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Simultaneous Determination of Ten Antibiotics in Natural Water Samples by Capillary Electrophoresis with Electrochemiluminescence Detection coupled with Hollow Fiber -Solid Phase Extraction

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A novel method for simultaneous determination of ten antibiotics in natural water samples was established based on purifing and enriching by hollow fiber (HF) solid phase extraction (SPE), separating by capillary electrophoresis (CE) and detecting by electrochemiluminescence (ECL). The effects of water sample pH, extraction time and extraction temperature on the extraction efficiency of ten antibiotics were studied. The optimized parameters of SPE with 0.2 g HF were determined as follows: water sample pH 6, extraction time 40 min and extraction temperature 50℃. The effects of separation buffer solution pH, ionic strength, separation voltage and additives on the separation efficiency of ten antibiotics were investigated. The selected CE separation solution is phosphate buffer solution (pH 6.5) containing 50 mmol/L NaCl and 35 mmol/L isopropanol. The separation voltage is 19 kV. All the ten antibiotics have good linear relationship. Their detection limits were 0.4 - 1.2 μg/L. The recoveries of water samples were 81.6% - 115.7%. The method is sensitive, accurate and rapid, and can be used to determine antibiotics in natural water samples directly.

Keywords: Antibiotic, Water sample, Hollow fiber, Solid phase extraction, Capillary electrophoresis

1. INTRODUCTION

Antibiotics are secondary metabolites produced by microorganisms (including bacteria, fungi and actinomycetes) or higher animals and plants in the process of life. They are resistant to pathogens or other activities and interfere with the development of other living cells. It mainly includes fluoroquinolones, β-lactams, cephalosporins and sulfonamides. Since the birth of antibiotics, it has played an important role in the treatment of various common bacterial diseases. However, with the wide use of antibiotics in clinical practice [1], drug-resistant bacteria soon emerged [2-4]. This has led to a crisis in the use of antibiotics.

Antibiotics not only kill pathogens, but also cause damage to human body. Drugs enter the stomach through the oral cavity, and then enter the blood through intestinal absorption, and are transported to various cells of the human body. Only the drugs that reach the lesion area can have bactericidal effect on pathogenic bacteria. The drugs in other tissues not only have no bactericidal effect, but also the metabolites are discharged from the body through the liver and kidney, which has certain damage to liver and kidney organs. Many antibiotics, such as chloramphenicol, lincomycin, tetracycline and erythromycin, need to be metabolized in the liver. In addition, many antibiotics, such as penicillin and streptomycin, can cause various allergic reactions [5, 6]. Sometimes even damage the nervous system, such as the central nervous system, hearing, vision and peripheral nervous system lesions and neuromuscular block. Finally, the abuse of antibiotics may cause the imbalance of flora and delay the treatment of diseases. Due to the influence of antibiotics, the species and quantity of various bacteria in normal flora will change [7]. Serious flora imbalance can lead to a series of clinical symptoms. This phenomenon is mainly seen in patients with long-term use of broad-spectrum antibiotics. In these patients, the bacteria that are sensitive to antibiotics are largely killed, while the non sensitive bacteria, such as staphylococcus aureus and candida albicans, take advantage of this opportunity to reproduce. This will cause pseudomembranous enteritis, candida albicans pneumonia, which is the so-called clinical double infection. These will bring great trouble to the treatment of the disease and produce serious adverse consequences. At present, the problem of bacterial resistance to antibiotics is very serious, which also poses a threat to human health.

There are hundreds of thousands of tons of antibiotics used by human and livestock every year. Most of these antibiotics could not be absorbed and utilized by human beings and animals, and finally discharged into the environment in their original form [8]. Water is an important gathering place of antibiotics in the environment [9-12]. The effect of common wastewater treatment process on many antibiotics is not ideal, which leads to a large number of antibiotics entering the water environment and causing environmental pollution. Then antibiotics migrate into human food and drinking water [13], which has a serious impact on human health. Therefore, it is of great significance to detect the residues of antibiotics in the environment.

The detection methods of antibiotics mainly include liquid chromatography (LC) tandem mass spectrometry (MS) [14-19], LC-ultraviolet (UV) [20-22], LC-fluorescence [23, 24], electrochemistry [25-27], fluorescence [28-30], enzyme linked immunosorbent assay [31,32] and colorimetry [33].

Capillary electrophoresis (CE) is a promising high-performance biochemical and medical separation method with short analysis time and less sample consumption. Electrochemiluminescence (ECL) based on tris (2, 2'-bipyridyl) ruthenium (II) ($Ru(bpy)_3^{2+}$) is an attractive analytical method for organic amines owing to its inherent high sensitivity, selectivity and stability. There are many reports on the separation and analysis of antibiotics by CE combined with conductivity [34-36], MS [37-39] and UV [40-42]. However, there are few studies on the separation and analysis of antibiotics by CE combined with ECL.

The residual antibiotics in water are in trace level, so it is difficult to determine them. Sample pretreatment technology has great influence on the sensitivity, efficiency and reliability of analytical methods. Solid phase extraction (SPE) is a new sample pretreatment technology, which integrates sampling, extraction and concentration, greatly speeding up the analysis and detection. Its significant

technical advantages have been widely concerned by analysts in the environmental [43-45], food [46-48] and pharmaceutical industries [49-51]. Hollow fiber (HF) with large surface area has been widely used [52-54]. Other functional stationary phases can be fixed on HF membrane template as reinforcers to make new HF composite materials [55, 56].

In this paper, antibiotics remaining in water sample were purified and enriched by HF-SPE method. Then ten antibiotics, benzylpenicillin (BEN), amoxicillin (AMO), cloxacillin (CLO), cefotiam (CTM), cefmetazole (CMZ), cefalexin (CEX), sulfamethoxazole (SMZ), sulfathiazole (STZ), norfloxacin (NOR) and pefloxacin (PEF), were separated and detected simultaneously by CE-ECL. Among the ten antibiotics, BEN, AMO and CLO are β-lactams, CTM, CMZ and CEX are cephalosporins, SMZ and STZ are sulfonamides, NOR and PEF are fluoroquinolones. The results show that the present method is sensitive and reliable for the simultaneous determination of ten antibiotics in water samples.

2. EXPERIMENTAL

2.1. Materials and drugs

Standard substances of benzylpenicillin, amoxicillin, cloxacillin, cefotiam, cefmetazole, cefalexin, sulfamethoxazole, sulfathiazole, norfloxacin and pefloxacin were purchased from National Institutes for Food and Drug Control (Beijing, China). Tris (2,2'-bipyridyl) ruthenium(II) dichloride hexahydrate ($Ru(bpy)_3Cl_2 \cdot 6H_2O$) was purchased from Alfa Aesar (Johnson Matthey, USA). Disodium hydrogen phosphate (Na_2HPO_4), sodium dihydrogen phosphate (NaH_2PO_4), sodium hydroxide (NaOH), sodium chloride (NaCl), isopropanol, ethyl orthosilicate, etnanol, hydrochloric acid (HCl), methanol and formic acid were all of analytical reagent grade and were purchased from Beijing Chemical Factory (Beijing, China). Polypropylene hollow fiber (inner diameter 600 μm and micropore 0.3 μm) was purchased from Tianjin Film Technology Co., Ltd (Tianjin, China).

2.2. Apparatus and conditions

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. Capillary (25 μm x 40 cm) 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.

CE conditions: Separation voltage is 19 kV. The separation medium is composed of phosphate buffer solutions (PBS) (pH 6.5) containing 50 mmol/L NaCl and 35 mmol/L isopropanol.

ECL conditions: Detection potential is 1.2 V (vs. Ag/AgCl). The detection medium is 40 mmol/L PBS (pH 5.8) containing 6 mmol/L $Ru(bpy)_3^{2+}$.

2.3. Hollow fiber treatment

The ethyl orthosilicate was added into ethanol solution, and 36% HCl was added under continuous stirring. After aged at room temperature for 24 h, the ethyl orthosilicate was completely hydrolyzed to silica sol. The polypropylene HF with a length of 1 cm was completely immersed in silica sol. After ultrasonic vibration at room temperature for 30 min, and HF was removed from the sol and dried at 120 ^{o}C for standby.

2.4. Sample preparation

The water sample was adjusted to pH 6.0 with 0.1 mol/L HCl solution. Shake well and let stand for 1 h. The supernatant was removed 10 mL to a 20 mL screw cap centrifugal tube, add 1.0 g NaCl and vortex to completely dissolved, raise the temperature to 50 ^{o}C, completely immerse 0.2 g processed HF in the solution, and extract for 40 min. After the extraction, transfer the hollow fiber to a test tube, add 2.0 mL methanol (containing 5% formic acid) as eluate, and shake it with ultrasonic for 5 min. Blow dry the solution with nitrogen, add 0.5 ml methanol water solution (1:1) along the pipe wall to dissolve the analytes. After passing through 0.22 μm microporous membrane, the filtrate was ready for use.

3. RESULTS AND DISCUSSION

3.1. Optimization of sample preparation conditions

Sample preparation conditions, such as pH of sample solution, extraction time and extraction temperature, have great influence on the collection of target analytes. In this paper, the recoveries of ten antibiotics were used as test indexes to study the influence of sample preparation conditions.

3.1.1 pH of sample solution

The effects of pH of the sample solution at 3, 4, 5, 6 and 7 on the recoveries of ten antibiotics were investigated. The results are shown in Figure 1. With the increase of pH value of sample solution, the recoveries of 10 antibiotics shows a trend of "first increase and then decrease", and reaches the maximum at pH = 4-6. The maximum recovery of SME appeared at pH = 4, and other 9 antibiotics at pH = 6. Therefore, we choose the pH of the sample solution to be 6. The pH values of SPE in literatures are mostly weak acid [44, 46-49, 51, 54], which is consistent with our conclusion.

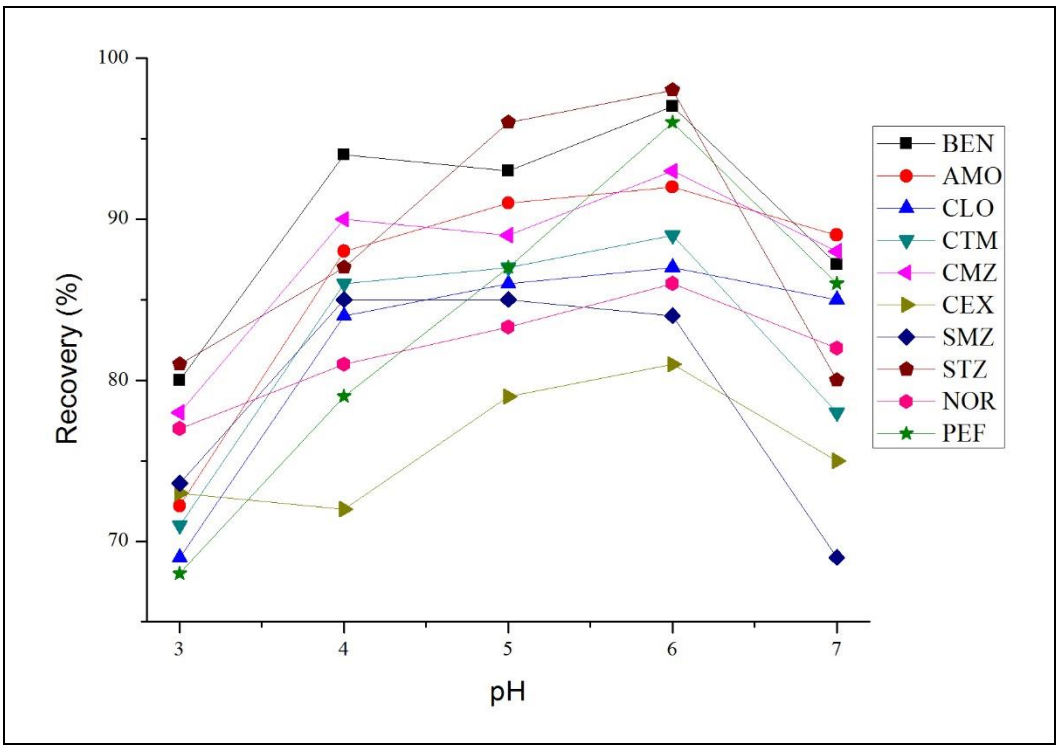

Figure 1. Effects of pH of sample solution on the recoveries of ten antibiotics under extraction time 40 min and extraction temperature 50℃.

3.1.2 Effect of extraction time

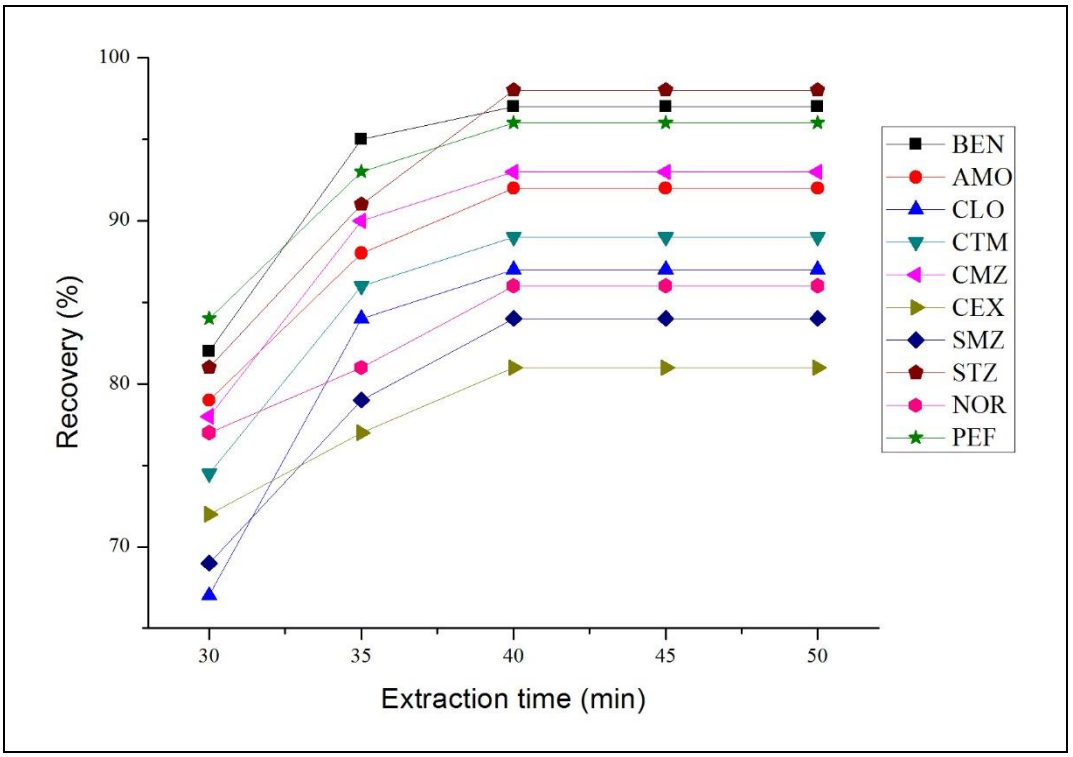

Figure 2. Effects of extraction time of sample solution on the recoveries of ten antibiotics under water sample pH 6 and extraction temperature 50℃.

The effects of different extraction time on the extraction efficiencies of ten antibiotics were shown in Figure 2. With the prolongation of extraction time, the extraction efficiency of ten antibiotics increased continuously, and reached stability after 40 min. There was no significant difference in extraction efficiency after 40 min. Some laboratories use hollow fiber to extract food ingredients, and the extraction time is more than 60 minutes [53, 55], but it seems unnecessary in our experiments. So we determined that the extraction time was 40 minutes.

3.1.3 Effect of extraction temperature

This experiment investigated the effects of different extraction temperature on the extraction efficiencies of ten antibiotics, as shown in Figure 3. With the increase of extraction temperature, the extraction efficiencies of ten antibiotics substances increased first and then decreased, and reached the maximum at 50 ºC. When hollow fiber is used as solid phase extraction agent, higher temperature is not conducive to maintain its shape [56]. Most of the operating temperatures in the literature are less than 60 ℃. So we chose 50 ℃ as our extraction temperature.

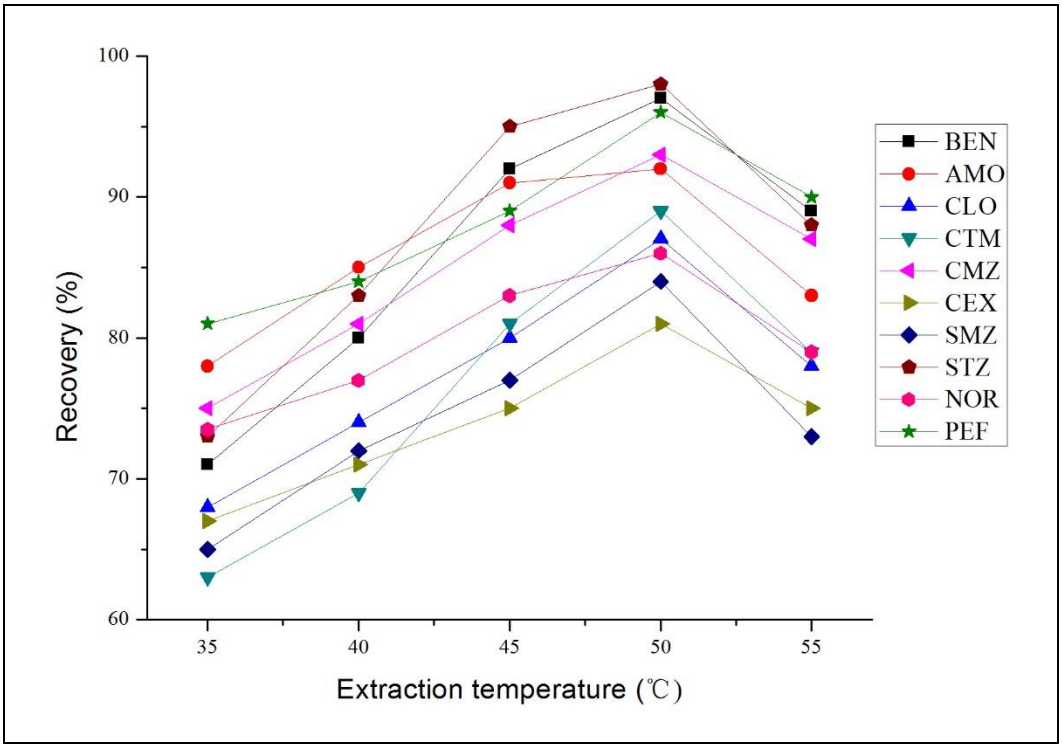

Figure 3. Effects of extraction temperature of sample solution on the recoveries of ten antibiotics under water sample pH 6 and extraction time 40 min.

3.2. Optimization of capillary electrophoresis parameters

Capillary electrophoresis conditions, such as pH of separation PBS, ionic strength of PBS,

separation voltage and additives, have great influence on the separation of target analytes. In this paper, the resolutions of the same type of antibiotics which is difficult to separate, such as BEN/AMO, BEN/CLO, AMO/CLO, CTM/CMZ, CTM/CEX, CMZ/CEX, SMZ/STZ and NOR/PEF, were used as test indexes to study the influence of different capillary electrophoresis parameters.

3.2.1 pH of separation PBS

The acidity of separation PBS is an important condition affecting the separation effect. When the pH of the PBS changes from 6 to 8, the resolutions of 8 pairs of analytes are shown in Figure 4. With the increase of the pH of separation PBS, the resolutions of 8 pairs of analytes shows a trend of "first increase and then decrease", and reaches the maximum at pH = 6.5-7.5. At pH 6.5, the resolutions of 7 pairs of analytes reached the maximum value, so we chose 6.5 as the pH value of separation buffer solution. The pH values of separation PBS in literatures [35-37, 40, 42] are mostly weak acid, which is consistent with our conclusion.

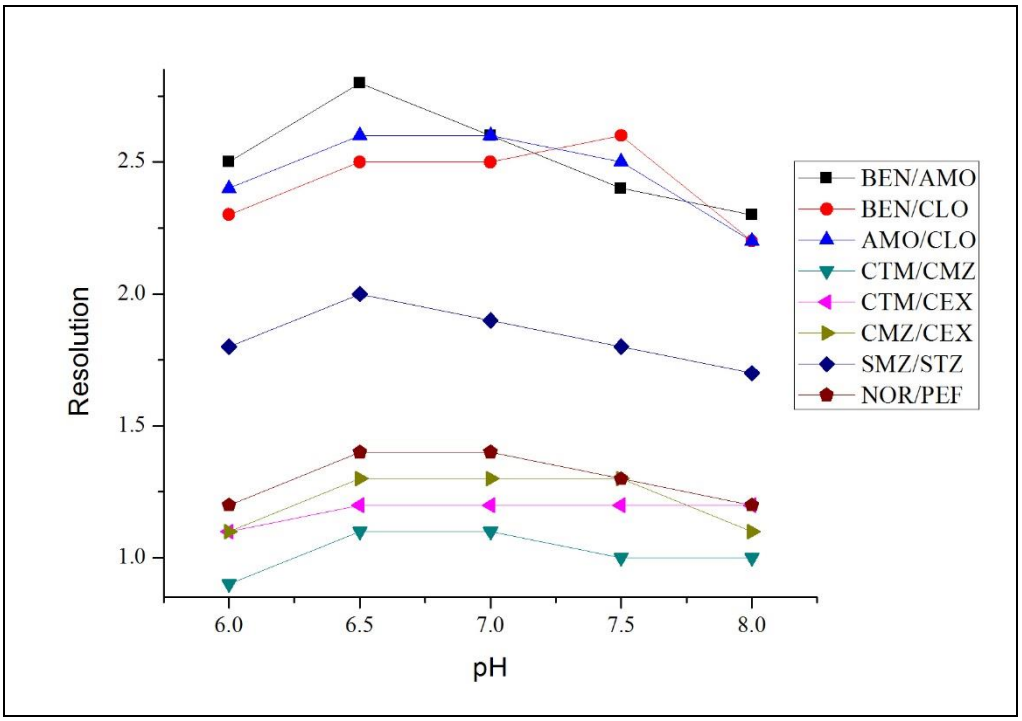

Figure 4. Effects of pH of separation PBS without inorganic salts and additive on the resolutions of ten antibiotics.

3.1.2 Ionic strength of separation PBS

The ionic strength of separation PBS is another important condition affecting the separation effect. The migration velocity of the target can be changed by adjusting the ionic strength of the medium [35]. In this experiment, the effect of ionic strength on resolution was investigated by adding different quality of NaCl [37-40, 42]. The results are shown in Figure 5. With the addition of NaCl, the

ionic strength increased. The resolutions of 8 pairs of analytes showed different trends. When the concentration of NaCl is 50 mmol/L, the resolutions of 8 pairs of analytes are relatively large. Other inorganic salts, such as Na_2SO_4 [36], NH_4Cl [34] or $(NH_4)_2SO_4$ [41], can also be used to change the ionic strength of the solution.

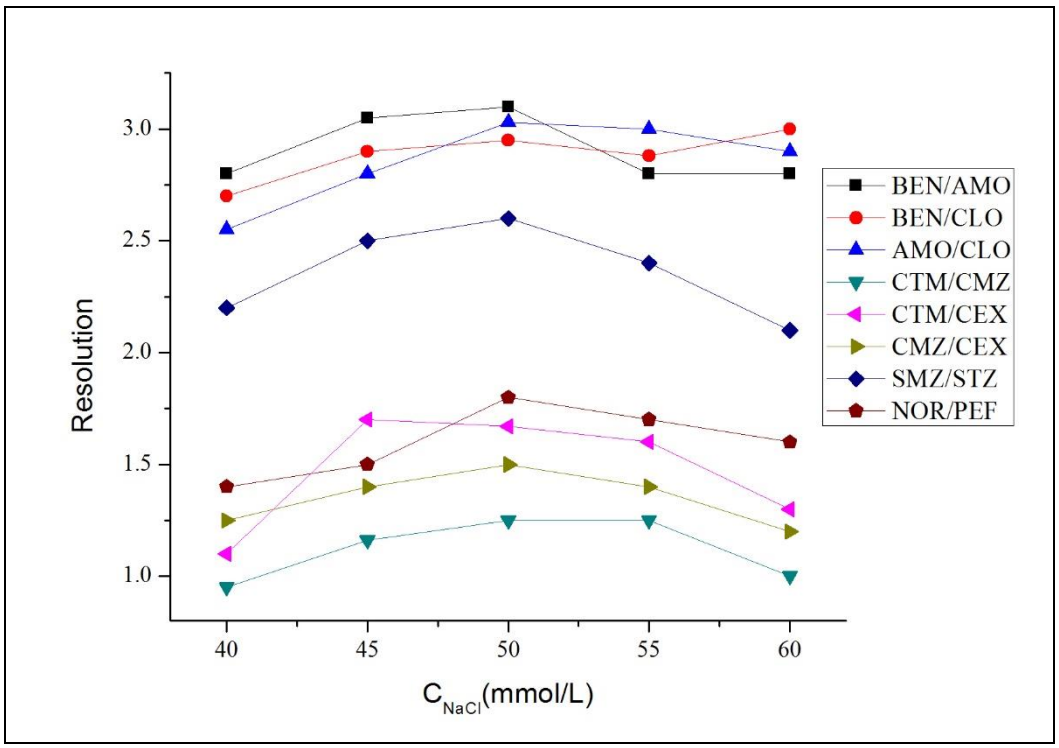

Figure 5. Effects of ionic strength of separation PBS (pH 6.5) without additive on the resolutions of ten antibiotics.

3.1.3 additive in separation PBS

PBS is often used as separation medium for capillary electrophoresis. However, in this experiment, CTM/CMZ, CTM/CEX, NOR/PEF and CMZ/CEX cannot be completely separated if only PBS is used. Our in-depth study found that isopropanol has a great influence on their separation. Figure 6 shows the effect of different concentrations of isopropanol on the resolutions of 8 pairs of analytes. With the increase of concentrations of isopropanol in separation PBS, the resolutions of 8 pairs of analytes showed different trends. When the concentration of isopropanol is 35 mmol/L, all of the resolutions of 8 pairs of analytes are greater than 1.5, which is the basic condition for a pair of analytes to be completely separated [35]. In the literature, some research groups used cyclodextrin [37] and polyvinylpyrrolidone [41] as additives to improve the separation of difficult to separate substances, and achieved good separation results.

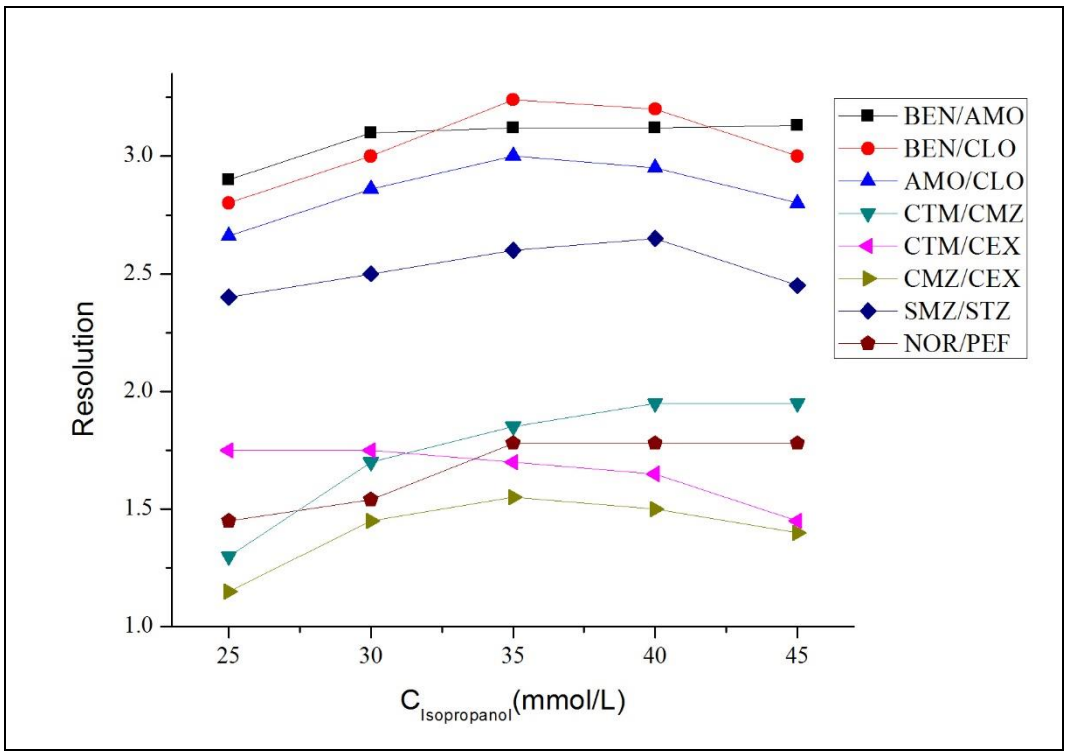

Figure 6. Effects of additive in separation PBS (pH 6.5) containing 50 mmol/L NaCl on the resolutions of ten antibiotics.

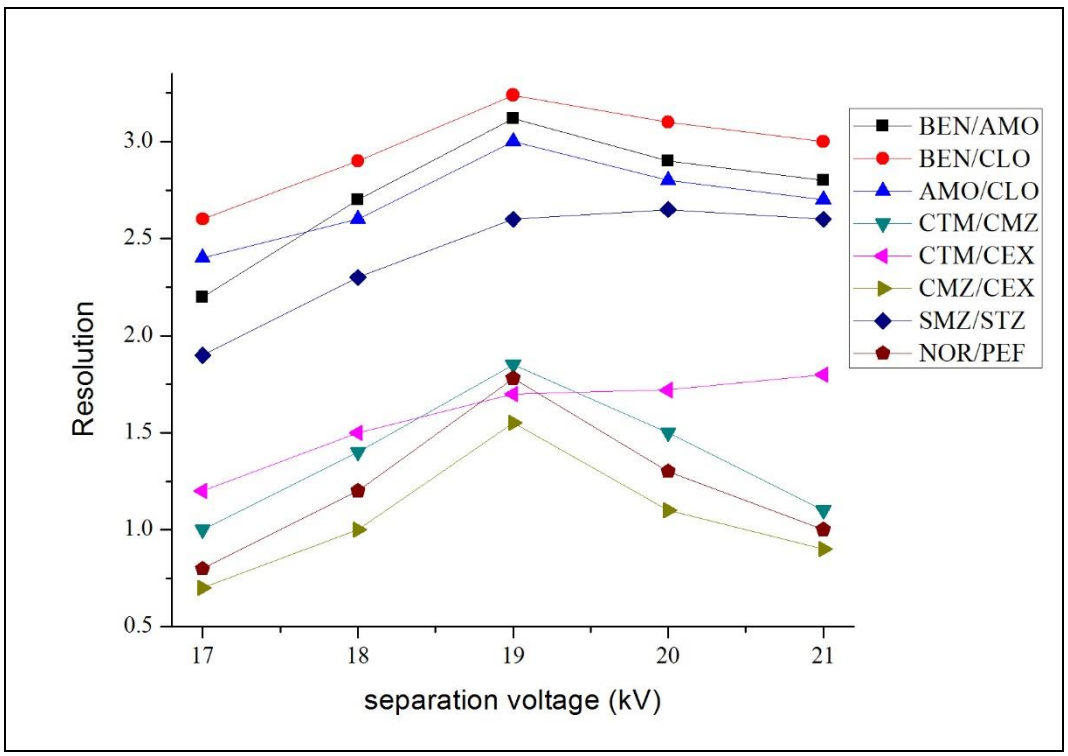

Figure 7. Effects of separation voltage on the resolutions of ten antibiotics under PBS (pH 6.5) containing 50 mmol/L NaCl and 35 mmol/L isopropanol.

3.1.4 Selection of separation voltage

The separation voltage affects the migration time of components, and then changes the resolution of components. In this experiment, the separation voltages from 17 kV to 21 kV are investigated. The results are shown in Figure 7. As you can see, 19 kV is the best separation voltage. When the separation voltage exceeds 25 kV, Joule heat will cause a lot of noise. When the separation voltage is lower than 15 kV, the analyte migration is slow and the signal is weak. In the literature, the separation voltage is generally between 15 kV and 25 kV [34-42].

3.3 Methodology

A series of antibiotic standard solutions were prepared and determined according to the determined experimental method. With mass concentration as abscissa and ECL intensity as ordinate, the working curve is drawn as shown in Figure 8. It can be seen that there is a good linear relationship between the concentration of each antibiotic and its ECL intensity in a certain concentration range under the determined experimental conditions.

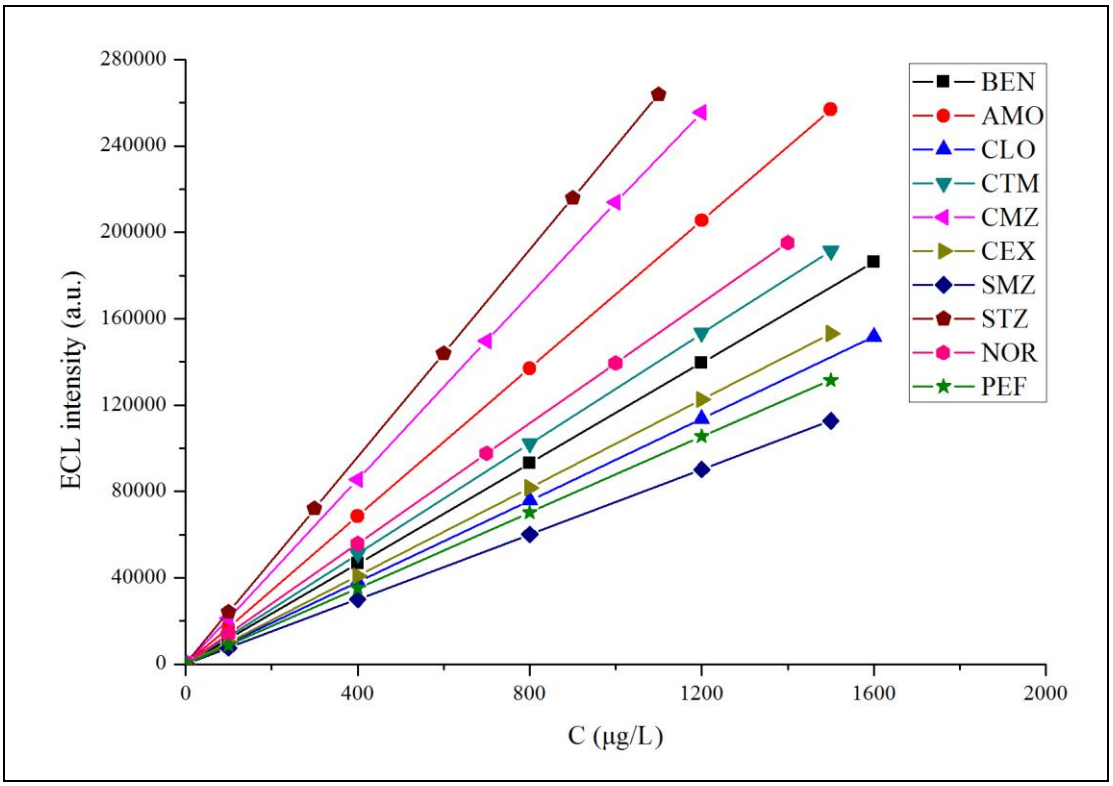

Figure 8. Working curves of ten antibiotics under the established CE and ECL experimental conditions.

The linear relationships, linear ranges and detection limits of ten antibiotics were investigated. The results were summarized in Table 1.

Table 1. Regression equations, linear ranges and detection limits of ten antibiotics under the established CE and ECL experimental conditions.

Number	Antibiotic	Regression Equation	Linear Range/(μg/L)	Detection Limit/(μg/L)
1	BEN	$I = 116.3C + 48.5$	1.5-1600	0.9
2	AMO	$I = 171.2C + 54.1$	1.8-1500	1.2
3	CLO	$I = 94.7C + 64.3$	1.2-1600	0.7
4	CTM	$I = 127.6C + 31.8$	0.8-1500	0.4
5	CMZ	$I = 213.9C + 27.7$	0.8-1200	0.5
6	CEX	$I = 102.1C + 62.2$	1.0-1500	0.6
7	SMZ	$I = 75.1C + 36.2$	0.7-1500	0.4
8	STZ	$I = 239.7C + 112.6$	0.9-1100	0.5
9	NOR	$I = 139.4C + 66.0$	1.1-1400	0.6
10	PEF	$I = 87.7C + 43.5$	1.2-1500	0.6

3.4 Sample analysis

The residues and recoveries of ten antibiotics in water samples from cattle farm, chicken farm and river were studied. The recoveries of ten antibiotics in the actual samples are 81.6% - 115.7%. Residual antibiotics were detected in all three water samples, and the results are shown in Table 2.

Table 2. Analysis results of actual water samples under the established CE and ECL experimental conditions.

No.	Antibiotic	Measured value(μg/L)			Added value (μg/L)	Recovery （%, n=7）		
		Sample1*	Sample2**	Sample3***		Sample1	Sample2	Sample3
1	BEN	ND	2.1	ND	50	89.2	91.8	99.1
2	AMO	5.3	ND	ND	50	95.6	82.3	88.5
3	CLO	ND	ND	ND	50	86.9	105.4	93.1
4	CTM	ND	ND	ND	50	87.2	83.3	101.9
5	CMZ	3.8	ND	ND	50	102.5	92.9	115.7
6	CEX	ND	ND	ND	50	91.1	108.4	98.3
7	SMZ	ND	4.2	ND	50	81.6	86.5	101.1
8	STZ	ND	ND	3.2	50	107.8	88.3	98.4
9	NOR	ND	ND	ND	50	96.0	102.5	87.5
10	PEF	ND	1.4	ND	50	97.6	98.4	110.4

*Cattle farm drainage **Chicken farm drainage ***Ordinary river water

4. CONCLUSION

This work demonstrated a new analytical procedure for simultaneous determination of ten antibiotics in natural water samples by HF-SPE-CE–ECL. The ten antibiotics could be well separated and analyzed with high sensitivity, wide linear range, and good reproducibility. This method can be directly used to determine various water samples.

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