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Determination of Four Residues of Fluoroquinolones with Similar Structure in Fish by Modified QuEChERS Protocol Coupled to Capillary Electrophoresis (CE) with End-Column Electrochemiluminescence (ECL)

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A new method was established for simultaneousyl determining ciprofloxacin (CIP), enrofloxacin (ENR), norfloxacin (NOR) and pefloxacin (PEF) in fish by capillary electrophoresis (CE) coupled with end-column electrochemiluminescence (ECL) with modified QuEChERS. The structural differences of 4 FQs are too small to separate them by conventional CE. However, their separation efficiency can be improved by adjusting the composition of separation buffer. The parameters about ECL analysis and CE separation were investigated in detail. The use of methanol and sodium sulfate in QuEChERS can improve the pretreatment effect of the sample. The optimum experimental conditions include analysis conditions (detection potential 1.20 V vs. Ag/AgCl, $Ru(bpy)_3^{2+}$ concentration 6 mmol/L, phosphate buffer solution concentration 40 mmol/L and pH 7.0 in ECL detection cell), separation conditions (separation voltage 13.0 kV, 17.5% cyclodextrin solution (v/v) as additive, phosphate buffer solution concentration 20 mmol/L and pH 5.0 in capillary), and sample conditions (injection time 7 s and injection voltage 12.0 kV). The limits of detection (3σ) of this method were 8.8×10^{-5} mg/mL for CIP, 3.5×10^{-6} mg/mL for ENR, 7.5×10^{-5} mg/mL for NOR and 2.7×10^{-6} mg/mL for PEF. The relative standard deviations (RSD) were less than 2.6% for ECL intensity and less than 2.3% for migration time. This method was successfully utilized to simultaneously determine CIP, ENR, NOR and PEF in fish.

Keywords: Fluoroquinolones; Residue; Fish; CE-ECL; QuEChERS

1. INTRODUCTION

Fluoroquinolones (FQs) are a kind of important synthetic antibiotics, which are widely used in the prevention and treatment of aquatic product diseases because of their broad antibacterial spectrum, strong bactericidal power and convenient use [1,2]. However, improper and excessive use of these

drugs will cause FQs residual pollution to aquatic products. Long term consumption of animal food containing FQs residues will lead to drug resistance of pathogenic bacteria and indirectly affect human health [3,4]. Therefore, it is very important to establish an efficient and sensitive method to detect FQs residues in fish.

Numerous methods have been employed to analyze FQs residues, such as LC-MS [5-10], fluorescence [11-15], electrophoresis [16-19], LC-UV [20-22], spectrophotometry [23] and chemiluminescence [24]. Capillary electrophoresis (CE) is a promising high-performance biochemical and medical separation method with short analysis time and less sample consumption. It has good separation ability for molecules with similar structure. Electrochemiluminescence (ECL) based on tris (2,2'-bipyridyl) ruthenium (II) (Ru $(bpy)_3^{2+}$) is an attractive analytical method [25-27] for organic amines owing to its high resolution, high sensitivity and high stability. CE separation couple with end-column ECL analysis (CE-ECL) have been widely studied and used to analyze various drugs [28–36], antibiotics [37], enzymes [38], alkaloids [39–41], amines [42], hormones [43] and pesticide residues [44,45] in different foods, pharmaceuticals, animals and plants. FQs contain tertiary amino group structure, and the molecular structure is similar. It is a good attempt to separate and analyze them with CE-ECL.

The matrix of fish is complex, and the residual FQs are mostly in trace level. Sample pretreatment technology has great influence on the sensitivity, efficiency and reliability of analytical methods. The QuEChERS (quick, easy, cheap, effective, rugged and safe) is an efficient pretreatment method based on dispersed solid phase extraction (SPE) [46], which integrates extraction and purification. It has become the standard pretreatment method of American Association of Analytical Chemists and European Standardization Committee. The QuEChERS method has many advantages, such as short pretreatment time, simple operation and less amount of organic solvents. However, the traditional QuEChERS method is mainly applied to substrates with more water content and less matrix interference, such as vegetables and fruits [47-49]. The modified QuEChERS methods are based on the specific improvement of complex substrates such as fish and poultry [50-53].

Among the FQs, ciprofloxacin (CIP), enrofloxacin (ENR), norfloxacin (NOR) and pefloxacin (PEF) have little difference in molecular structure (see figure 1) [54]. It is challenging to separate and analyze them. In this paper, the fish was treated with QuEChERS method, then CIP, ENR, NOR and PEF were separated and detected simultaneously by overall optimization of CE-ECL conditions. The results show that the present method is sensitive and reliable for the simultaneous determination of 4 residues of FQs with similar structure in fish.

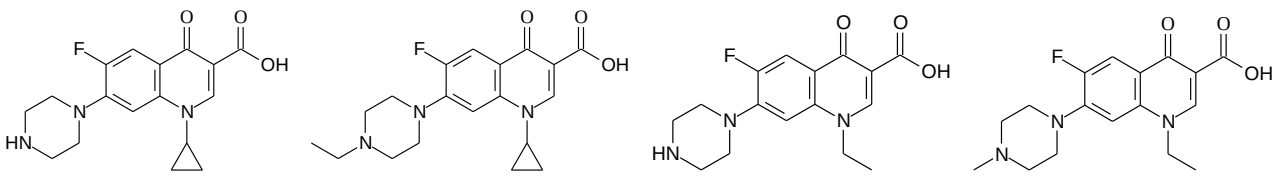

Figure 1. Structure of ciprofloxacin, enrofloxacin, norfloxacin and pefloxacin.

2. EXPERIMENTAL

2.1. Materials and Reagents

Tris (2,2'-bipyridyl) ruthenium (II) dichloride hexahydrate ($Ru(bpy)_3Cl_2·6H_2O$) was purchased from Alfa Aesar (Johnson Matthey, USA). Disodium hydrogen phosphate (Na_2HPO_4), sodium dihydrogen phosphate (NaH_2PO_4), ethyl acetate, acetonitrile, methanol, sodium hydroxide (NaOH), anhydrous magnesium sulfate ($MgSO_4$), anhydrous sodium sulfate (Na_2SO_4), primary secondary amine (PSA), neutral alumina (NA), polyvinyl pyrrolidone, cyclodextrin, sodium dodecylsulfate, sodium carboxymethyl cellulose, tween 80, n-propyl alcohol and iso-propyl alcoholwere all of analytical reagent gradeand were purchased from Beijing Chemical Factory (Beijing, China). Standard substances of ciprofloxacin (CIP), enrofloxacin (ENR), norfloxacin (NOR) and pefloxacin (PEF) were purchased from National Institutes for Food and Drug Control (Beijing, China).

2.2. Apparatus

CE-ECL was performed on a MPI - B multi-parameter chemiluminescence analysis test system (Xi'an Remex analytical instruments Co., Ltd., Xi'an, China). Cyclic voltammetry and potentiostatic method were carried out in a three electrodes system with a platinum working electrode of 500 μm in diameter, an Ag/AgCl reference electrode of 300 μm in diameter and a platinum wire auxiliary electrode of 1 mm in diameter. Uncoated capillary (25μm x 40 cm, Yongnian Optical Fiber Factory, Hebei, China) was rinsed respectively with 0.1 mol/L NaOH solution for 20 min, secondary distilled water for 10 min and running buffer for 15 min before use.

2.3. Solutions preparation

$Ru(bpy)_3^{2+}$solutions were prepared with $Ru(bpy)_3Cl_2·6H_2O$ and secondary distilled water. Phosphate buffer solutions (PBS) were prepared with disodium hydrogen phosphate, sodium dihydrogen phosphate and secondary distilled water. NaOH solution was prepared with NaOH and secondary distilled water. Standard solutions of CIP, ENR, NOR and PEF were prepared with their standard substances and secondary distilled water. All solutions used in the experiment must be filtered through a 0.22 μm cellulose acetate membrane.

2.4. Sample preparation

Grass carp is fished from wild reservoirs in the suburbs. Feed with common fish food, and use CIP, ENR, NOR and PEF for daily disease prevention. They will be slaughtered two months later. The fish muscle was treated, homogenized and stored at −20 °C.

Accurately weigh 2.0 g of crushed homogeneous fish meat, put it in a 50 mL centrifugal tube with cap, add 2 mL water, scroll for 1 min on the vortex oscillator, add 10 mL mixed solution of acetonitrile and methanol (v/v=4/1), scroll for 1 min, place it on the ultrasonic oscillator for 20 min,

scroll, put it in the ice water bath. Centrifuge at 5000 r/min for 5 min. Take 8 ml of supernatant into another 15 ml centrifuge tube with cap. Add QuEChERS purification powder (0.4 g Na_2SO_4, 0.4 g NA and 0.25 g PSA) into the centrifuge tube. The centrifuge tube was rotated for 1 minute and centrifuged at 5000 r/min for 5 min. The supernatant was accurately removed, dried on a nitrogen blower at 50 ℃, and dissolved in 1.0 ml methanol water (1:1). This sample preparation process is improved from our original work [55]. After passing through 0.22 μm microporous membrane, the filter fluid can be waiting for later use.

3. RESULTS AND DISCUSSION

3.1. Optimization of parameters in QuECHERS

The 4 FQs in this study belong to weak polar or medium polar compounds. The main extraction reagents are ethyl acetate, acetonitrile or methanol. When ethyl acetate is used as extraction reagent, the extract is darker in color, and more oily substances will remain after nitrogen blowing. It shows that weak polar matrix components are brought out in the extraction process, which increases the difficulty of subsequent purification. Acetonitrile has the function of protein precipitation, which can reduce the matrix effect to some extent as reported in the literature [55]. In this experiment, the recovery of FQs extracted by methanol is better than that of acetonitrile, but pure methanol as extractant has subsequent salting-out effect. Through in-depth study, it is found that using acetonitrile/methanol (v/v=4/1) mixture as extractant can not only ensure a good recovery of 4 FQs, but also facilitate the follow-up treatment process. Therefore, the mixed solution of acetonitrile and methanol (v/v=4/1) was used as the extraction reagent.

Most of the previous QuEChERS method used $MgSO_4$ as the extraction salt to make the target substance enter the organic phase [47-53]. In this experiment, however, the recoveries of 4 FQs were poor by using $MgSO_4$. This may be due to the chelation of FQs with Mg^{2+}, which results in low target recovery. The neutral Na_2SO_4, which does not react with FQs, was used as the extraction salt and good recoveries were obtained. C18 and PSA are the most commonly used adsorbents, and their purification effects are compared. The results show that PSA can not only remove carbohydrate and fatty acids from the sample matrix, but also the recovery of analyte is much higher than that of C18. This conclusion is also supported by the work of others from National Center for Biotechnology Information [56]. In addition, NA can be combined with PSA to remove the fat in the sample solution. Therefore, NA and PSA are adopted.

3.2. Optimization of detection conditions

3.2.1 Concentration of $Ru(bpy)_3^{2+}$

$Ru(bpy)_3^{2+}$ is the ECL reagent in the system. It is oxidized to $Ru(bpy)_3^{3+}$ on the working electrode [57], and then reacts with the reducing organic amine to produce the excited state product $[Ru(bpy)_3^{2+}]^*$, which emits photons when it returns to the ground state [58]. It can be seen that the initial concentration of $Ru(bpy)_3^{2+}$ has an effect on the ECL intensity. The ECL intensity increased

obviously with increasing the concentration of $Ru(bpy)_3^{2+}$. The background signals, however, increased markedly when its concentration exceeded 6 mmol/L. In order to obtain high *S/N* value, high sensitivity and appropriate reagent consumption, 6 mmol/L $Ru(bpy)_3^{2+}$ was selected. After working for 2 h, it is necessary to replace the $Ru(bpy)_3^{2+}$ solution to eliminate the change of concentration of $Ru(bpy)_3^{2+}$ [59].

3.2.2 Detection potential

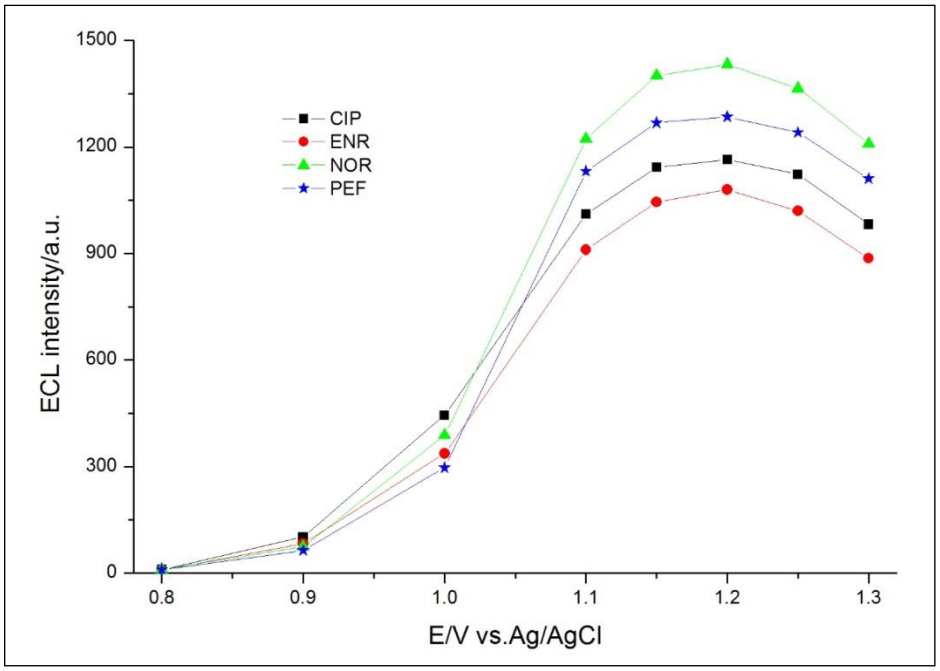

Figure 2. Effect of detection potential on ECL intensity under $Ru(bpy)_3^{2+}$ concentration 6 mmol/L, phosphate buffer solution concentration 40 mmol/L and pH 7.0 in ECL detection cell.

The effect of detection potential in the range of 0.80–1.30 V (vs. Ag/AgCl) on ECL intensities of 5 mg/mL CIP、ENR、NOR and PEF under specific detection conditions was shown in figure 2. As you can see, their ECL intensities were very weak when the detection potential is lower than 1.0 V, because $Ru(bpy)_3^{2+}$ can't be oxidized at this potential [60]. The ECL intensities firstly increased and then decreased with the detection potential from 1.00 V to 1.30 V. The ECL signals reached maximum at 1.15-1.20 V for CIP and PEF and 1.20 V for ENR and NOR, respectively. Therefore, the detection potential was set at 1.20 V (vs. Ag/AgCl) by comprehensive consideration.

3.2.3 pH of buffer in ECL cell

The effect of pH values of phosphate buffer solution (PBS) on ECL intensities of 5 mg/mL CIP、ENR、NOR and PEF under specific detection conditions was shown in figure 3. The ECL intensities increased with pH value from 4.0 to 6.5 and then decreased at higher pH value than 7.0. Because of be

the competition of the reaction of $Ru(bpy)_3^{3+}$ with OH^- ions at higher pH values [61]. The maximum ECL intensities appeared at pH 6.5-7.0 for CIP and PEF and 7.0 for ENR and NOR. Therefore, pH 7.0 of PBS can be used as the detection buffer.

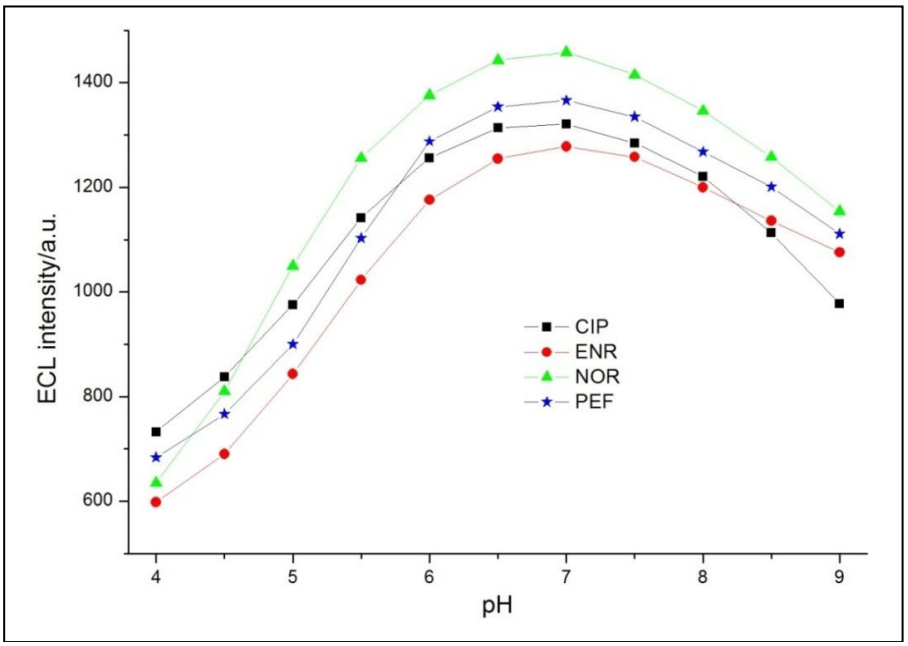

Figure 3. Influence of pH of phosphate-buffer in ECL cell on ECL intensity under detection potential 1.20 V vs. Ag/AgCl, $Ru(bpy)_3^{2+}$ concentration 6 mmol/L and phosphate buffer solution concentration 40 mmol/L in ECL detection cell.

3.2.4 Concentration of PBS in ECL cell

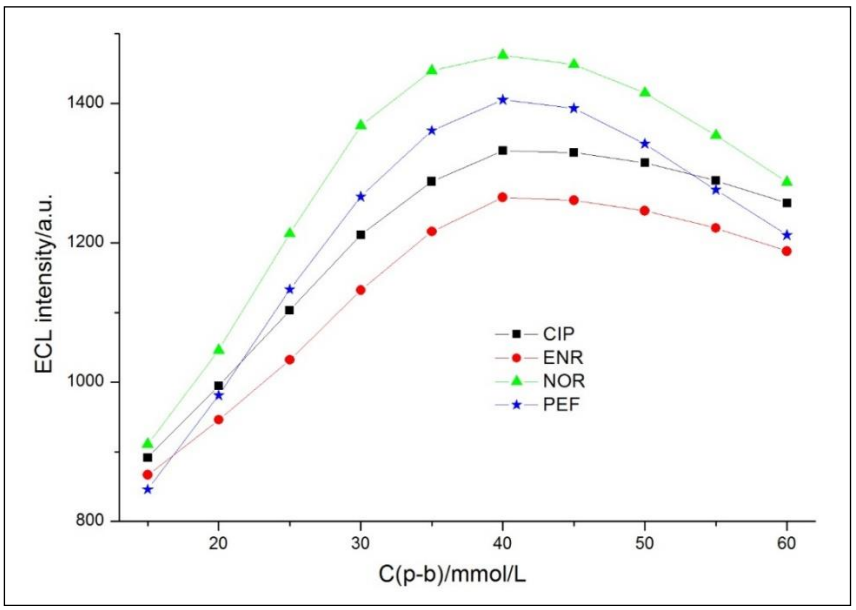

Figure 4. Influence of concentration of phosphate-buffer in ECL cell on ECL intensity under detection potential 1.20 V vs. Ag/AgCl, $Ru(bpy)_3^{2+}$ concentration 6 mmol/L and phosphate buffer solution pH 7.0 in ECL detection cell.

The effect of concentration of PBS in the detection cell on ECL intensities of 5 mg/mL CIP、ENR、NOR and PEF under specific detection conditions was shown in figure 4. As you can see, the maximum ECL intensity appeared at 40-45 mmol/L for CIP and ENR and 40 mmol/L for NOR and PEF. Therefore, the buffer concentration of 40 mmol/L was used as the detection buffer in our experiment. Most of the concentrations of PBS reported in the literature are greater than 30 mmol/L [25-27, 62].

3.3. Optimization of separation parameters

3.3.1 Selection of separation buffer

The only difference between CIP and ENR is that the nitrogen atom bonded to the hydrogen or the ethyl groups. The only difference between NOR and PEF is that the nitrogen atom bonded to the hydrogen or the methyl groups. The structure difference between them is too small to be separated by general electrophoresis [63]. When there is no additive in the separation buffer, their electrophoretic peaks overlap and cannot be separated. In order to obtain good resolution, the effect of polyvinylpyrrolidone, cyclodextrin, sodium dodecylsulfate, sodium carboxymethyl cellulose, Tween 80, n-propyl alcohol and iso-propyl alcohol on their separation were studied by adding them into the separation buffer, respectively. The results showed that polyvinylpyrrolidone, n-propyl alcohol and iso-propyl alcohol had obvious influence on the separation of CIP and ENR, sodium dodecylsulfate and sodium carboxymethyl cellulose had obvious influence on the separation of NOR and PEF, and cyclodextrin and Tween 80 had great influence on the separation of CIP、ENR、NOR and PEF. Cyclodextrin is especially effective in improving their separation. The influence of cyclodextrin volume fraction in separation buffer on separation was further studied. The results showed that 4 FGs could be separated completely when the volume fraction of cyclodextrin in separation buffer was 17.5%. In following experiments, 17.5% cyclodextrin solution (v/v) containing phosphate was used as the separation buffer.

3.3.2 Injection voltage and injection time

The amount of capillary electric injection is directly related to the injection voltage and injection time [60]. The effects of injection voltage from 4-20 kV on the ECL intensities of 4 FGs were studied by fixing the injection time at 10 s. The results show that the ECL intensities of the four molecules increase sharply before 11 kV with the increase of injection voltage, then slowly, and the reproducibility deteriorate gradually after 15 kV. The effects of inject time from 2-20 s on the ECL intensities of 4 FGs were studied by fixing the injection voltage at12 kV. The results show that the ECL intensities increase sharply for 4 FGs before 6 s with the injection time, and then slowly for them. However, due to the introduction of more analytes into the capillary and overload may occur, so a longer injection time is unfavorable [59]. Therefore, 6-10 s and 11-15 kV are selected by considering signal sensitivity and separation efficiency together.

3.3.3 Separation voltage

The separation voltage has a great influence on the separation of four FGs [61]. We have studied the relationship between them in the range of 8–20 kV. For all of them, ECL intensities increased with separation voltage from 8 to 14 kV, and then they slowly decreased from 14 to 20 kV. The baseline noise significant increase when the separation voltage was higher than 14 kV. On the one hand, the Joule heat increased with the increase of separation voltage which will make the noise enlarge. On the other hand, the more effluent from the capillary, the lower concentration of Ru(bpy)32+ on the electrode surface [60]. That will reduce the efficiency of light emitting. To obtain a high ECL intensity and high resolution, lower separation voltage than 14 kV is necessary.

3.3.4 The pH of separation buffer and concentration of phosphate

The pH value of the separation buffer and concentration of phosphate can affect the electro osmotic flow (EOF) and ionization degree of the analytes in the capillary, and then affect the migration time, sensitivity and resolution of the analytes [60]. The results showed that when the pH value was more than 6, the four FGS could not be separated completely in electropherogram, the resolution was not improved with the increasing of concentration of phosphate from 5–22 mmol/L, and the bad separation effect, long migration time and unstable baseline appeared when its concentrations was higher than 22 mmol/L. This may be due to the increase of Joule heating caused by the increase of ionic strength. This phenomenon is also supported by literature work [64]. In order to obtain ideal separation and short migrating time, smaller buffer pH than 6 and lower buffer concentration than 22 mmol/L are necessary.

3.3.5 Separation conditions

When multi-components are simultaneously determined, the overall optimization of separation conditions is particularly important [55]. The experimental results show that the migration times and the peak profiles are the main factors of influencing the separation of components. The migration time mainly depends on the electrophoresis ionic strength and the separation voltage. The electrophoresis ion strength can be appropriately changed by adjusting the concentration and pH value of the buffer solution. The component peak profile is related to the sampling volume and the migration time of the component. The sampling volume can be changed by adjusting the injection voltage and injection time. Although the long migration time is beneficial to the separation of components, it is easy to cause the peak broadened and the column effect decreased. Considering these conditions, the electrophoresis separation diagram of a mixed solution comprising 4 FGs (see figure 5) was obtained through a large number of comprehensive optimization experiments. The separation conditions were determined: separation buffer of 17.5% cyclodextrin solution (v/v) containing 20 mmol/L phosphate (pH 5.0), separation voltage of 13.0 kV, sample injection time of 7 s and sample injection voltage of 12.0 kV. It can be seen that 4 FGs can be completely separated under these conditions.

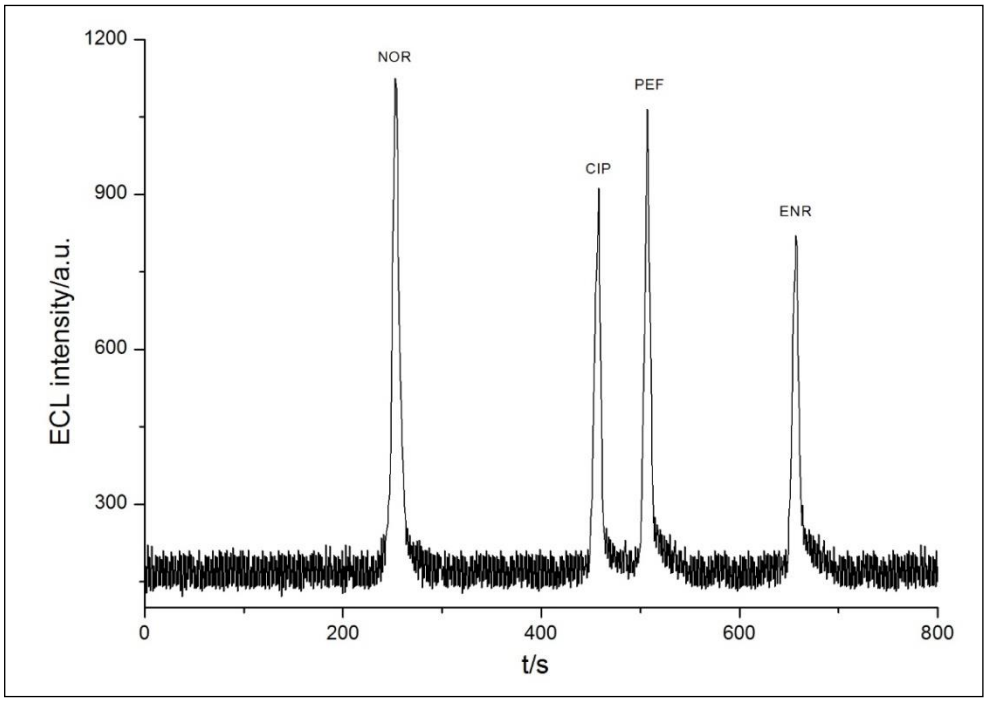

Figure 5. Electrophoretogram of mixture of 4 standard FGs under analysis potential 1.20 V, $Ru(bpy)_3^{2+}$ concentration 6 mmol/L, phosphate buffer solution concentration 40 mmol/L and pH 7.0 in ECL detection cell, separation voltage 13.0 kV, 17.5% cyclodextrin solution (v/v) as additive, phosphate buffer solution concentration 20 mmol/L and pH 5.0 in capillary, and injection time 7 s and injection voltage 12.0 kV.

3.4 Method performances

The optimized CE–ECL experimental conditions include analysis conditions (detection potential 1.20 V vs. Ag/AgCl, $Ru(bpy)_3^{2+}$ concentration 6 mmol/L, phosphate buffer solution concentration 40 mmol/L and pH 7.0 in ECL detection cell), separation conditions (separation voltage 13.0 kV, 17.5% cyclodextrin solution (v/v) as additive, phosphate buffer solution concentration 20 mmol/L and pH 5.0 in capillary), and sample conditions (injection time 7 s and injection voltage 12.0 kV). Under the optimal conditions, the analytical results of 4 FGs were summarized in Table1.

Table 1. Regression equation, repeatability and detection limit of four analytes.

Drug	Regression Equation	Linear Range/(g/L)	RSD_I/%	RSD_t/%	Detection Limit/(g/L)
CIP	$I = 251.5C + 52.8$	$2.5\times10^{-4}\sim4.9\times10^{2}$	2.6	1.7	8.8×10^{-5}
ENR	$I = 226.8C + 106.3$	$7.1\times10^{-5}\sim6.0\times10^{3}$	1.8	2.1	3.5×10^{-6}
NOR	$I = 305.3C + 76.6$	$8.8\times10^{-4}\sim6.2\times10^{2}$	1.6	1.9	7.5×10^{-5}
PEF	$I = 279.7C + 82.1$	$5.4\times10^{-5}\sim7.7\times10^{3}$	2.3	2.3	2.7×10^{-6}

* I: ECL intensity. C: mass concentration. RSD_I: RSD of ECL intensity. RSD_t: RSD of migration time.

3.5 Sample analysis

The filtrate of grass carp treated by modified QuEChERS was directly separated and analyzed by CE-ECL under the optimal conditions. The results are shown in figure 6. The component peaks appeared more in figure 6 than in figure 5. This indicates that not only 4 FGs, but also other components are detected simultaneously.

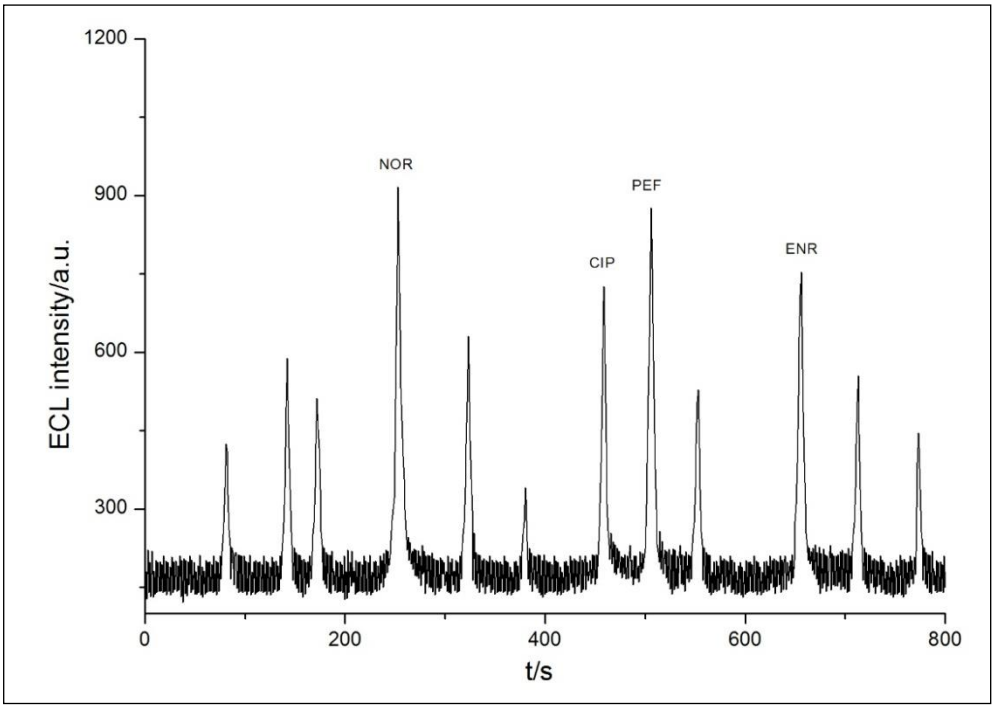

Figure 6. Electrophoretogram of fish sample original liquid under analysis potential 1.20 V, $Ru(bpy)_3^{2+}$ concentration 6 mmol/L, phosphate buffer solution concentration 40 mmol/L and pH 7.0 in ECL detection cell, separation voltage 13.0 kV, 17.5% cyclodextrin solution (v/v) as additive, phosphate buffer solution concentration 20 mmol/L and pH 5.0 in capillary, and injection time 7 s and injection voltage 12.0 kV.

In order to further determine the peak location of the target, the CE - ECL measurement of a mixture solution of containing 1 ml standard solution (5 mg/mL CIP, 5 mg/mL ENR, 4 mg/mL NOR, and 4 mg/mL PEF) and 5 ml the filtrate of grass carp sample was performed under the optimal conditions. The results were shown in figure 7.

Compared with figure 6, the luminescence intensity of the four peaks in figure 7 is significantly increased, which can accurately determine the location of CIP, ENR, NOR and PEF.

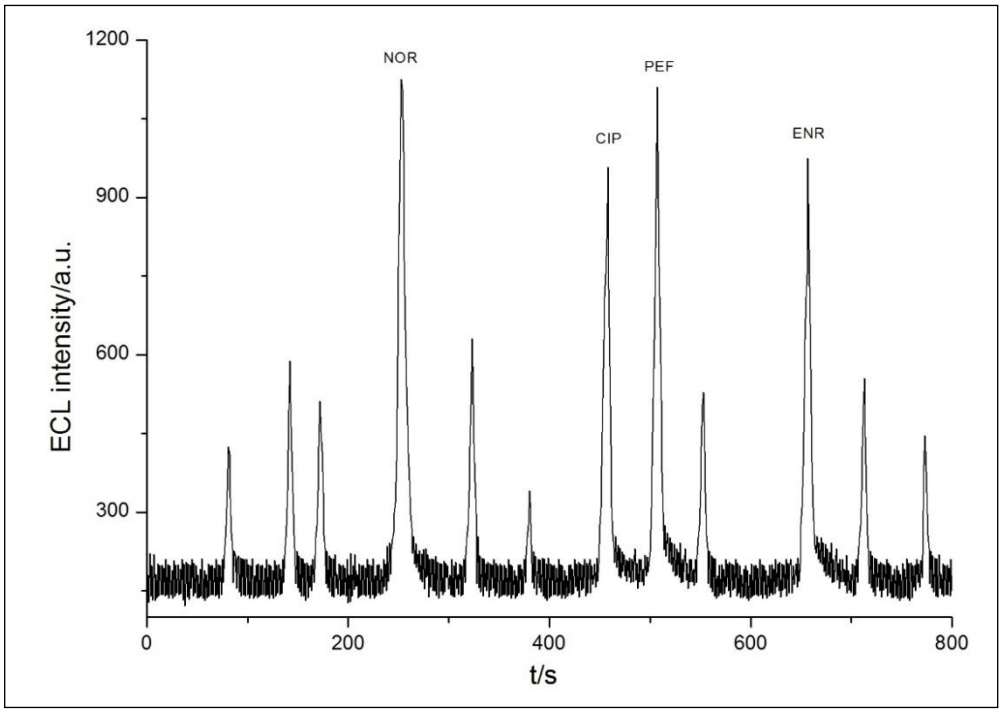

Figure 7. Electrophoretogram of fish sample spiked with standards under analysis potential 1.20 V, $Ru(bpy)_3^{2+}$ concentration 6 mmol/L, phosphate buffer solution concentration 40 mmol/L and pH 7.0 in ECL detection cell, separation voltage 13.0 kV, 17.5% cyclodextrin solution (v/v) as additive, phosphate buffer solution concentration 20 mmol/L and pH 5.0 in capillary, and injection time 7 s and injection voltage 12.0 kV.

4.CONCLUSION

This paper firstly demonstrated an analytical procedure for simultaneous determination of CIP, ENR, NOR and PEF by improved CE coupled with end-column ECL and modified QuEChERS. The four analytes with similar structure can be separated and analyzed well in less than 12 minutes by comprehensive optimization of CE-ECL conditions. It was successfully utilized to directly simultaneously detect CIP, ENR, NOR and PEF in fish sample.

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