE that is its low sensitivity. This article discusses some applications of CE developed by our research group in the food safety field, mainly focused on contaminants such as mycotoxins [7], or residues derived from the use of veterinary drugs [8] and pesticides [9].

2. Sample treatments compatibles with CE

Solid-phase extraction (SPE) has been widely used in combination with CE for preconcentration and clean-up purposes to determine contaminants and residues. Sorbents based on non-polar interactions lead to low conductivity extracts, which is key to get high peak efficiencies in CE. Some CE-based methods developed in our group involved the use of hydrophilic-lipophilic balance (HLB) cartridges for the monitoring of sulfonamides in meat [10], sulfonylurea herbicides in water and grape samples [11] and neonicotinoid insecticides in waters [12]; or mixed cation exchange (MCX) cartridges for the extraction of 5-nitroimidazoles from milk [13]. In some cases, two steps-SPE procedures were needed to ensure a high preconcentration factor and a very clean extract. For example, combining mixed anion exchange (MAX) and HLB cartridges for the determination of quinolones in milk [14] or HLB and Alumina N cartridges for the extraction of β-lactams from meat [15] and milk [16]. Other SPE materials with highest selectivity, such as molecularly imprinted polymers (MIPs) or immunoaffinity columns (IACs) have been also used for the treatment of complex matrixes before CE analysis, providing cleaner sample extracts and simpler processes than usual SPE sorbents. We have applied MIP-SPE to the determination of quinolones in milk and pig kidney [17] or aminoglycosides in honey [18] and IACs in the monitoring of aflatoxins in rice [19].

Also, improved or miniaturized liquid-liquid extraction procedures such as salting-out assisted liquid-liquid extraction (SALLE) or dispersive liquid-liquid microextraction (DLLME) have been satisfactorily applied. Recently we developed a SALLE procedure as the first analytical proposal based on CE-UV for the control of the insecticide fipronil in eggs [20]. In 2017 fipronil was involved in a European health alert due to its presence in fresh hen eggs because of an illicit use in poultry farms. We determined fipronil and the major metabolites, fipronil-sulfone and fipronil-sulfide by micellar electrokinetic chromatography (MEKC), using 50 mM ammonium perfluorooctanoate (APFO) pH 9.0 with 10% (v/v) methanol (MeOH) as background electrolyte (BGE). Acetonitrile (MeCN) was used as extraction solvent in presence of ammonium sulphate, achieving recoveries higher than 83% and limits of detections (LODs) of 90 µg/kg for fipronil.

DLLME was applied for the extraction of the mycotoxin patulin in juice samples, using a mixture of 2-propanol and chloroform as dispersive and extraction solvent, respectively, achieving a preconcentration factor of 10 [21]. MEKC-UV detection was used for its separation from 5-hydroxymethylfurfural (HMF), its main analytical interference, using a BGE consisting of 35 mmol/L sodium tetraborate buffer (pH 9.0), 65 mmol/L sodium dodecyl sulfate (SDS) and 5% (v/v) MeCN. A LOD of 0.6 µg/L and recoveries higher than 75% were obtained. DLLME was also applied in the determination of carbamate residues in juices by MEKC-UV [22] or combined with a capillary zone electrophoresis (CZE)-MS method as clean up procedure for the determination

of the benzimidazoles (anthelmintic agents) in chicken and pork meat [23]. The deproteinization of samples and extraction was carried out with MeCN, adding $MgSO_4$ and NaCl as salting-out agents. The organic layer (MeCN, used as dispersant in DLLME) containing the benzimidazoles was mixed with the extractant (chloroform) and both were injected in water, resulting in a cloudy solution. The final extract was compatible with CE analysis, obtaining recoveries higher than 70%.

Recently we have applied a QuEChERS (quick, easy, cheap, effective, rugged, and safe) procedure to the determination of neonicotinoids and boscalid in pollen and honeybee samples, which show toxic effects to beneficial and non-target insects such as pollinators. To avoid the sample dilution associated to this procedure, which compromise signal sensitivity in CE, a scaled-down QuEChERS was developed. It involved a lower organic solvent consumption and the use of Z-Sep$^+$ as dispersive sorbent in the clean-up step [24].

3. On-line preconcentration strategies

Another option to improve sensitivity in CE is the application of on-line preconcentration approaches or stacking techniques, in which the analytes are concentrated inside the capillary [25,26]. Stacking is based on electrophoretic principles and requires samples with lower conductivity than the BGE. Analytes get stacked at the boundary between these two zones as they migrate faster in the sample zone than in the BGE. The simplest one is named normal stacking mode (NSM) and we applied it to the determination of benzimidazoles in meat by CZE-MS/MS [23]. Separation was carried out using 500 mM formic acid (pH 2.2) as BGE, at 25 kV and 25°C. To improve sensitivity a mixture of 30:70 MeCN/water was used as injection solvent at 50 mbar for 75 s. Sensitivity enhancement factors from 74 to 317, were obtained (Figure 1).

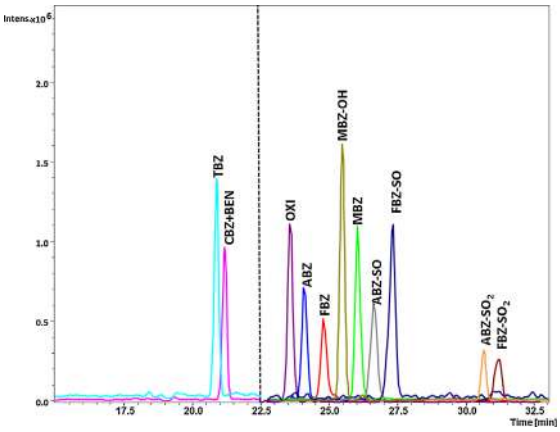

Figure 1. Electropherogram of benzimidazoles in meat by CZE-MS/MS (25 µg/kg (TBZ, CBZ + BEN), 50 µg/kg (OXI, ABZ, FBZ, MBZ, FBZ-SO, ABZ- SO_2) and 100 µg/kg (MBZ-OH, ABZ-SO, FBZ-SO_2). With permission from [23]. Copyright (2017) Elsevier.

Other stacking modes are field-amplified sample injection (FASI) or large-volume sample stacking (LVSS), which involve electrokinetic injection or hydrodynamic injection, respectively. LVSS implies the introduction of a high volume of sample into the capillary. In this case, the sample matrix must be pumped out from the capillary in order to preserve separation efficiency. Pumping is carried out with external pressure or with the electroosmotic flow (EOF). The direction of pumping must be always opposite to that of the electrophoretic movement of charged solutes, and its velocity lower than the electrophoretic velocity of the charged solutes. Using this strategy, only positive or negative solutes can be effectively concentrated at one time. Concentration factors of more than 100 are reported for LVSS, improving LODs from two orders of magnitude. Two modalities exist in LVSS, with or without change of polarity. For the case of anions, LVSS with polarity switching is a mode that permits to control the EOF in CZE separations, involving high EOF conditions to carry the separate analytes to the detector. This is done by introducing hydrodynamically a large plug of low conductivity sample into the capillary and applying negative voltage at the injection end. The large solvent plug is then electroosmotically pushed out of the capillary while the negative species stack-up at the boundary between the sample zone and the BGE. Once the main part of the low-conductivity zone has been pushed out of the capillary, the positive voltage is applied to carry out the separation. We have used this strategy in a CZE-UV method for the monitoring of sulfonylurea herbicides in grapes [11], β-lactams in milk [16] or sulfonamides in meat [27]. Although satisfactory improvements in sensitivity can be achieved, there are some points to consider. For example, LVSS is not compatible with MS and difficult to automate, but is a good option for UV detection.

Sweeping is another preconcentration strategy applied in MEKC mode, in which the analytes are focused into a narrow band within the capillary, thereby increasing the sample volume that can be injected without any loss of efficiency. It is based on the interactions between an additive (i.e., a pseudo-stationary phase or micellar media) in the separation buffer and the sample in a matrix that is free of additive. It involves the accumulation of charged and neutral analytes by the pseudo-stationary phase that penetrates the sample zone and ‘‘sweeps’’ the analytes, producing a focusing effect. We applied this mode to the determination of aflatoxins in rice by MEKC-LIF, using 20 mM borate buffer with 30 mM SDS (pH 8.5) and 7% MeCN and the same separation buffer without SDS as solvent of the injected sample [19]. The sample injection time was increased from 10 to 200 s, achieving a preconcentration factor of 4. Satisfactory results in terms of sensitivity were also obtained using this procedure in the determination of carbamate pesticides in juices by MEKC-UV [22] or in the monitoring of neonicotinoids and boscalid in pollen and honeybee [24].

We have also explored another preconcentration approach named cation selective exhaustive injection

coupled to sweeping MEKC (CSEI-sweeping-MEKC). It combines two on-line preconcentration techniques, (FASI) and sweeping. Selectivity is also enhanced since electrokinetic injection is performed and only positively charged species enter the capillary. This strategy was satisfactorily applied to the determination of nitroimidazole residues in eggs, with LODs in the range of 2.1–5.0 µg/kg [28].

4. In-line preconcentration strategies

A different approach for preconcentration in CE consists of in-line coupled SPE-CE, which is based on chromatographic principles [29]. A small amount of extraction sorbent is placed in the inlet of the separation capillary. Then, the usual steps in SPE (conditioning, loading, washing and elution) are carried out. Microliters of sample are typically injected, which significantly improves sensitivity. Different designs have been developed for the construction of an analyte concentrator (AC). In our group, we selected those based on packed beds without frits, using sorbent particles in the AC with higher diameters than the internal diameter of the capillary. This design avoids the problems related with the frits, such as disturbance of the EOF and, in some cases, bubble formation leading to band broadening, current disruptions, and migration time irreproducibility (Figure 2).

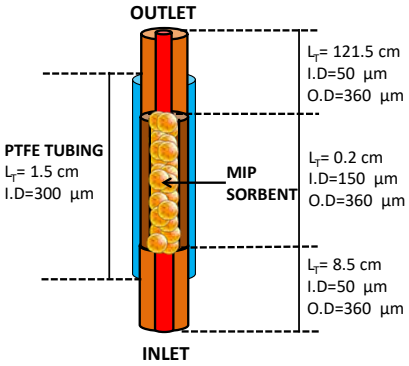

Figure 2. Analyte concentrator used in the in-line MISPE–CE–MS/MS method applied to the determination of quinolones in milk samples [31].

This strategy was used for the determination of quinolone antibiotics in chicken meat and milk by CZE-MS, using a BGE of 50 mM ammonium acetate at pH 9.1, being separated as anions but detected as cations by ESI+. In these cases, the analyte concentrators were homemade with typical sorbents used in off-line SPE for the analysis of quinolones, such as mixed-mode cation exchange (MCX) for their determination in meat [30] or specifically molecularly imprinted polymers (MIPs) for their determination in milk [31]. The MIP material provided greater selectivity but, when used as an in-line AC, sample loading had to be done at lower flows than for MCX to ensure that the specific interactions between the sorbent and the analytes occurred. As a result, only 22 µL of sample was injected during a 15-min injection in contrast to 135 µL that were injected when using the MCX-based AC. LODs ranged from 40-140 ng/kg for the MCX AC, which was 10 times lower than those obtained using MIPs (1.0-1.4 µg/kg). It should be noted that the main difficulty of using ACs is to make the SPE procedure compatible with the optimal conditions for the electrophoretic separation.

5. Capillary electrochromatography

Capillary electrochromatography (CEC) is a mode that combines the advantages of LC and CE, been a hybrid separation technique which shows high efficiency and selectivity. In a CEC separation, the mobile phase is propelled through the stationary phase into the capillary by the EOF generated as a result of applying an electric field instead of a hydraulic pressure. The plug-like profile of EOF involves much higher CEC column efficiency than that reached by a pressure-induced flow at the same linear velocity in the same column, resulting in a peak resolution improvement. We have proposed CEC for the determination of 5-nitroimidazoles in milk (Figure 3), applying SALLE as sample treatment and using packed laboratory-made columns [32]. The capillary columns were produced by carrying out a high-pressure packing procedure using acetone as the driving solvent and uncapped C18 silica particles (5 µm particle size) as packing material. The frits in the column were produced by sintering the stationary phase, heating the packed material for 20 s with a nichrome ribbon connected to a power supply. Lab-made C18 silica packed capillaries (40 cmx50 µm i.d.) were also employed for the analysis of benzimidazole residues in waters [33].

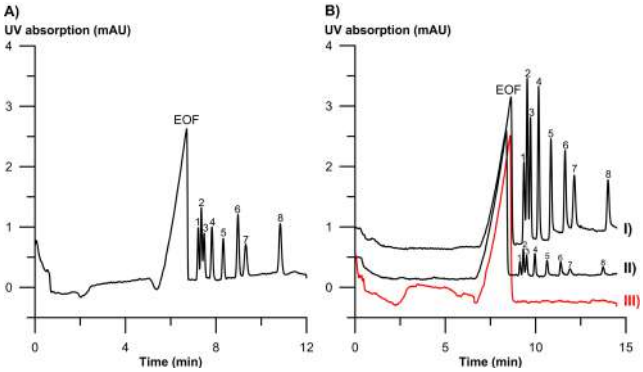

Figure 3. CEC-UV analysis of A) 5-nitroimidazole standard solution (1.2 µg/L, except carnidazole, 2.4 µg/L) and B) milk samples pretreated by a SALLE-SPE procedure and fortified at: I) 350 µg/L (carnidazole, 700 µg/L), II) 50 µg/L (carnidazole, 100 µg/L), and III) blank sample. 1, ronidazole; 2, metronidazole; 3, ternidazole; 4, secnidazole; 5, ornidazole; 6, dimetridazole; 7, carnidazole; 8, ipronidazole. With permission from [32]. Copyright (2015) Elsevier.

6. Laser induced fluorescence detection

Laser induced fluorescence (LIF) detection is a very sensitive and selective detection technique for CE. The powerful laser excitation source is focused in a precise way on the capillary detection window, so the quantum

yield is very high. Its limitation is due to the reduced availability of laser sources, with one specific wavelength. Since some quinolones show native fluorescence at low pH, LIF detection (325 nm He–Cd laser) was coupled with CZE for their determination in bovine raw milk and pig kidney samples [17]. A BGE consisting of 125 mM phosphoric acid solution at pH 2.8 with 36% MeOH was used. The method provided very low detection limits, ranging from 0.17 to 0.98 µg/kg for milk and 1.10 to 10.5 µg/kg for kidney. MEKC-LIF (325 nm) combined with sweeping was also evaluated for the determination of aflatoxins B1, B2, G1 and G2 in rice samples [19]. This method was very sensitive and avoided the post-column derivatisation required in the LC-fluorescence method.

7. Mass spectrometry detection

The use of tandem mass spectrometry (MS/MS) is considered the most convenient detection technique for the control of chemical hazards in food by CE, because it provides an adequate sensitivity, and unambiguous evidence for identification and quantification at trace levels. Efficient and robust interfaces for the hyphenation of CE with MS are now commercially available, contributing to further development and implementation of CE-MS applications [34].

In the case of polar compounds, CZE-MS is a very powerful alternative to LC-MS. A representative example is the determination of aminoglycoside residues. These antibiotics are highly polar compounds, and are poorly retained in reverse phase LC. Ion-pair chromatography is an alternative strategy for their determination, but requires the addition of an ion-pair reagent (mainly trifluoroacetic acid or heptafluorobutyric acid) in the mobile phase. These ion-pair reagents are rarely volatile acids and can seriously affect the performance of MS, causing ionization suppression of analytes and contamination of the ion source. Other option is the use of hydrophilic interaction chromatography (HILIC), which presents a major drawback related to the need to add salts to the mobile phase to improve resolution, which hinders the use of MS detectors. To overcome these limitations, we developed the first CZE-MS/MS method for the analysis of aminoglycosides in honey using an ion trap (IT) and a sheath-flow interface for CE-MS hyphenation [18]. The BGE consisted of ammonium formate buffer at pH 2.2 to avoid the analyte interactions with the silanol groups of capillary walls. Moreover, to improve the reproducibility of migration time, a pressure of 50 mbar was applied during the separation to counteract the absence of the EOF. Separation of nine compounds was achieved in less than 9 min, obtaining LODs between 0.4 and 28.5 µg/kg. A similar method was proposed for the monitoring of benzimidazole residues in meat samples [23].

Of special interest are those CE-based methods intended for the simultaneous analysis of multiclass antibiotics. As an example, we evaluated CZE-quadrupole-time-of-flight (Q-ToF)-MS for the determination of fifteen antibiotic residues (i.e., eight tetracyclines and seven quinolones) in milk samples, obtaining full scan and full MS/MS spectra for quantification/confirmation purposes in a single run. The method showed good linearity for all analytes and the relative standard deviations (RSDs) were below 13% in terms of peak area precision [35].

In general, CE-MS has traditionally been limited to the analysis of charged compounds by CZE mode. The analysis of neutral compounds by MEKC-MS presents several drawbacks, such as suppression of the analyte signal and contamination of the MS related to the use of non-volatile surfactants (e.g., SDS). To overcome this limitation, we checked the use of perfluorocarbon-based volatile surfactants such as APFO. The compatibility of APFO as the pseudo-stationary phase in MEKC-MS was demonstrated successfully in the determination of 25 carbamates in juices samples using an IT-MS [36]. The separation was carried out in approximately 35 min using a 100 mM APFO solution (pH 9.0) as running buffer. To improve the sensitivity of the method, a sweeping-based approach was applied in which sample solution consisted of 75 mmol/L APFO (pH 9.0). Vortex-assisted surfactant-enhanced emulsification liquid–liquid microextraction was applied as sample treatment, using a mixture of 100 mmol/L APFO (pH 9.0), acting as an emulsifier (530 µL), and chloroform as extraction solvent (1300 µL), achieving LOQs lower than 5 µg/kg. We have also proposed a method for the determination of neonicotinoids and boscalid in pollen and honeybee samples, using MEKC coupled with a new QqQ-MS detector, achieving higher sensitivity, with limits of quantification (LOQs) below 11.60 and 12.52 µg/kg, respectively. Two positive samples of pollen were found, containing imidacloprid and thiamethoxam. Imidacloprid was also found in a sample of honeybees.

Recently we have developed the first method based on CE for the determination of emerging mycotoxins, such as enniatins (ENNs) and beauvericin (BEA). Despite the absence of easily ionizable groups, the ionophoric character of these compounds makes them compatible with a non-aqueous CE (NACE) method coupled to Q-ToF-MS. Separation is achieved in 4 min using as BGE 40 mM ammonium acetate in 80:20 (v/v) MeCN-MeOH. Higher selectivity can be achieved when compared to LC due to the formation of exclusive CE adducts such as $[M+CH_3CH_2NH_3]^+$. The method was validated for wheat samples, obtaining LOQs between 5 and 10 µg/kg and recoveries higher than 87.3%, being possible to tentatively identify and confirm other untargeted ENNs [37].

8. Conclusions

A few years back, the use of CE as a reliable tool in food safety seemed promising although there were some doubts as well. However, whether CE could achieve the sensitivity required to be used in reference laboratories or the coupling CE-MS was going to be robust enough for

routine methods were unclear. Nowadays, important advances have been made and some questions have been revealed. From the results, we could conclude that CE could be complementary or even a real alternative to chromatographic methods for the monitoring of residues and contaminants in food, being particularly useful in those cases where chromatography has found some limitations such as the determination of highly polar or ionic compounds. In this regards, further developments based on CE could be expected in the future in this field.

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