Review Article

Studying Analytical Methods for Monitoring of Antibiotics in Environmental Waters, A review

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Abstract

In recent years, there has been a rise in interest in the study of antibiotic occurrence in the aquatic environment due to the negative consequences of prolonged exposure and the potential for bacterial antibiotic resistance. Most antibiotic residues from treated wastewater end up in the aquatic environment as they are not eliminated in facilities that treat wastewater. Antibiotics must be identified in influent and effluent wastewater using reliable analytical techniques for several reasons. Firstly, monitoring antibiotic presence in aquatic environments. Secondly, assessing environmental risks, computing wastewater treatment plant removal efficiencies, and estimating antibiotic consumption. Therefore, this work aims to provide an overview of existing approaches for determining antibiotics in complicated matrices including wastewater. Because it is currently the most effective and often used analytical method for determining antibiotic residue, liquid chromatography linked to tandem mass spectrometry was chosen.

Keywords: Antibiotics, Analytical Methods, Environmental waters, Review

1. Introduction

Identifying current contaminants in numerous surface water bodies worldwide, including personal care and pharmaceutical products, hydrocarbons [1], and petroleum products, has presented environmentalists with a problem [2]. Pharmaceuticals are a class of newly emerging, environmentally hazardous substances that are extensively employed in human medicine. They may arrive in the environment as conjugates, metabolites, parent chemicals, or all. The consumption of pharmaceuticals has increased in recent years as a result of improvements in medical care [3]. Pharmaceuticals are now classified as emerging contaminants due to their essential increase in [4]. Drugs have been detected at concentrations as low as a few µg/L in surface waters and wastewater. The most extensively researched categories of medicines are antibiotics, steroid compounds, analgesics/nonsteroidal anti-inflammatory medications, and anti-inflammatory drugs [5]. Healthcare effluents, generally produced by all parts of medical facilities, including hospitals, are a significant source of new pollutants in many developing nations. Among these pollutants are heavy metals [6], bacteria and genes resistant to antibiotics, and antibiotic residues [7].

Antibiotics are necessary for the treatment of many infectious diseases, including potentially fatal tuberculosis [8]. They have been found in drinking water as well as wastewater, surface and groundwater, and other aquatic environments [9–11]. The presence, durability, and destiny of these organisms in the environment are of increasing interest since low antibiotic doses can encourage the growth of antibiotic-resistant bacteria. The use of antibiotics in animal husbandry has led to an increase in pathogenic bacteria strains that are resistant to antibiotics, posing a significant health threat. People can come into contact with antibiotic-resistant bacteria or resistance genes from animals [12].

Recent years have seen evidence of antibiotic-resistant bacteria proliferating, which has become a global health concern. Many antibiotics, including trimethoprim, clindamycin, sulfamethoxazole, and loxacin, are included in the most recent updated list of substances. Wastewater treatment plant (WWTP) emissions are a main source of antibiotics that end up in environmental waters. Nowadays, the creation of advanced methods for the detection of antibiotics in wastewater influent and effluent is essential to achieving many objectives. Some of them are assessing the possible issues that may arise from the presence of these compounds in wastewater and evaluating the efficacy of WWTPs in removing them [13].

In the medical field, antibiotics are widely used to treat bacterial infections as well as to encourage animal growth and increase livestock yield. Although a sufficient withdrawal period is advised, public health worries about antibiotics circulating up the food chain have surfaced in the past ten years. These residues could consist of the original, unchanged compound as well as metabolites and/or conjugates. They might cause allergic reactions in those who are already hypersensitive, directly hurting customers [14].

Because antibiotics are poorly metabolized in both human and animal species, a significant portion of them are excreted into environmental samples via manure. Antibiotic residues are easily transmitted across the food chain and are encountered by both plants and animals. Aminoglycoside antibiotics, for instance, have half-lives of 2 to 3 hours in plasma and 30 to 700 hours in tissues. Additionally, sulfonamide antibiotics, such as sulfamethoxazole, have a poor rate of biodegradation, allowing them to linger in the environment for extended periods [15].

Antibiotics can enter and accumulate in the human body in a variety of ways. The development in living standards has made food safety and quality a major concern in today's world. A plentiful, wholesome, and safe supply of food is essential for one's physical, social, and economic well-being. The European Union has developed pertinent guidelines for figuring out the maximum residue limits of medications in food that are derived from animals. The goal of this idea is to provide a sustainable solution for animal feed. However, fruits and vegetables as well as food derived from animals may get contaminated by the antibiotics still present in their bodies. Water that has been recovered for irrigation and organic fertilizers made from animal dung and municipal waste are employed in agriculture. Antibiotic residues in soil are mostly caused by animal feces, which is utilized as an excellent and high-yield organic fertilizer. Furthermore, without being disposed of safely, more than 80% of animal excrement was applied straight to the soil. Because antibiotics degrade easily in soil settings and dissolve easily in water, it is easy for plants to absorb antibiotics and their metabolites. Antibiotics enter the body through the food chain and damage people's health when they eat tainted fruits and vegetables [16].

There are various routes by which antibiotics are discharged into the aquatic environment. Since they are typically not well absorbed by the body, they are eliminated into the sewage system through urine and feces, either unaltered or altered. Numerous studies have demonstrated that medicines are not completely removed during wastewater treatment procedures. Pharmaceuticals are thought to be one of the main causes of the environmental presence of WWTPs. Medications and their metabolites have been discovered in WWTP effluents. As a result, they have access to both surface and groundwater. The presence of trace amounts of these bioactive chemicals presents a potential harm to aquatic and soil species. Antibiotics are also one of the main causes of their presence in aquatic environments [17,18].

The main source of antibiotics in the environment is human and animal excretion of partially digested antibiotics. Waste from pharmaceutical production procedures and the disposal of leftover antibiotics could be other sources. Antibiotics are known to be added to municipal wastewater by both commercial and residential establishments. Additional possible sources of antibiotic contamination in surface and groundwater include surface runoff from concentrated animal feeding operations, wastewater treatment plant effluent, and industrial facilities, such as pharmaceutical plants. To effectively assess the dangers, consequences, and potential effects of these goods, it is crucial to be aware of the quantities of these antibiotics released into the aquatic environment [19].

Antibiotics are substances that function to either destroy or hinder the growth of microorganisms. They can be synthetic or semi-synthetic compounds that naturally create antibacterial molecules. These medications are used to treat and prevent illnesses in both people and animals. These substances inhibit metabolic pathways, protein synthesis, cell membrane structure, and nucleic acid function, affecting various aspects of life [20].

Antibiotics are without a doubt the most effective medication family. The treatment of illnesses and the advancement have benefited greatly from antibiotics. As a result of drug use or abuse, antibiotic resistance may pose a serious risk to both humans and animals. Antibiotic prophylaxis was necessary for the treatment of infectious disorders as well as other ailments to prevent associated infections. According to research, the main cause of the development which lessens the action of antibiotics is antibiotic-resistance genes. The body may become dangerously overloaded with antibiotics. Long-term absorption of antibiotic residues in food can have negative health effects, such as mutagenesis and allergy. Nevertheless, drug buildup can also damage the ecological environment, prevent the growth of gastrointestinal flora, and make harmful bacteria more resistant to drugs [16].

2. Analytical methods

Antibiotic residues are assumed to be the source of antibiotic-resistant bacterial strains, which is why it is so important to find them in environmental samples. It is also critical to remember that both humans and animals are potential pollutants due to the large amounts of antibiotics they consume and the continuous release of these drugs into the environment. Runoff, discharges, and compost are influenced by domestic wastewater treatment, pharmaceutical companies, animal feeding operations, aquaculture infiltration, and animal dung containing antibiotics. Therefore, it is believed that point and non-point source discharges of wastewater from cities and farms are the cause of antibiotic contamination in surface and ground waterways. Antibiotic residues can remain in the environment for a long time as a result of insufficient treatment because the wastewater treatment process itself is unable to eliminate these substances [21].

The low concentrations of chemicals are typically found in ambient waters, along with the highly complex matrices under study, making analyzing antibiotics in the environment a challenging undertaking. The necessity to monitor these analytes at low concentration levels of ng/L necessitates the development of sensitive analytical techniques. It is essential to perform a pre-concentration step before detection. Liquid chromatography (LC) analysis often comes after solid phase extraction (SPE). These days, injecting water samples straight into an ultra-high-performance liquid chromatography (UHPLC) system with mass spectrometry detection is a new trend. Analytes can be precise without the requirement for pre-concentration [12].

The aquatic environment has been shown to contain antibiotics. As a result, residual analytical approaches are currently the method of choice for classifying and tracking antibiotics. These techniques need to be straightforward to use, and time-efficient when analyzing environmental sample data. We try to condense recently reported analytical techniques for the identification of antibiotics in environmental sample data in this study.

2.1. Analytical process

2.1.1. Sampling

Five steps usually comprise the entire analytical procedure: sample preparation, chromatographic separation, detection, data processing, and sampling. Sampling and sample preparation account for over 80% of the analytical time, making them the most critical steps in the analytical process. Filtration is an additional crucial component in the sampling procedure. It is usually done as soon as the material gets to the lab. Glass-fiber filters measuring 0.45 or 0.2 µm are typically used for the filtration process. Either centrifuging the sample or performing the second filtering right before the sample preparation stage are options. Filtration is required to get rid of particles from water samples that could clog SPE cartridges and cause the sample preparation process to go significantly more slowly.

2.1.2. Sample pre-treatment and extraction procedure

In environmental analysis, sample preparation is an essential step. The physical and chemical characteristics of the analytes under study, as well as matrices, have a significant impact. The primary objectives are to extract analytes from the matrix, concentrate, and prepare the analytes in the sample for chromatographic analysis later on. Processing the extract and getting the sample ready for chromatographic analysis later on are common steps in the sample preparation procedure. The majority of the time, SPE has handled the pre-concentration and cleanup. The polarity of the analytes and the sample matrix must be taken into consideration while choosing the best SPE sorbent. Traditional SPE sorbent chemistries include ion-exchange materials, polymeric materials, and chemically linked silica. Using the online SPE connection, the sample preparation phase can be completed.

2.1.3. Analytical methods in the antibiotics analysis

During the initial research period in the manufacturing of new medical equipment, the analytical methods play a crucial role in assessing the effectiveness and safety of the products [22]. Several techniques for determining the important participants in this class in a range of environmental samples were analyzed [23]. In contrast, MS/MS is necessary for the identity of residues in wastewater. MS detection can be used to confirm the molecular structure of the material or to identify and quantify it, as it is in most research. This mode gives structural information and enables compound confirmation [12].

Analyte separation in chromatography was primarily accomplished using C18 analytical columns. Typically, the mobile phases for the LC separation were methanol or acetonitrile mixed with water. All published multi-residue investigations employed gradient elution. To increase the MS detection and analyte ionization in the examination of medicines. Antibiotics and other chemicals from several pharmacological families were identified using UHPLC. With the use of columns filled with sub-2 m particles, UHPLC is a contemporary technology that allows sample components to be eluted in much narrower. This improves chromatographic resolution and increases peak capacity since the short column elutes sample components quickly. It was examined how fast the UHPLC system performed vs the traditional HPLC system that used 5 µ particles. Because of the system's low dead volume, which allowed for short equilibration durations (less than one minute) the analysis time was significantly reduced [12].

Even though spectrophotometric methods can be used to identify environmental and pharmaceutical samples due to their simplicity and low cost [24–26], the most effective and popular method currently available for determining antibiotic residues is LC-MS/MS. In addition, ionization mass spectrometry has been used to examine the materials, including minute pharmaceutical substances [27]. Among the topics covered in this paper were the mass spectrometric behavior of eighteen carefully chosen antibiotics.

Pressurized liquid extraction (PLE) and LC–APCI-MS–MS were used to establish an analytical method for tiamulin and other macrolide and ionophore antibiotics from soil. SPE with a cartridge was used to clean up the extracts following the 30-minute PLE extraction of the analytes from the soil. The antibiotics were separated using LC in 35 minutes. Spiked soil was used in recovery trials, with dosages ranging from 1 to 2000 mg/kg. The macrolides erythromycin and roxithromycin showed recovery rates ranging from 43 to 94% (RSD 20–23%) when measured against a macrolide internal standard. The ionophore salinomycin showed a recovery rate of 76% (RSD 29%), and the pleuromutilin tiamulin showed perfect recovery. The detection limits varied between 0.2 and 1.6 µg/kg. The highest concentration of 0.7 µg/kg of tiamulin was discovered in the soil sample [28].

To identify the most beneficial antibiotics (tetracyclines and sulphonamides) used in aquaculture, HPLC with MS/MS detection was created and refined. A straightforward extraction process that omitted any cleanup phase was assessed to maximize the recovery of analytes from fish samples. For quantification, a standard calibration curve produced in the mobile phase was utilized since no matrix effects were observed. Fish samples free of antibiotics were spiked at various concentrations and subjected to an optimized HPLC technique analysis. The methodology that was suggested offered detection limits for the antibiotics that were tested within the range of 1.2-16 µg/kg, which is less than the maximum residue level set by the European Union, which is 100 µg/kg. Ultimately, an analysis was conducted on commercial fish samples sourced from various regions to verify the efficacy of the devised methodology [14].

Nine target antibiotics were subjected to analysis of variance using response surface methodology. It was discovered that the extraction recoveries were dependent on the pH, elution solvent volume, and Na4EDTA concentration as independent factors. All target antibiotics underwent a pH-dependent extraction process, with pH serving as a key model term. Following method validation under ideal operating circumstances, recoveries for antibiotics in groundwater samples and spiked river water samples ranged from 50 to 117% [29].

Online SPE and LC-MS/MS were used to analyze sewage samples from hospitals, nurseries, slaughterhouses, and source water samples from the Chongqing region of three Gorge Reservoir for the antibiotics. The hospital had the highest concentration of ofloxacin in any water environment. The wastewater treatment plant's antibiotic removal range was 18–100% When compared to secondary treatment, antibiotics were eliminated more effectively during primary treatment [19].

Using HPLC-MS/MS, samples of different samples were examined for up to 29 different chemicals. Antibiotics were identified in all of the surface waters. Samples taken in the spring had the greatest quantities of erythromycin (300 ng/L). Certain compounds found and features of the environment point to agricultural input in certain instances. By using a rapid immunoassay technique to examine several liquid manure samples, sulfadimidine was found to be present. Even after seven months, the liquid manure-fertilized soil exhibited a sulfadimidine content of 15 µg/kg dry weight that could be extracted using accelerated solvent extraction (ASE). This shows that some antibiotics are highly stable in soil and manure [30].

An analytical multi-method is described for the detection of antibiotics in water samples. The analytes are classified as macrolid antibiotics, among other antibiotic families. Samples were enhanced facultatively by SPE or by universal freeze-drying. LC with electrospray–tandem MS detection was used for the analysis. In chromatography, distinct eluents and columns are needed. With one exception, mean recovery rates were over 70%. Tetracycline quantitation limits were set at 50 ng/l and 20 ng/l for the remaining drugs [31].

Clinical management especially in critical can be achieved through the monitoring of plasma antibiotic medication levels. Following the addition of ceforanid, the plasma sample was subjected to SPE before HPLC analysis. On a C8 symmetry column, chromatographic separation was obtained using a gradient mode mobile phase that included a mixture of phosphate buffer and acetonitrile. Between 200 and 400 nm was the wavelength used for detection. The technique devised demonstrated linearity throughout the 2.5–60 µg/mL concentration range for every antibiotic present in the plasma samples. Precision varied from 0.9 to 12.2% and accuracy from 93.2 to 107.1%. The technique is suitable for the quick assessment of plasma concentrations for therapeutic monitoring applications and has been used with plasma samples taken from patients receiving lactam antibiotics [32].

A technique for identifying antibiotics in hospital wastewater has been created and approved. The calibration of them including penicillins and nitroimidazoles was effectively accomplished using analog internal standards. Ion suppression/enhancement effects were caused by matrix components that were examined. Two effects were noted: the MS response varied briefly and was generally suppressed. Significant temporal fluctuations in the analyte concentration were seen in the hospital sewage water. The concentrations of the analytes ranged (in µ/L) from 3.6–101.0 for ciprofloxacin, 0.1–90.2 for metronidazole, 0.4–12.8 for sulfamethoxazole, 0.2–7.6 for ofloxacin, 0.6–7.6 for trimethoprim, and 0.6–6.7 for doxycycline [17].

A SPE method that is both sensitive and strong was created, and it involves LC–ESI–MS to determine fluoroquinolones, trimethoprim, sulfamethoxazole, and cephalosporines. Sample recoveries were found to be greater than 80%. The method used for identification was LC-ESI-MS/MS. The quasimolecular ions $[M+H]^+$ peaks allowed for the determination of molecular masses, while the structural assignment was made possible by the fragment ions of $[M+H]^+$ ions acquired by MS/MS. Using the quasimolecular ions $[M+H]^+$ of the parent chemicals were used to quantify the data. It was discovered that a few antibiotics were present in the surface waters of some lakes in Hyderabad, India [33].

The article developed a procedure that used LC-MS/MS and SPE to identify eleven sulphonamide chemicals in drinking and surface waters. Analyte recoveries in drinking water and surface water matrices at varying fortification levels consistently surpass 87%. Depending on the chemical, surface water sample quantification limits range from 0.005 to 0.021 µg/L; and the precision of the inter-day approach is less than 12%. Water samples from drinking and surface sources were examined for matrix effects [10].

In addition to tracking the presence of leftover antibiotics in the agricultural setting, an analytical technique for identifying four types of antibiotics in soil and river water was created. Target VAs were quantified by LC-MS/MS after SPE was used to extract soil samples using the McIlvain buffer solution. According to the study's findings, the recovery in soil ranged from 40.2-149.3% and in river water from 62-12%. The residual VA concentrations in water samples near Korea's Muhan watershed were then measured using this ideal technique. The quantities of the seven antibiotics that were found varied from 1.45 to 9.04 µg/kg in arable soil and river water, respectively, ranging from 0.014 to 0.309 µg/L. This technique is likely to be utilized as primary data for investigating the incidence and fate of antibiotics in agricultural contexts [34].

A UPLC-MS/MS assay was developed for the rapid and highly sensitive quantification of several antibiotics. The mobile phase was supplied in a gradient elution mode at 500 µl/min and comprised two components: (A) ammonium acetate and (B) acetonitrile acidified with 0.1% formic acid. The run took 2.75 minutes in total. Both the multiple-reaction monitoring and turbo-ion spray-positive modes identified ions. For the quantification of the antibiotics in serum samples over a wide concentration range, the test demonstrated accuracy and reproducibility [35].

The report by Turiel presents the findings of degradation research conducted in river water samples using the (fluoro) quinolone antibiotics ciprofloxacin and oxolinic acid. HPLC-UV was used to track the breakdown of these compounds at room temperature for five months. Two distinct mechanisms of degradation—photo- and bio/chemical—were seen in each case, albeit at varying rates. After three months, ciprofloxacin was broken down, however after five months in storage, 80% of oxolinic acid was still intact. With the use of tandem MS-MS and MS, the breakdown chemicals were analyzed [18].

Using a single SPE coupled to LC has been used to analyze many antibiotics in chlorine-disinfected drinking water. The majority of the quantitation limits in drinking water were less than 10 ng/L. The technique of standard addition was employed for quantification as the concentrated sample matrix usually resulted in ion suppression during electrospray ionization. Certain antibiotics can react with chlorine residuals in drinking water. However, ascorbic acid is a useful agent for quenching chlorine without interfering with the stability and analysis of the antibiotics in water. Using this technique, research found that several antibiotics were present in drinking water [11].

The review was conducted using a survey, and information was obtained by presenting the results of each method. Among the many analytical technologies used to identify antibiotics, Table 2 shows the list of antibiotics with different details in the corresponding matrices, proving that LC-MS/MS is the most remarkable and advanced technology for estimating multi-class antibiotics with low sensitivity.

Table 1. Analytical methods for the determination of antibiotics in environmental waters

Method	Range of concentrations	(R^2)	LOD	Application	Ref.
LC-MS/MS	5–50 ng/L	0.999	<10 ng/L	Drinking water	[11]
LC-MS/MS	0.5–500 ng/L	0.95–0.99	0.8-25 ng/L	Ground, surface, and treated water samples	[29]
LC-MS/MS	20–2000 ng/L	0.997–0.999	3.2–6.2 ng/L	Lake water and sewage effluent samples	[36]
HPLC	1.26–127.49 ng/L	>0.995	1–17.5 ng/L	Groundwater, river water, and wastewater	[37]
HPLC-electrospray-MS/MS	–		10–5000 ng/L	Ground and surface water samples	[38]
LC-Fluorescence	0.05–5 µg/L	0.9924–0.9994	3.1–11.2 ng/L	Influent and effluent water from sewage	[39]
LC-Fluorescence	1.0–200 ng/L	0.998–0.999	1.0–679 ng/L	Tap water	[40]
UPLC-MS	–	≥0.993	10–50 ng/L	Pond water	[41]
HPLC	1.0–800 ng/mL	0.9986–0.9996	0.25–0.50 ng/mL	Environmental water	[42]
HPLC	10–3000 µg/L	0.9957–0.9989	8.0–20 ng/L	Lake and river water	[43]

The analysis of antibiotics requires a more adaptable, rapid, and sensitive method. This could have a big impact on how these compounds are analyzed to produce better, more affordable results. Thus, the objective of the review was to give a summary of the analytical methods that were used to determine the antibiotics in environmental waters.

Conclusion

Improved techniques for detecting and quantifying antibiotics have been developed as a result of the recent rise in the use of antibiotics in several fields. The latest methods developed to identify the different antibiotics in environmental waters are summarized in this review. In the antibiotic extraction methods discussed in these papers, the target analytes are usually extracted from environmental samples using a suitable solvent. Finally, the collected antibiotics are usually identified using HPLC, the most popular detection technique. SPE has become the most widely used sample treatment method for detecting antibiotics in environmental samples because of its advantages and greater compatibility with green analytical chemistry.

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