Study on Detection of Antibiotic Contents in Water around Landfill Sites

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Abstract [**Objectives**] An ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method was established for simultaneous determination of 26 antibiotics in the water around landfills. [**Methods**] After an HLB solid-phase extraction column was activated, and a water sample, which was adjusted with phosphoric acid to a pH of (2 ± 0.5) and added with 500 mg of disodium EDTA, was loaded, and 5 ml of water and 20% methanol water was added for washing. Next, 10 ml of elution solution was added for elution, and the collected eluate was evaporated under reduced pressure at 40 ℃ to near dryness, and 1 ml of reconstitution solution was added to a constant volume. An ACQUITY UPLC BEH C18 (100 mm × 2.1 mm, 2.6 μm) chromatographic column was adopted for LC separation by gradient elution with 0.1% formic acid aqueous solution-acetonitrile as the mobile phase. For MS detection, the MRM mode was adopted for collection, and the positive and negative ion modes were switched for simultaneous determination, and the internal standard method was used for quantification. [**Results**] The correlation coefficient R2 was greater than 0.99 in the linear range of each target substance. The limits of detection ranged from 0.15 to 3.00 ng/L, and the limits of quantitation were between 0.80 and 10.00 ng/L, and the recoveries ranged from 77.9% to 104.85%. [**Conclusions**] The method has high sensitivity, good accuracy and strong practical value.

Key words Landfill; Antibiotics; Ultra high performance liquid chromatography-tandem mass spectrometry

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Antibiotics refer to a class of secondary metabolites that are produced by microorganisms or higher animals and plants in the process of life activities and have anti-pathogen or other activity or artificially-synthesized analogues[1-3]. Antibiotics enter the environment through various channels such as sewage treatment plants and landfills[4-5]. Long-term "pseudo-persistent" antibiotics will not only produce toxicity to organisms, but also induce resistance genes and enhance human drug resistance, thus causing long-term potential risks to human health and the entire ecosystem. Domestic waste landfills are the final places for stacking solid waste, and landfill leachate accompanies the whole life cycle of the landfill operation. At present, China has gained more knowledge on the research of antibiotic pollution in surface runoff of rivers and lakes[6-10]. In this study, a landfill site was selected as a typical source of pollution, and surface water and groundwater around the landfill site was collected as the research objects, in which 26 typical antibiotics with high detection rates in water bodies were detected. A rapid ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) method for simultaneous analysis of antibiotics was established by focusing on optimizing the enrichment of pH value during solid-phase extraction, chromatographic conditions and MS parameters. The method has a wide linear range, good sensitivity and high accuracy. The method was successfully applied to the analysis of water samples around the actual landfill site, providing another reliable analysis method for simultaneous determination of various endocrine disruptors in the water around landfill sites, which has strong practical value.

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Materials and Methods

Experimental instruments and reagents

Instrument: Ultra-high performance liquid chromatography-tandem massspectrometry (AB 4500, Allen-Bradley, USA); MFV-24 nitrogen blowing instrument (Guangzhou Detai Instrument Technology Co., Ltd.); solid-phase extraction device (Oasis MCX, 500 mg, 6cc, Waters, USA); Milli-Q ultra-pure water instrument (Millipore, USA); TG16W high-speed centrifuge (Changsha Pingfan Instrument and Apparatus Co., Ltd.); 0.45 μM microporous filter membrane and solid-phase extraction small column (Dikma Technologies).

Standards: Sulfadiazine, sulfamethoxazole, sulfathiazole, sulfamerazine, sulfisoxazole, sulfamethythiadiazole, sulfadimidine, prinzone, sulfaquinoxaline, sulfamonomethoxine, sulfadimethoxypyrimidine, sulfadoxine, enrofloxacin, ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, lomefloxacin, sarafloxacin, danofloxacin, oxytetracycline, tetracycline, doxycycline, aureomycin, enoxacin, sulfisomidine, sulfadoxine-D3, sulfadimethoxine-D6, norfloxacin-D5, ciprofloxacin-D8 and enrofloxacin-D5, all purchased from Shanghai Anpel Laboratory Technologies Co., Ltd.; methanol (chromatographically pure), acetonitrile (chromatographically pure) and formic acid (chromatographically pure),

purchased from Merck KGaA; ultrapure water.

Preparation of solutions

Preparation of standard stock solution: First, a 0.005 0 g of solid standard sample was accurately weighed with an electronic balance and dissolved with methanol. Next, the obtained solution was added in a 5 ml brown glass bottle to prepare a standard stock solution with a concentration of 1 mg/ml, which was sealed and stored in a refrigerator at 4 ℃ for later use.

Preparation of standard intermediate solution: First, 100 μl of 1 mg/ml standard stock solution was pipetted into a 10 ml volumetric flask with a pipette of 1 – 100 μl. Next, the transferred solution was diluted with methanol to prepare a standard solution with a concentration of 10 μg/ml.

Preparation of standard working solution: Different volumes of the 10 μg/ml standard intermediate solutions of the 26 target compounds were accurately transferred into different 10 ml volumetric flasks. Next, mixed standard solutions with different concentrations were prepared by diluting with 20% methanol water.

Elution solution: Methanol: ethyl acetate: ammonia (150∶150∶6).

Reconstitution solution ∶ Water ∶ methanol ∶ acetonitrile ∶ formic acid (40∶5∶5∶0.05).

Phosphate buffer solution: 19.3 g sodium phosphate monohydrate +10 ml phosphoric acid, with pH adjusted to 2.

Collections of samples

In July 2022, 13 surface water samples were collected from the vicinity of the urban landfill site in Dejiang County, Tongren City. At each sampling point, a 1 L brown hard glass bottle was rinsed three times, and then groundwater (shallow groundwater) 10 – 30 cm below the water surface was collected in the monitoring well. The pH value of the water sample was adjusted to a value equal to or lower than 3 with concentrated sulfuric acid, and it was transported to the laboratory for refrigeration at 1 – 5 ℃ in the dark. All samples were treated and analyzed within 48 h.

Pretreatment of samples

Extraction: Each water sample was stood still, and a 500 ml of water sample was added with 50 μl of internal standards and adjusted with phosphoric acid to a pH of (2 ± 0.5). Next, 500 mg of disodium EDTA was added.

Purification: An HLB column (500 mg, 6 ml) was placed in a solid-phase extraction device, and 6 ml of methanol and 6 ml of water were added. After discarding the effluent, a liquid to be purified was added into the small column, which was then added with 5 ml of water, and rinsed with 20% methanol water. Next, 10 ml of elution solution was added for elution, and the eluate was collected. The collected eluate was evaporated under reduced pressure at 40 ℃ to near dryness, and 1 ml of reconstitution solution was added to a constant volume. The obtained solution was filtered through a microporous filter membrane to get a filtrate for analysis by instruments.

LC and MS analysis conditions

An ACQUITY UPLC BEH C18 (100 mm × 2.1 mm, 2.6 μm) column was used to separate target objects. The separation was carried out with a column temperature at 35 ℃, a sample injection volume of 2 μl, and a flow rate at 0.4 ml/min. The mobile phase C was 0.1% formic acid, and the mobile phase B was 100% acetonitrile. The gradient elution was started with 98% C for 0 min, followed by 98% – 90% C in 0 – 1.5 min, 90% – 90% C in 1.5 – 2.0 min, 90% – 75% C in 2.0 – 2.5min, 75% – 50% C in 2.5 – 4.5 min, 50% – 98% C in 4.5 – 4.6 min, and 90% C in 4.6 – 5.5min. For MS detection, the time window of MS was divided by the MRM mode to collect positive and negative ions. An electrospray ionization source (ESI) was used in the positive ion mode. Other parameters were as follows: curtain gas pressure (CUR) 30 psi, collision gas (CAD) 9, electrospray voltage 4 500 V, auxiliary gas 1 pressure (GS1) 55 psi, auxiliary gas 2 pressure (GS2) 55 psi, interface heating gas (IHe): On, auxiliary heating gas temperature 550 ℃, and ion source temperature 150 ℃. Specific parameters are shown in Table 1.

Results and Analysis

Optimization of chromatographic conditions

In this study, the separation effects of ACQUITY UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm) and ACQUITY UPLC BEH C18 (100 mm × 2.1 mm, 2.6 μm) with different lengths were compared. The results showed that the 50 mm column was too short, and the resolution of the 26 antibiotics was not good, while the 100 mm chromatographic column was better. In order to obtain chromatographic peaks well separated with good peak shapes, the separation effects using acetonitrile and methanol as mobile phases were compared in this study. When methanol was used as the mobile phase, the resolution and peak shapes of some substances were not good, and the sensitivity of some substances was reduced, but the above situation did not occur in acetonitrile. The mobile phase (ultrapure water) did not achieve a high response to quinolones, so an attempt was made by adding 0.1% formic acid to the mobile phase (ultrapure water), which improved the response to quinolones. A chromatogram with good peak shapes, strong signals and good separation effects was achieved for all 26 antibiotics. The total ion chromatogram of 26 antibiotics is shown in Fig. 1.

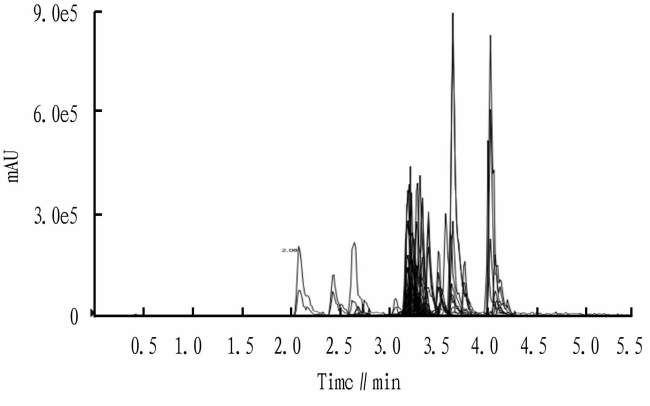

Fig. 1 Total ion chromatogram of 26 antibiotics

Table 1 MS parameters of 26 antibiotics

Compound	Parent ion//m/z	Daughter ion//m/z	Declustering potential//v	Collision energy//ev	Capillary voltage//kv	Ionization mode
Sulfadiazine	251.1	156.1*	86	23	3.0	ESI^+
	251.1	92.0	86	33		
Sulfamethoxazole	254.1	156.0*	81	22	3.0	ESI^+
	254.1	92.0	81	33		
Sulfathiazole	256.2	156.0*	76	22	3.0	ESI^+
	256.2	92.0	76	33		
Sulfamerazine	265.1	92.0*	77	23	3.0	ESI^+
	265.1	155.9	77	24		
Sulfisoxazole	268.1	156.0*	76	23	3.0	ESI^+
	268.1	92.0	76	34		
Sulfamethythiadiazole	271.0	156.0*	80	21	3.0	ESI^+
	271.0	92.0	80	35		
Sulfadimidine	279.1	186.2*	84	25	3.0	ESI^+
	279.1	92.0	84	26		
Prinzone	285.1	156.0*	81	22	3.0	ESI^+
	285.1	92.0	81	37		
Sulfaquinoxaline	301.1	156.1*	84	24	3.0	ESI^+
	301.1	108.0	84	37		
Sulfamonomethoxine	281.1	156.0*	84	24	3.0	ESI^+
	281.1	92.0	84	38		
Sulfadimethoxypyrimidine	311.0	156.0*	84	23	3.0	ESI^+
	311.0	92.0	84	20		
Sulfadoxine	311.0	156.0*	76	25.4	3.0	ESI^+
	311.0	92.0	76	34.57		
Enrofloxacin	360.1	316.1*	80	28	3.0	ESI^+
	360.1	245.1	80	36		
Ciprofloxacin	332.1	288.1*	80	25	3.0	ESI^+
	332.1	245.1	80	33		
Norfloxacin	320.1	276.1*	80	26	3.0	ESI^+
	320.1	233.1	80	35		
Ofloxacin	362.2	318.1*	80	26	3.0	ESI^+
	362.2	261.1	80	38		
Pefloxacin	334.1	316.1*	80	27	3.0	ESI^+
	334.1	290.2	80	25		
Lomefloxacin	352.0	265.0*	80	33	3.0	ESI^+
	352.0	308.1	80	28		
Sarafloxacin	386.1	342.1*	90	28	3.0	ESI^+
	386.1	299.1	90	37		
Danofloxacin	358.1	340.1*	77	30	3.0	ESI^+
	358.1	314.1	77	24		
Oxytetracycline	461.1	426.1*	30	24	3.0	ESI^+
	461.1	443.0	19	24		
Tetracycline	445.0	410.0*	31	24	3.0	ESI^+
	445.0	427.0	20	24		
Doxycycline	445.2	428.3*	80	23	3.0	ESI^+
	445.2	410.2	80	34		
Aureomycin	479.0	462.0*	26	24	3.0	ESI^+
	479.0	444.2	26	24		
Enoxacin	321.2	234.0*	90	30	3.0	ESI^+
	321.2	303.1	90	27		
Sulfisomidine	279.1	124.0*	85	27	3.0	ESI^+
	279.1	186.1	85	21		
Sulfadoxine-D3	314.0	156.0*	84	27	3.0	ESI^+
Sulfadimethoxine-D6	317.0	156.0*	84	27	3.0	ESI^+
Norfloxacin-D5	325.0	307.0*	80	30	3.0	ESI^+
Ciprofloxacin-D8	340.3	322.0*	70	25	3.0	ESI^+
Enrofloxacin-D5	325.0	307.0*	80	25	3.0	ESI^+

The mark * stands for ion for quantification.

Drawing of working curves

In this study, the mixed standard solution of the 26 antibiotics was diluted with 20% methanol aqueous solution, and prepared into a series of mixed standard solutions with mass concentrations of 10, 50, 80, 100, 200 and 500 ng/ml, respectively. The concentration of internal standard substance was 50 ng/ml. Working curves were drawn taking the area of quantitative ion mass spectrum peak of corresponding antibiotic as the ordinate and the mass concentration as the abscissa. The linear equations and regression coefficients are shown in Table 2. From the table, it can be seen that there was a good linear relation between the peak areas and mass concentrations of the 24 target substances, and the linear correlation coefficient R^2 of each substance was higher than 0.99.

Table 2 Linear equations and correlation coefficients of 26 antibiotics

Compound	Retention time min	Linear equation	Correlation coefficient R^2
Sulfadiazine	2.09	$y=0.012\ 01x-0.039\ 13$	0.998
Sulfamethoxazole	3.64	$y=0.003\ 83x-0.011\ 09$	0.998
Sulfathiazole	2.43	$y=0.007\ 50x-0.044\ 53$	0.996
Sulfamerazine	2.64	$y=0.002\ 99x-0.019\ 41$	0.992
Sulfisoxazole	3.77	$y=0.008\ 40x-0.029\ 07$	0.995
Sulfamethythiadiazole	3.28	$y=0.005\ 09x+0.020\ 58$	0.993
Sulfadimidine	3.19	$y=0.016\ 37x+0.020\ 80$	0.997
Prinzone	3.53	$y=0.003\ 04x-0.014\ 38$	0.998
Sulfaquinoxaline	4.08	$y=0.010\ 64x-0.042\ 65$	0.993
Sulfamonomethoxine	3.50	$y=0.007\ 08x-0.046\ 86$	0.998
Sulfadimethoxypyrimidine	4.02	$y=0.036\ 11x-0.170\ 44$	0.992
Sulfadoxine	3.64	$y=0.037\ 11x-0.125\ 13$	0.999
Enrofloxacin	3.33	$y=0.031\ 67x-0.048\ 43$	0.996
Ciprofloxacin	3.21	$y=0.002\ 37x-0.006\ 47$	0.999
Norfloxacin	3.18	$y=0.019\ 71x-0.061\ 05$	0.998
Ofloxacin	3.19	$y=0.051\ 55x-0.104\ 90$	0.999
pefloxacin	3.22	$y=0.051\ 05x-0.188\ 98$	0.999
Lomefloxacin	3.28	$y=0.006\ 44x-0.027\ 19$	0.998
Sarafloxacin	3.39	$y=0.029\ 86x-0.092\ 49$	0.999
Danofloxacin	3.31	$y=0.007\ 09x-0.046\ 79$	0.997
Oxytetracycline	3.05	$y=3\ 029.10x-13\ 971.16$	0.998
Tetracycline	3.20	$y=4\ 148.86x-10\ 950.64$	0.998
Doxycycline	3.57	$y=13\ 443.28x-18\ 714.04$	0.997
Aureomycin	3.50	$y=3\ 704.80x+16\ 285.95$	0.999
Enoxacin	3.18	$y=0.001\ 41x+0.001\ 59$	0.998
Sulfisomidine	3.19	$y=0.005\ 73x+0.023\ 80$	0.996

Recoveries and limits of detection

The mixed standard solutions of 26 endocrine disruptors were accurately added to 500 ml of ultra-pure water and Watsons purified water, respectively, to carry out a recovery test, and the recoveries and precision of the method were investigated. The spiked concentration levels were low (5.00 ng/L), medium (20.00 ng/L) and high (100.00 ng/L). The limits of detection ranged from 0.15 to 3.00 ng/L, and the limits of quantitation were between 0.80 and 10.00 ng/L, and the recoveries ranged from 77.9% to 104.85%. The results are shown in Table 3.

Table 3 Recoveries and detection limits of 26 antibiotics

Compound	Spiked concentration 20 ng/L	Spiked concentration 100 ng/L	Spiked concentration 150 ng/L	Limit of detection ng/L	Limit of quantification ng/L
Sulfadiazine	78.5	88.6	101.2	0.30	1.00
Sulfamethoxazole	89.4	99.3	79.8	1.00	5.00
Sulfathiazole	89.2	96.4	80.5	1.00	5.00
Sulfamerazine	88.5	87.5	99.7	3.00	10.00
Sulfisoxazole	79.8	103.6	94.7	1.00	5.00
Sulfamethythiadiazole	83.8	105.3	87.5	1.00	5.00
Sulfadimidine	89.4	81.2	99.6	0.30	1.00
Sulfadimidine	102.6	79.5	101.6	2.00	8.00
Sulfaquinoxaline	78.3	102.3	85.7	0.50	2.00
Sulfamonomethoxine	88.7	98.6	78.9	1.00	5.00
Sulfadimethoxypyrimidine	89.6	93.1	89.5	0.25	1.00
Sulfadoxine	89.3	96.4	85.2	0.15	0.80
Enrofloxacin	99.6	87.9	92.4	0.50	2.00
Ciprofloxacin	90.5	87.4	98.3	0.80	3.00
Norfloxacin	95.3	96.2	104.3	1.00	5.00
Ofloxacin	89.6	94.8	98.2	0.30	1.00
Pefloxacin	83.5	79.4	104.8	0.50	2.00
Lomefloxacin	86.1	91.6	102.9	0.30	1.00
Sarafloxacin	86.0	90.1	85.3	0.50	2.00
Danofloxacin	99.6	86.3	88.0	0.50	2.00
Oxytetracycline	104.3	84.2	93.5	3.00	10.00
Tetracycline	77.9	87.3	90.3	2.00	8.00
Doxycycline	80.4	108.2	99.2	0.50	2.00
Aureomycin	94.7	90.7	83.2	2.00	8.00
Enoxacin	90.1	88.6	81.0	2.00	8.00
Sulfisomidine	90.3	79.3	93.4	0.30	1.00

Table 4 Data of actual sample test

Point location	Sulfadiazine // μg/L	Ofloxacin // μg/L	Sulfadimidine // μg/L
WS001	0.200	0.530	0.990
WS002	0.024	0.120	0.089
DB013	–	0.021	–
DB014	–	0.012	–
DB015	–	0.014	–
DB016	–	0.048	–
DB017	–	0.054	–
DB018	–	0.023	–
DB019	–	0.023	–
DB020	–	0.022	–

Actual sample analysis

The determination method established in this study was applied to the analysis of antibiotics in samples from 13 locations around the landfill site in Dejiang County, Tongren City. Three antibiotics were detected in total, and the detection data are shown in Table 4. Among them, ofloxacin had the highest detection frequency, and was detected at 8 detection points, with a detection rate of 61.5%. The detection concentration of sulfadimidine was the highest, with a value of 0.99 μg/L. The results indicated that this analysis method has good practical value for the determination

of antibiotics in water samples around landfill sites.

Conclusions and Discussion

This study established an LC-MS/MS analysis method that could simultaneously detect the contents of 26 antibiotics in the water surrounding the landfill site. The samples were enriched by an HLB solid-phase extraction column and then determined by LC-MS. The limits of detection ranged from 0.15 to 3.00 ng/L, and the limits of quantitation were between 0.80 and 10.00 ng/L, and the recoveries ranged from 77.9% to 104.85%. Three antibiotics were detected in the actual samples. Among them, ofloxacin had the highest detection frequency, and was detected at 8 detection points, with a detection rate of 61.5%. The detection concentration of sulfadimidine was the highest, with a value of 0.99 μg/L.

The results indicated that the method has high sensitivity and good accuracy. This study provides a rapid, accurate and reliable analysis method for the determination of antibiotics in the water around landfill sites, which has strong practical value.

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(Continued from page 11)

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