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Liquid chromatography, a valuable tool in the determination of antibiotics in biological, food and environmental samples

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ABSTRACT

This review is the result of a survey across the bibliography about the determination of several antibiotics in biological, food and environmental samples by liquid chromatography. Their determination in those samples is usually made in clinical monitoring, food safety and environmental studies. A brief description of the pharmacological activity is provided, to complement the relevance of the topic bioanalytical method. Exposure to antimicrobial agents, which can be evaluated by the analysis of biological fluids, comes mainly from their extensive use as veterinary agents in industrial animal farming, via food chain and residual water poured to the environment. Common columns and mobile phases are C18 ones and mixtures of aqueous buffers, acetonitrile and methanol, respectively. Retention times of these analyses are 20–30 min with column temperatures ranging from 15 to 45 °C and injection volumes of 10–20 μL. Detection is mainly performed by UV–Visible absorbance and MS/MS detection in positive mode, excluding glycopeptides where fluorescence was used. These procedures exhibit adequate analytical performances: good selectivity, precision, linearity range, ruggedness and sensitivity, though variable trueness. The future trend in the management and control of antibiotics in the here studied samples should be the development of automatized on-line detection protocols (sample processing coupled to chromatographic separation) for currently studied antibiotics and new methods for unknown metabolites and the transformation products.

1. Introduction

Drugs refers to a heterogeneous group of substances with different pharmacokinetic and pharmacodynamic behaviour. They exert a specific action on some structures or functions of the microorganism, they have high biological potency acting at low concentrations and toxicity is selective, with minimal effect on cells from human organism. They are largely used in human medicine [1–3].

The term 'antibiotic' is commonly used to name a very diverse range of compounds, natural, semi-synthetic or synthetic, displaying antibacterial activity. The main groups of antibiotics are: penicillins, cephalosporins, carbapenems, tetracyclines, macrolides, aminoglycosides, amphenicols, sulfonamides, nitroimidazoles, nitrofurans and quinolones. These compounds have been employed for many years in food producing animals, like intensive high-density husbandry, apiculture and aquaculture, for the treatment of infectious diseases. Additionally, they may be used as prophylactic agents and to promote growth, thus to increase the economic profit of the activity [4].

However, their widespread and indiscriminate administration and misuse has resulted in the occurrence of antibiotic residues in edible tissues. Medium and long-term exposure of population to low amount of these compounds is a public health concern, related to several disorders, such as weakening of the intestinal flora, allergy reactions, mutagenesis, teratogenesis, carcinogenesis and the emergence of antibiotic-resistant bacterial strains and human antibiotic resistance. This might bring about an outbreak of infections, which cannot be treated with the current antibiotic arsenal, and then give rise to serious consequences for individual patients and increase the costs of medical care. Zoonotic bacteria

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may also get the immunity to the antibiotics in the living animal, and be lately transmitted to other ones and to the consumers by means of the food chain or by direct contact. What's more, they can reach considerable concentrations in the environment and disrupt the ecological balance. To prevent this, several practices have been recommended to producers to rationalize the use of antibiotics, like the administration of therapeutic doses only to infected or at risk animal until the desired clinical response and under the supervision of a veterinary, and expand the withdrawal period. Within the frame of its objective of protecting human health and maintaining the perception of European food products as healthy and high-quality and responding to the concern among population and public agencies about the risks coming from the excessive use of antibiotics, the EU, by the Commission Regulation 37/2010 [5], has set maximum residue limits (MRLs) for most of them in a large variety of animal derived food products [6–11]. MRL ranged from 10 to 6000 μg/kg depending on the drug and sample. In some food samples, the drug is defined as "not for use in animals raised for food purposes" and it should not be found at any concentration [5]. Another point of entry to the environment is communal wastewater, fundamentally through urine and haeces of patients, either in its prime form or as a metabolite or even from dosage left after finishing the treatment, as patients usually buy more medicament pharmaceutical than needed for the treatment. As far as this is concerned, the excess is sometimes taken out with the normal rubbish or even poured down by the drain, what also represents an important source of pollution by drugs. However, there is not current regulation regarding the release of pharmaceuticals into municipal wastewater [12].

Antibiotic therapies are based on controlling and decreasing the number of viable microorganisms, so that the immune system is able to eliminate all of them. According to the germ-antibiotic interaction, these drugs can be classified depending on their activity in the serum or tissues into bactericides, with lethal action leading to bacterial lysis, and bacteriostats, preventing the development and bacterial multiplication but without destroying the cells. In this last case, when the antibiotic is removed, the microorganism can multiply again [1,3].

There are several types of classifications: according to the spectrum of action, mechanism of action and pharmacokinetics (absorption, distribution, elimination) and pharmacodynamics. Therefore, clinicians need to understand the relationship between drug exposure and their effects, both desirable (bacterial death in our case) and undesirable (development of tolerance or toxicity). Antibiotics can be classified according to the way in which death or bacterial inhibition occurs in time-dependent antibiotics and concentration-dependent antibiotics. In the case of time-dependents (beta-lactams and macrolides) the success of the treatment is given by maintaining the concentrations above the minimum inhibitory concentration (MIC) for as long as possible in doses (T > MIC). In the case of concentration-dependents, therapeutic success is given to achieve a good peak concentration (peak/MIC) or a good area under the curve (AUC/MIC), depending on the drug. A description of the chemical structure, antibiotic effects and pharmacology of the antibiotic by groups is below provided [1–3]. The general structures can be seen in Fig. 1.

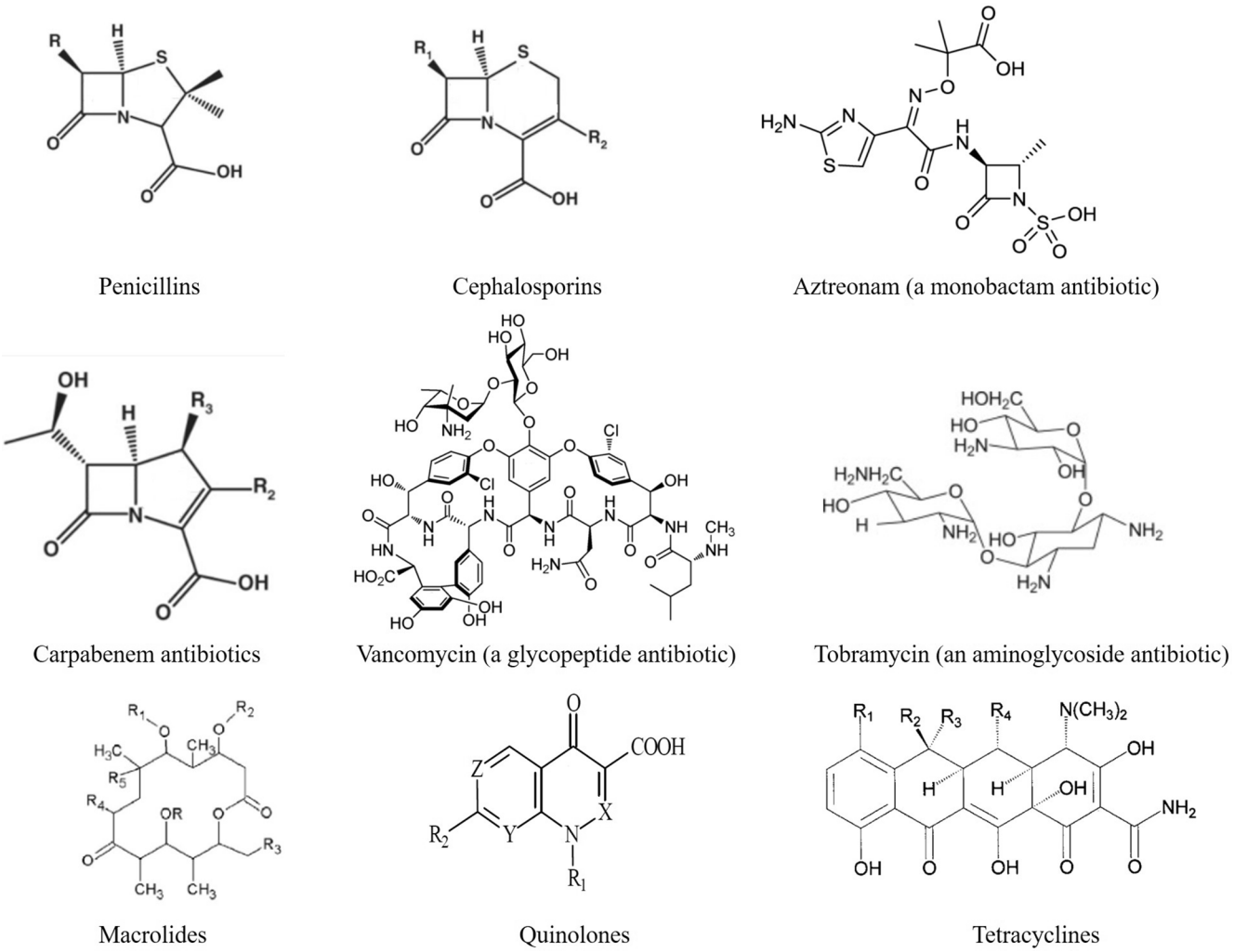

Fig. 1. General structure of the main antibiotic groups.

1.1. Beta-lactam antibiotics

Group of antibiotics of natural origin or semi-synthetic that are characterized by the presence of a beta-lactam ring in their structure. They constitute the largest family of antibiotics and the most widely used in clinical practice. These are compounds with a slow bactericidal action, relatively independent of plasma concentration, which present little toxicity and have a wide therapeutic range. Its spectrum has been extended over the years by the incorporation of new molecules with higher activity against gram-negative bacilli. Nevertheless, the progressive appearance of acquired resistances has limited its empirical use and its effectiveness in certain situations. The beta-lactam ring is very unstable and can easily undergo a variety of reactions such as hydrolysis, molecular rearrangement, and polymerization. The key to maintaining the quality of β–lactam antibiotics is the control of related substances.

Within the beta-lactams we can find gram-positive, gram-negative and spirochetes. They are not active on mycoplasmas because they lack the cell wall, nor on intracellular bacteria. The natural resistance of mycobacteria is due to the production of beta-lactamases, probably linked to a slow penetration by the characteristics of the wall.

Beta-lactam antibiotics are bactericidal agents that inhibit the synthesis of the bacterial cell wall and also induce an autolytic effect. The destruction of the bacterial cell wall occurs as a consequence of the inhibition of the last stage of peptidoglycan synthesis. Peptidoglycan is made up of long chains of carbohydrates, formed by the repetition of molecules of N-acetylmuramic acid and N-acetylglucosamine. The muramic acid binds tetrapeptide chains that bind to each other to form a mesh, directly (gram-negative) or by a pentapeptide (gram-positive). The beta-lactams inhibit precisely this union or transpeptidation, the last stage of the synthesis of the cell wall. In this way, the wall is weakened and can be broken by the intracellular osmotic pressure. For the beta-lactams to act, it is necessary that the bacteria be in the multiplication phase, since that is when the cell wall is synthesized. Regarding to their pharmacodynamics, beta-lactams are antibiotics with slow bactericidal activity, relatively independent of the plasma concentration reached.

They can be classified into four different subgroups: penicillins, cephalosporins, monobactams and carbapenems:

1.1.1. Penicillins

They are a group of antibiotics of natural and semisynthetic origin that contain the nucleus of aminopenicillanic acid, which consists of a beta-lactam ring linked to a thiazolidin ring (Fig. 1). The compounds of natural origin are produced by different species of *Penicillum spp*. Penicillins differ from each other by substitutions at position 6 of the ring, where changes in the side chain can induce modifications in antibacterial activity and pharmacokinetic properties. They can be classified into natural penicillins, penicillins resistant to staphylococcal penicillinase, aminopenicillin, carboxypenicillin, ureidopenicillin. Regarding to their pharmacology, oral absorption differs in different penicillins. The antistaphylococcal penicillins, oxacillin and dicloxacillin, are stable to gastric acid and are suitably absorbed. Penicillins are distributed in many compartments such as lungs, liver, muscle, bone and placenta. Penetration in the eye, brain, cerebrospinal fluid and prostate is poor in the absence of inflammation. In the blood, beta-lactams circulate as free substances or bound to plasma proteins, this connection being related to the half-life of the antibiotic; only the free fraction of the drug is active and capable of penetrating the extracellular space.

1.1.2. Cephalosporins

They are products of natural origin derived from products of the fermentation of *Cephalosporium acremonium*. They contain a nucleus consisting of a 7-aminocephalosporanic acid formed by a beta-lactam ring attached to a dihydrothiazine ring (Fig. 1). Most cephalosporins are parenterally administered, although there are an increasing number of oral formulations such as cephalexin, cephradine, cefadroxil, cefuroximeaxetil and others. Good concentrations are obtained in biological fluids and serum and good intracellular concentrations are not obtained. Cefotaxime, ceftriaxone, cefoperazone and cefepime enter the CSF reaching high concentrations.

1.1.3. Monobactams

Aztreonam (Fig. 1) is the only monobactam available for clinical use. It has a second thiazole ring, but it is not fused to the beta-lactam ring (Fig. 1). It exhibits excellent activity on aerobic and facultative gram-negative bacteria. On the contrary, it lacks activity against gram-positive and anaerobic bacteria. Other examples of monobactams are tigemonam, nocardicin A, and tabtoxin. Adverse effects to monobactams can include skin rash and occasional abnormal liver functions.

1.1.4. Carbapenems

As far as we know, this subgroup displays the largest spectrum of bactericidal activity among the beta-lactams (Fig. 1). Imipenem is the first carbapenem developed for clinical use. It is a semi-synthetic derivative produced by *Streptomyces* spp. or *Pseudomonas aeruginosa*. Regarding to their pharmacology, these compounds are parenterally administered by means of intravenous injection. High plasma concentrations are usually reached rapidly and they are widely distributed.

1.2. Glycopeptides

These antibiotics act on the bacterial wall. Currently there are two drugs in clinical use: vancomycin (Fig. 1) and teicoplanin. Vancomycin is a reduced-spectrum bactericidal antibiotic. It was introduced in 1956 but due to its toxicity was relegated. *Corynebacterium jeikeium* (multiresistant) and *Enterococcus* are resistant to beta-lactams or aminoglycosides. Teicoplanin has a structure similar to vancomycin and a similar activity profile.

Their mechanism of action is related to the inhibition of the synthesis and assembly of the second stage of peptidoglycan from the cell wall by forming a complex with the D-alanine portion of the pentapeptide precursor. It binds quickly and firmly to bacteria and exerts its bactericidal effect without a period of induction, but only on microorganisms in active multiplication. Vancomycin is poorly absorbed if administered orally. It is not administered intramuscularly because of the intense pain it causes at the injection site. It has a variable penetration at the central system level, although it improves when the meninges are inflamed. Both glycopeptides are eliminated by the kidneys, so the dose should be adjusted in the case of renal failure.

As clinical indications, glycopeptides must be restricted use drugs, reserved for the hospital setting. They will be used in case of suspicion or confirmation of infections caused by the multi-resistant germs mentioned above.

1.3. Aminoglycosides

Their chemical structure consists in two or more amino sugars linked by glycosidic bonds to an aminocyclitol ring (2-deoxystreptamine in most cases) as shown in Fig. 1. According to the amino sugars, they are classified into families. Tobramycin is available in presentation for ophthalmologic use. They are highly polar, polycations soluble in water and generally stable to heat and pH changes between 5 and 8.

Because of their physicochemical properties, these compounds are difficult to determine by high performance liquid chromatography (HPLC). They are basic and very hydrophilic, making extraction from these complex biological matrices difficult. Besides, they are also thermally labile, and then non-analyzable by gas chromatography (GC) or gas chromatography coupled to mass spectrometry (GC–MS). Although liquid chromatography coupled to mass spectrometry (LC–MS) should be useful to quantify these compounds, to date only two methods have been reported, both using ionspray LC–MS [4].

Numerous farmers tend to administrate aminoglycosides (AGs) to

treat parasites and bacterial infections in animals. In recent years, the addition of antibiotics to feeds has become increasingly popular because the antibiotics can enhance the conversion rate of the feed and improve bulk absorption of nutrients by animals. The AGs that have a broad antibacterial spectrum are favoured by animal husbandry and veterinary medicine as growth promoters and feed additives. However, the long-term use of the AGs may result in harmful side effects for population. AG drug residues in edible animal tissues enter the human body through the food chain, and might cause severe ototoxicity and nephrotoxicity [13].

Their combination with penicillin, ampicillin or a glycopeptide acts synergistically, except when the strains are highly resistant to aminoglycosides. Aminoglycosides are active against most species of tobramycin, amikacin and netilmicin have a similar activity, with exceptions: tobramycin.

The aminoglycosides act by irreversibly binding to the 30S subunit of the ribosome, interfering with the correct reading of the genetic code with the consequent blockage of the protein synthesis of the bacteria. In spite of the advances in the knowledge of the way of acting of these antibiotics, the last mechanism of the death of the bacterium (bactericidal effect) is not known, since it cannot be explained by the simple inhibition of the synthesis of the proteins.

Regarding to their pharmacokinetics and pharmacodynamics, aminoglycosides have poor oral absorption and need to be administered parenterally. Aminoglycosides are distributed in the extracellular volume.

Aminoglycosides display some adverse effect, like nephrotoxicity, phototoxicity and neuromuscular blockade, and to lesser extent skin rashes, fever due to antibiotics, spinal depression, hemolytic anemia and antagonism of factor V of coagulation.

Regarding to their clinical indications, aminoglycosides are effective in the treatment of infections where the presence of aerobic gram-negative bacilli is suspected, including *P. aeruginosa*. In general, this group of antibiotics is used in combination with a beta-lactam or a glycopeptide since these combinations are synergistic.

1.4. Macrolides

Macrolides (erythromycin, clarithromycin, azithromycin), lincosamines (lincomycin and clindamycin), ketolides and streptogramins are antibiotics that share a similar mechanism of action but have a different structure (Fig. 1). Macrolides are classified according to the number of carbons: 14 carbons (erythromycin and clarithromycin), 15 carbons (azithromycin) and 16 carbons (spiramycin). Clarithromycin is more active than other macrolides, while azithromycin is less active on gram-positive bacteria.

They act by binding to the 50S subunit of the ribosomal RNA in a reversible manner. The union is carried out by the formation of hydrogen bonds between different hydroxyl radicals of the macrolide and certain rRNA bases. This causes a blockage in transpeptidation and translocation reactions.

Their pharmacokinetics and the pharmacodynamics are very similar between the different macrolides. Erythromycin is available as topical, intravenous and oral preparations. Clarithromycin and azithromycin come in oral and intravenous presentations. The intestinal absorption of erythromycin and azithromycin diminished in the presence of food, so its administration should be kept away from them. They diffuse through the membrane due to their lipophilic character and probably due to the existence of an active transport dependent on calcium. The concentration in the cellular cytoplasm is several times higher than the serum. This determines that they are not suitable antibiotics when bacteraemia is suspected.

Macrolides diffuse sparingly through the meninges, so they are not suitable for the treatment of meningitis. In general, they pass to saliva, bronchial secretions and breast milk, where they reach concentrations>50% of the serum, but do not spread to fetal tissues. They are eliminated by bile in the form of metabolites and active product. The biliary concentration is higher than the serum concentration. They are not suitable for urinary infections. The macrolides develop a slow antibacterial activity, predominantly time dependent and with EPA effect. The activity is considered bacteriostatic against most microorganisms. MICs are significantly lower at alkaline pH (=8) because the non-ionized form diffuses better through the cytoplasmic membrane. The addition of serum reduces the MIC (increases the activity) of some macrolides, particularly that of azithromycin and spiramycin and, to a lesser degree, that of clarithromycin.

The most frequent adverse effects of macrolides, and especially erythromycin, are gastrointestinal complaints (abdominal pain, nausea and vomiting) due to the prokinetic activity of erythromycin itself, and especially its metabolites formed in the acidic environment of the stomach. They are observed more frequently in the population under 40 years of age, especially when the antibiotic is administered intravenously in rapid perfusion.

1.5. Quinolones

Quinolones are broad-spectrum synthetic antibiotic agents used in the treatment of livestock and in aquaculture. In addition, they are a group of chemotherapeutic agents (agents with antibiotic activity with selective toxicity) and they are not produced by microorganisms. They are derived from a basic molecule formed by a double ring structure containing an N-residue in position 1 (Fig. 1). Different substitutions, including the inclusion of fluorine residues, have derived from nalidixic acid to the fluorinated quinolones. Some of them bear a heterocyclic piperazinyl ring attached to the central ring system by the nitrogen atom (position R1). In general, quinolone carboxylic acids are amphoteric with poor water solubility between pH 6 and 8 [4]. Quinolones are bactericidal antibiotics and act by inhibiting DNA-girase, an enzyme that catalyzes the supercoiling of chromosomal DNA, which ensures adequate cell division [14].

Quinolones are classified into generations. The first-generation quinolones (nalidixic acid and pipemidic acid) have activity on enterobacteria and are inactive. The second generation (norfloxacin and ciprofloxacin) are called fluoride, since they incorporate a fluorine atom and have much greater activity on gram-negative. The third generation (levofloxacin, gatifloxacin) retain activity on gram-negative and improve activity on gram-positive. The fourth generation (moxifloxacin, trovafloxacin) retain activity on gram-negative and increase the activity on gram-positive [14].

Quinolones interact with two different but related sites within the bacterial cell: DNA gyrase and topoisomerase IV. The first is more sensitive to the action of the quinolones in the case of gram-negative germs, while in gram-positive the most sensitive is topoisomerase IV. The quinolones inhibit the synthesis of DNA and at high concentrations also the RNA. Regarding to their pharmacokinetics and pharmacodynamics, quinolones are well absorbed after oral administration, showing a very good bioavailability. The serum concentrations achieved with oral administration are similar to those achieved intravenously. Food does not affect absorption. The elimination is mostly renal in pipemidic acid and levofloxacin, others have non-renal elimination (moxifloxacin) and others have elimination by both routes (ciprofloxacin and norfloxacin). The quinolones exhibit bactericidal activity dependent concentration [14].

1.6. Tetracyclines [15]

Tetracycline (a semisynthetic derivative of chlortetracycline which is isolated from *Streptomyces aureofaciens*) is a broad spectrum antibiotic, congener of polycyclic naphthalene carboxamide (Fig. 1); used for treatment of infections caused by both gram-positive and gram-negative microorganisms. It exhibits bacteriostatic activity against a large and diverse range of aerobic and anaerobic gram-positive and gram-negative

bacteria; though it is more active against gram-positive microorganism. However, acquired resistance is common. It is not active against fungi [14].

Tetracycline acts by binding reversibly to the 30S subunit of the bacterial ribosome. This inhibits addition of amino acids to the growing peptide and interrupts the protein synthesis.

Absorption of tetracyclines may be impaired by ingestion of cations like Ca^{2+}, Mg^{2+}, Al^{3+}, Fe^{2+}, Fe^{3+} and Zn^{2+}. These metals bind to the tetracyclines to form poorly soluble complexes. Tetracyclines are widely distributed in body [14].

Formerly, tetracyclines were prescribed against several common infections, including bacterial gastroenteritis, pneumonia and urinary tract infections. However, numerous strains of bacteria causing these infections now are resistant and other agents have superseded tetracyclines [14].

2. Objectives and methodology

The main goal of the paper is to present the results of a review across the literature on the determination of the above-listed antibiotics in biological, environmental and food samples by liquid chromatography, homing in on sample pretreatment, the chromatographic conditions (separation and detection), and the results (run time and validation parameters). Antibiotic groups have been selected on the basis of being the most used in human medicine (the description of the antibiotics was extracted from several books). We have chosen these three sorts of matrices, as they are key to estimate, control and prevent drug exposure. Indeed, their determination in biological samples is a direct measure of their clinical exposure, in food to appraise drug abuse during the production step and the early detection of contaminated food batches, and in environmental samples, to evaluate contamination in the environment. The study was restricted to methods based on liquid chromatography, as it is well known it is the golden standard method for this kind of matrices and analytes. Paper search was performed by scopus using as keywords the different groups of antibiotics, "liquid chromatography" and the different sort of samples (food, biological and environmental). The selection was restrained to the most relevant publications. For each procedure, we will show the analytes and matrices, the main experimental conditions and analytical performance; classified by antibiotic active ingredients. Finally, we will display a comparison between the methods developed for each group.

3. Results and discussion

The development of reliable quantification methods to determine antibiotics in biological, food and environmental samples is critical to assessing the current status of environmental pollution and impact caused by antibiotic residues.

Currently, reversed-phase high-performance liquid chromatographic (RP-HPLC) coupled to mass spectrometry (MS) is undoubtedly, the gold-standard technique for the determination of drugs in these matrices. The exceptional performances of this powerful technique MS arise from the integration of the separation power of HPLC, the ability of providing specific fragmentation spectra of organic compounds of MS, the automation of the introduction of the sample and the existence of adapted software (for both management and visualization of data) and libraries, as well as the flow of information between analysts: versatility, useful for non-volatile and thermally labile analytes (unlike GC), possibility to develop own assays in a short frame of time (then not depending on external manufacturers), use for both identification and quantification purposes, structural elucidation, multianalyte determination in the same run, adaptable to the specific needing of the laboratory, absence of interferences by cross-reactivity with metabolites and other substances, possibility of detecting unknown metabolites or degradation products, easy automation, highly-sample-throughput, and usually high analytical performances (selectivity, sensitivity, ruggedness, trueness and precision). It can be used to extract a large quantity of information from the samples, and able to analyze a large number of samples per day, making it useful for routine analysis. The main drawbacks are the excessive economic disbursement for acquisition and maintenance (although the cost per analysis is reduced if it is intensely used), easy-to-contaminate and damage, use large amount of organic solvents and requires a strong purification and clean-up step, which turns tedious, long and difficult to perform in complex samples like food and clinical ones. Regardless of their lower analytical performances, other detectors such as UV–Visible absorbance and fluorescence (FLD) are most used, because of higher physical robustness, their low price and easy maintenance, which makes the resulting techniques (HPLC-UV, DAD or FLD) widely accessible [16].

Complex matrix, such as biological and food samples are difficult to analyze. For this reason, frequently a sample treatment step previous the analysis of antibiotics by LC is required in order to purify, clean, avoid some possible matrix interfering compounds from the sample or extract and pre-concentrate the target compounds from the studied sample. Otherwise, the antibiotics are in a low concentration, and then a preconentration is required. Consequently, last decades it has been a special effort to develop accurate, precise, fast and economical sample preparation methods. Moreover, all of these characteristics must be combined with the guarantee of sample integrity and the analyte stability.

There are a considerable number of publications describing analytical methods for the confirmation and quantification of veterinary drug residues in a biological, food and environmental samples by methods based on HPLC [4]. The chromatographic conditions and the validation results are discussed in 3.1 (Tables 1-3), while the sample treatment in 3.2 (Tables 4-6).

3.1. Chromatographic conditions

3.1.1. Beta-lactam antibiotics

a) Penicillins: many bioanalytical methods, like microbial inhibition tests and immunoassays, have been developed for the individual determination of penicillins, although liquid chromatography (LC) is the preferred technique for the resolution of penicillin mixtures. Methods using Ultra-performance LC (UPLC) only requires 3–5 min [17–19], though methods based on the use of conventional LC require nearly 1 min [20], 10 min [21,22], 15 min [23,24] or up to>30 min [25,26,27]. The chromatographic conditions to emphasize are the usage of C18 columns, where the majority of articles have in common. Only few penicillin determination procedures use HILIC or C8 columns. The common use of RP-HPLC with C18 columns is due to the interactions with the hydrophobic matrix based on the polarity of the molecules, using organic mobile phases mainly containing acetonitrile or methanol. Retention can be increased by adding salts to the mobile phase [17,21,23,25–28]. Otherwise, C8 are used when shorter retention times are desired [18,27], and HILIC columns offer strong retention and isomeric selectivity, demonstrating low ion exchange properties [29].

As the chemical structure of penicillins do not include strong chromophore or luminophore moieties, LC methods usually involve MS [18–20,25,29,30] or UV detection [17,21–24,26,28]. Absorbance wavelength are lower than or close to 250 nm, thus the signal can be easily interfered by background signals coming from sample matrix. UV detectors are mostly complemented with diode array detectors to select the best wavelength for the analysis [23]. Luminescence detection is an alternative to the use of more expensive MS detection or low selective UV detection, but it has been barely described for the determination of penicillins using LC, where wavelengths tend to increase much more than UV detection, down to 500 nm [31].

Finally, water, methanol and acetonitrile with formic acid has been the most commonly preferred solvents for the mobile phases, exhibiting good mass-spectral performance, high peak intensities and minimal tailing [18,20,21,25,29].

The previous analytical methods have been validated in terms of

Table 1
Summary of the determination conditions and analytical performances for each antibiotic in biological samples.

Analyzed substances (matrix) [Reference]	Separation conditions	Detection conditions	Run time and Validation Data
PIP, MER, CFT, FLU(human plasma) [17]	C18, 20 °C, mobile phase 0.2% phosphoric acid (A, pH 2.2) – Acetonitrile (B), gradient program: 5%B 1 min, 20% 5 min, 70% 5 min, 5% 4 min, flow rate 1 mL/min.	UV detector: 210, 230, 260, 306 nm	Calibration range: 2–200 μg/mLPrecision < 9% Trueness < 11%
CFP, MER, CIP,MOX, linezolid, PIP(human serum) [18]	C8, reverse phase, 30 °C, Vinj = 15 μL, mobile phase A (10 mM ammonium formate in H_2O – formic acis (99.9:0.1, v/v) – B (MeOH), gradient mode: 7%B 0.1 min, 65%B 0.5 min, 95%B 1.5 min, 7%B 2 min.Flow rate 0.5 mL/min. Run time 4 min.	MS-ESI + detection.	Concentration range 0.25–400 mg/LIPrecision: < 15%Trueness: 89.1%LOQ < 8.2%
PIP, AMO, CFT, CEF, MER (human plasma) [19]	UPLC-MS/MS, C18 column, 50 °C, Vinj = 40 μL, mobile phase: 0.1% formic acid (A) – 2 mmol/L NH_4Ac in MeOH (B), gradient program: 2%B 0.4 min, 98%B 0.5 min, 98%B 1 min, total run time 2.5 min, flow rate 0.4 mL/min.	MS-ESI + detection	Concentration range 0.5–100 mg/LPrecision < 20%; Recovery 67–100%LOQ 0.52–11.4 mg/L
AMO, clavulanic acid (Human plasma) [20]	LC-MS/MS, C18, mobile phase: 2 mM NH_4Ac – Acetonitrile (20:80, v/v), flow rate 0.8 L/min.	MS-ESI- detection.	Concentration range: 25.28–31500.68 ng/mL; Trueness: 98.22–102.24%LOQ < 50.43 ng/mL; CV < 3.55%Analysis time < 1 min
PIP, TAZ(Residual blood human samples) [21]	C18, 30 °C, Vinj = 1–9 μL, mobile phase: MeOH (A) – Acetonitrile/0.1% TFA (B), gradient program: 0–30%B 5 min, 0%B 5.1 min, total run time 7 min, flow rate 0.8 mL/min.	DAD-UV detector at 214 nm.	LOQ < 3.0 μg/mlTrueness and precision < 25%
PIP, TAZ(Human plasma) [22]	RP-HPLC, C18, 40 °C, mobile phase: 3:97 (v/v) Acetonitrile/H_2O with 0.1% TFA, gradient program: 5%A, 45%A by parabolic gradient curve 10 min, flow rate 1.2 mL/min.	UV detection 218/254 nm	Concentration range 1.0–200 μg/mLLOD > 0.78 μg/mL; LOQ > 0.20 μg/mLCV < 6%; Recovery 92.00–101.56%
CFP, CFT, CEF, MER, PIP(Human plasma) [27]	C8 symmetry column, 25 °C, Vinj = 40 μL, mobile phase: Acetonitrile (A) – phosphate buffer (B), flow rate 1 mL/min, gradient program: 5%A 5 min, 50%A 21 min, 5% 5 min, run time 35 min.	UV detection at 200–400 nm.	Concentration range 2.5–6.0 μg/mLTrueness > 93.2%; Precision < 12.2%Recovery > 57.4%
PIP, TAZ(Human blood) [28]	C18, mobile phase: 0.02 M NH_4Ac – Acetonitrile (76:24, v/v, pH 650), flow rate 1 mL/min.	UV detector, 223 nm.	Precision < 8.6%Serum concentration < 150 mg/L < 4xMIC
AMO, AMP, FEN, FLU, PIP, CDX, CFZ, CFP, CEF, LIN, MER, TAZ (Human plasma) [30]	, C18, 40 °C, Vinj = 1 μL, mobile phase: 1 mM CH_3COOH: CH_3COONH_4 buffer (A) – 5% Acetonitrile (B), gradient program: 100%A 1 min, 21%B 1 min, 99%B 1 min, 1 min re-equilibrium, flow rate 0.6 mL/min.	UPLC-MS/MS ESI (+)- detection	Recovery 52.2–96.1%Precision < 6.3%; LOQ > 0.69 μg/mL
Penicillin-V(Human plasma) [31]	C8, 40 °C, mobile phase: 0.01 M H_3PO_4 – Acetonitrile (from 80:20 to 40:60), isocratic flow rate 1.5 mL/min, run time 20 min.	UV absorbance detection.	LOQ > 50 ng/mL; Recovery > 90%Accuracy > 30 μg/L
Carbapenem(Mouse serum) [33]	C18, 30 °C, Vinj = 10 μL, mobile phase: A (0.1 M phosphate buffer) – B (MeOH), gradient program; 77:22 to 92:8, flow rate 1 mL/min.	UV detection at 300 nm.	Recovery 100.4–109.5%Precision < 2.7%, LOD 20–40 ng/mL
Fosfomycin(Human plasma and urine) [34]	HILIC HPLC column, 24 °C, Vinj = 0.1–0.5 μL, isocratic mobile phase: 2 mM NH_4Ac, pH 4.8 (85/15, v/v), flow rate 0.3 mL/min.	MS-ESI- interface.	Trueness −7.2 – 3.3%; Precision > 9.1% Recovery > 68%; LOQ > 0.1 μg/mL
TCP(Human plasma) [35]	C18; 40 °C; mobile phase water with 0.1% formic acid (A) and 0.1% formic acid in acetonitrile (B). Gradient: 0–1 min, 0% B; 1–2 min, 0–100% B; 2–3 min, 100% B; 3–3.5 min, 100–0% B; 3.5–6.5 min, 0% B. Flow rate: 0.5 mL/min Injection volume 1 μL.	MS-ESI + detection	Concentration range 1.0–50.0 μg/LTrueness 87–112%Precision < 7.6%Run time 6.5 min
PAR, DPR, VCM, AMK, FZ, CFL, PRE, DEX, FUR, KET(Human urine sample) [37]	RP-HPLC, C18, 22 °C, mobile phase: 0.05% TFA in H_2O (A) – MeOH (B) – Acetonitrile (C), flow rate 0.75 mL/min, DAD detector range of 200–450 nm.	Fluorescence detector at 355 and 415 nm.	Concentration range 0.1–12 μg/mL.Precision 0.38–6.90%Trueness −4.04–0.04%Recovery 95.96–102.85%
GEN(Kidney and inner ear cells) [42]	RP-UHPLC-ESI-QTOF-MS, C18, 24 °C, Vinj = 5 μL, mobile phase A: H_2O; B: Acetonitrile; both with 0.1% formic acid (v/v), gradient profile: 0–2 min: 5% B; 2–10 min: 5–100% B; flow rate 0.5 mL/min.	MS-ESI(+) detection mode.	Trueness −3.2 – 6.2%
GEN(Bovine plasma, urine, milk, animal kidney) [44]	C18, 30 °C, Vinj = 30 μL, mobile phase: 0.11 M TFA: Methanol (A) – Acetonitrile 5%(B)	UV–Visible absorbance detection.	LOQ > 3.3 ng/mLTrueness 92–104%;Precision: 3–20%
AMK(Human skin sample) [45]	RP-C18, 45 °C, Vinj = 10 μL, mobile phase: Acetonitrile – water–HAc (47:53:0.1 v/v/v), flow rate 1.5 mL/min.	UV detection at 365 nm.	Concentration range 1.64–49.21 μg/mL.; Precision: 3.89%Recovery > 93%
AMK(Human Plasma) [46]	RP-C18, Vinj = 10 μL, mobile phase: H_2O (A) – ACN (57:43, v/v), flow rate 0.8 mL/min. .	UV Detection at 230 nm.	Concentration range 10–52 nmol/mLPrecision < 5.80% ;Recovery < 91%
Erytromycin, azithromycin, tylosin, oleandomycin(Rat blood samples) [47]	RP-C18, mobile phase NH_4Ac (pH 7.0; 0.25 M) – Acetonitrile – Methanol (40:50:10, v/v/v) at 1 mL/min.	Fluorescence detection.	LOQ < 0.05 μg/mLPrecision:< 10%; Recovery > 80%
MOX, CIP, daptomycin, caspofungin, isavuconazole (Human plasma) [56]	C18, 55 °C, Vinj = 10 μL, mobile phase A (H_2O–IPA–Formic acid (90:10:0.1, v/v/v) – NH_4Ac 2 mM) – B (MeOH–IPA–Formic acid (90:10:0.1, v/v/v –NH_4Ac 2 mM), gradient program: 0%B to 100%B linearly, 0.9 until equilibrium, run time 5.5 min.	MS-ESI + detection.	Trueness 95.9–116.6%Precision < 10,8%LOQ > 0.075 mg/L
TCN(urine) [62]	HPLC-UV, C18, Vinj = 20 μL, mobile phase: 0.5% Formic acid (A) – Acetonitrile:MeOH (B) (2:1), isocratic mode with 80%A, flow rate 0.75 mL/min.	UV detection at 355 nm.	Concentration range 0.5–20 mg/LLOD 0.17 mg/L; lOQ 0.5 mg/LPrecision < 8%; Recovery 91–105%

recovery, trueness, precision LOQ, LOD, RSD (%) and CV (%). In general, trueness, evaluated by recovery, for the determination of penicillins has been acceptable, exceeding 75%; while the precision of the methods has been acceptable (coefficient of variation < 20%) [19,26,29]. Moreover, most of the methods reported in the literature exhibited LOQs and LODs of several tens of ng/L, thus, trace quantities of antibiotics can be detected using these analytical techniques [21,24,26,28,29,31,32].

b) Cephalosporins: Reversed phase chromatography is preferentially used for the separation of cephalosporins, because even though the most polar molecules can be analysed on this type of stationary phase by ion-pairing chromatography such as C8 [26] or C18 [19,23,24]. All

Table 2
Summary of the determination conditions and analytical performances for each antibiotic for food samples.

Analyzed substances (matrix) [Reference]	Separation conditions	Detection conditions	Run time and Validation Data
OXO, FLUME, ENR, DIF, SAR (fish flesh) [6]	C18 - mobile phase: 0.065 M SDS, 12.5% 1-propanol and 0.5% TEA buffered at pH 3 – Injection volume: 20 μL – Flow rate 1 mL/min isocratic -	Fluorescence detection	Run time 18 min; Trueness: 87–110% Precision: < 6.4% LOQs (μg/kg) 5–30
DAN, DIF, CIP, SAR (honey) [7]	C18 - mobile phase: 0.05 M SDS, 1% 1-butanol and 0.5% TEA buffered at pH = 3, Injection volume: 20 μL – Flow rate 1 mL/min isocratic	Fluorescence detection: The excitation and emission wavelengths were 280 and 455 nm, respectively	Run time: 25 minLOQ: 10 μg/ kgTrueness: 81.0–103.4%Precision: <12.3%,
OXO, FLUME, MARBO, ENR (honey) [8]	C18- mobile phase: 0.05 M SDS /12.5% 1-propanol/0.5% TEA at pH 3, Injection volume: 20 μL – Flow rate 1 mL/min isocratic	Fluorescence detection	Run time: 15 minLOQ: 0.02–0.2 mg/ kgTrueness: 82.1–110.0%Precision (<9.4%)
OXO, DAN, CIP, ENR(selected meats) [9,10]	C18: mobile phase: 0.05 M SDS – 7.5% 1-propanol – 0.5% TEA buffered at pH 3Injection volume: 20 μL – Flow rate 1 mL/min isocratic	Fluorescence detection	Run time: 22 minLOQ: 0.01–0.05 mg// kgTrueness: 89.3–105.1%Precision: <8.3%
FLUME, MARBO, DIF, SAR (selected meats) [11]	C18: mobile phase: 0.05 mol/L sodium dodecyl sulfate − 8% 1-butanol − 0.5% TEA buffered at pH 3Injection volume: 20 μL – Flow rate 1 mL/min isocratic	Fluorescence detection	Run time: 19 minLOQ: 0.01–0.05 mg /kgTrueness: 83.9 to + 107.8% Precision: < 9.4%
SPC, HYG, STR, AMK, RIB, TOB, GEN, NEO(feeds) [13]	C18, 35 °C, Vinj = 40 μL, mobile phase: A (Acetonitrile/ H_2O, 5:95, v/v) – B (Acetonitrile/H_2O, 50:50, v/v), gradient program: 65%A:35%B 22 min, 30%A:70%B 4 min, 65%A:35%B 9 min, flow rate 1 mL/min.	Evaporative Light Scattering Detector	Calibration range 2.00–200 μg/mL. Recovery 61.2–104%Precision < 15%, LOD 0.2–0.7 mg/kg
CFX, CFL, CFP, CLO, DCL, OXA, PEV(Ewe milk) [23]	C18, 25 °C, mobile phase 25 mM phosphate buffer sol. (A, pH 3.4) – Acetonitrile (B), gradient program: 0–2 min, 15% B; 2–10 min, 15–75% B; 10–13 min, 75% B, flow rate 1 mL/min.	DAD-UV at 210 nm.	Recovery 79–96%LOQ 3.4–8.6 μg/kg. Precision: 4.9%
AMO, AMP, CLO, DCL, CFX, TCN, OTC(Muscle tissue and urine from pig) [25]	C18, Vinj = 10 μL. Mobile phase A: 0.1% formic acid in water, B: MeOH, gradient program: 98%A 5 min, 50%A 22 min, 95%B 24 min, 29 min, flow rate 0.2 mL/min..	MS-ESI(+) - detection mode	Recovery 90–107%Precision:<17%
TCN, OTC, DCN(Bovine milk) [26]	C18, Vinj = 20 μL, mobile phase: Acetonitrile (A) – 25 mM KH_2PO_4 buffer, pH 3.0 (B), gradient program: 0–10 min, 97–80% B; 10–20 min, 80–70% B; 20–55 min,70–70% B, flow rate 0.7 mL/min	UV detection at 260 nm.	Concentration range: 10–200 μg/ LLOQ > 9.8 μg/L; Precision: < 8.2%; Recovery : 70.6–121.5%
TCN, OTC, CTC, DOC(Prawns) [32]	40 °C, Vinj = 20 μL, mobile phase: 0.1% formic acid in H_2O (A) – 0.1% formic acid in Methanol (B), flow rate 400 μL/ min.	LC-MS/MS	Recovery 80–101%; LOD < 20 ng/ gLOQ < 20 ng/g; Precision: 2.1–9.8%
VCM, TCP(Animal feed) [36]	Biphenyl column, Vinj = 10 μL, mobile phase: methanol (A) and 5 mmoL/mL ammonium acetate aqueous solution containing 0.1% formic acid (B). Gradient: 0–1 min, 15% A; 1–17 min, 15–50% A; 17–25 min, 50% A; 25–27 min, 50–75% A; 27–37 min, 75% A; 37–38 min, 75–15% A; 38–40 min, 15%. Flow rate 0.5 mL/min	Detection: evaporative light scattering	Trueness: 72.0% to 105.4%LOD > 2 to 5 mg/kg
TLV, TCP, OVC, DVC, VCM(food and biological samples) [38]	BEH-C18: mobile phase: gradient of 0.1 M Formic acid (A) and methanol (B)	UPLC-MS-MS-ESI+	Run time: 6 min; LOQ: 1 ug/LTrueness: 83.4–102%Precision: <6.8%
PARO, NEO, APRA, HYG, GEN, SPC, STR, AMK, KANA, DHSTR (Meat) [39]	UHPLC-HILIC, mobile phase: mixture of solvents(A) – Acetonitrile (B) – 1% Formic acid in H_2O (C), gradient program: 0 to 0.5 min85% A-7.5 %B-7.5%C; 3.8 min 65% A-35%C;4.3 min 5 %A-45%C; 4.5 min 55%A-45%C; 6.5 min 5%A-95%C; 11 min 5%A-95%C, eq. time 10 min, flow rate 5 μL/min.	MS-MS	Precision < 15%LOQ 1–50 μg/ kgTrueness < 23%
STR, DHSTR(Milk and honey samples) [40]	C18, 30 °C, Vinj = 25 μL, mobile phase: Acetonitrile in H_2O (A) – PFPA, total run 5.5 min, flow rate 200 μL/min.	MS-ESI + detection	LOQ > 1 μg/kg.Precision < 15% Recovery > 81%
SPC, TOB, GEN, KAN, HYG, APRA, STR, DHSTR, AMK, NEO(Milk and muscle) [41]	LC-QTOF-MS, C18, Vinj = 20 μL, mobile phase: aq. sol. 10 mM NFPA (A) – Acetonitrile with 10 mM NFPA, gradient program: 95%A to 10%A 4 min, 1 min to 95%A, total run time 10 min.	MS-ESI + detection.	LOD 5–100 ng/g;LOQ 12.5–250 ng/ gRecovery 36.8–98%
STR(Honey sample) [43]	C18, 20 °C, Vinj = 90 μL, mobile phase HFBA – Acetonitrile (85:15), flow rate 0.2 mL/min..	MS-ESI + detection	Recovery : nearly 100%LOD > 3 μg/ kgPrecision 0.410%
DAN, ENR, ORB,OFL, NOR, LOM, FLE, CIP(Milk samples) [50]	C18, Vinj = 20 μL, mobile phase of 0.1% Formic acid (A) – Acetonitrile (B), isocratic flow 80%A – 20%B, flow rate 0.6 mL/min.	FLD detection; λex = 280 nm, λem = 450 nm	LOD 0.05–0.1 ng/g; LOQ 0.15–0.3 ng/ gPrecision: <15.8%Recovery 53.9–90.6%
Azithromycin, clarithromycin, erythromycin(Honey and skim milk) [51]	C18, 25 °C, mobile phase of 0.1% HCOOH (A) – Acetonitrile with 0.1% HCOOH (B), gradient program: 8%–20%B for 0–2 min, 20%–40%B for 2–4 min, 40%–80% B for 4–6 min,and 100%B for7–8 min. Mesoporous MCM-41 silica as sorbent.	MS-MS	Precision: 0.3–7.1%LOD 0.01–0.76 μg/ kgRecovery > 83.21%
Quinolones(Garlic peel) [52]	C18 at 35 °C, mobile phase MeOH (A) – 0.3% formic acid in H2O: 0.1% ammonium formate v/v (B, pH 2.9), run time 22 min, flow rate 0.3 mL/min.	UV-DAD detection	LOD 0.65–0.85 μg/mLRecovery 86.3–95.1%Precision < 4.1%
Sunitib, fluoroquinolones(Rabbit) [54]	C8, 40 °C, mobile phase: 20 mM NH_4Ac, pH 3.4 – Acetonitrile (60:40, v/v)	UV–Vis detection 431 nm.	Run time 6 minLOQ > 0.5 ng/mL, Precision < 10%
NOR, CIP, Nalidixic Acid, ORB, GAT, Naproxen(beef, pork and lamb) [55]	C18: 1. 7069 g of potassium di-hyrogen phosphate, 0.5–2.5 g of 1-heptane sulphonic acid, 116 mL (pH 8) and 14 mL (pH 6) of 0.1 M sodium hydroxide and 20 % acetonitrile,; Injection volume 10 μL; Flow rate: 1 mL/min isocratic; UV	UV-Absorbance detection at 254 nm and at 262 nm.	Run time 10 minConcentration range < 10–9

(*continued on next page*)

Table 2 (*continued*)

Analyzed substances (matrix) [Reference]	Separation conditions	Detection conditions	Run time and Validation Data
MARBO, CIP(Semi-skimmed and whole milk samples) [58]	C18, Vinj = 20 μL, 35 °C. Ternary mixture for mobile phase: Methanol (A), Acetonitrile (B) and 10 mM acetic acid (C) with gradient program, flow rate 0.7 mL/min.	Luminescence detection, λex = 340 nm, λem = 545 nm.	LOD < 35 ng/mLRecovery > 92% Precision < 10.7 %
TCN, DOC, OTC(Baby food samples) [59]	C18 at 35 °C, Vinj = 25 μL, mobile phase: A (0.04% Formic acid in H_2O) – B (0.04% Formic acid in MeOH), gradient program: 0–8 min 0% B, 8–9 min 45% B, 9–14 min 61% B, 14–15 min 0% B, 15–18 0% B. Flow rate 0.25 mL/min.	MS/MS	Trueness: 103 μg/kg.Precision < 23% LOD < 5 μg/kg
TCN, CTC, DC, OTC(Milk samples) [60]	C18-UV detector, Vinj = 20 μL, 30 °C, mobile phase: MeOH (A) – 0.010 M aq. oxalic acid (B), gradient mode: 0–4 min, 85–70%B; 4–5 min, 70%-50%B; 5–6 min, 50–25%B; 6–8 min, 25–50%B; 8–9 min, 50–70%B; 9–11 min, 70–85%B. Flow rate 0.25 mL/min.	Fluorescence detectionλem = 360 nm	LOD 0.95–3.6 μg/LRecovery > 92.38% Precision < 8.66%
TCN(Milk samples) [61]	C18, Vinj = 10 μL, mobile phase MeOH – acetonitrile – 0.01 M oxalic acid (3/12/85, v/v/v) for 10 min at 1.0 mL/min to the same mobile phase (5/18/77, v/v/v), same flow rate.UV detection	Fluorescence detectionλem = 350 nm	Calibration range: 5.0–500 μg/LLOQ: 3.56–4.32 μg/LPrecision < 6.7%; Recovery 84.1–95.8%
CTC (supermarket meat)[63]	C18, 30 °C, Vinj = 20 μL, mobile phase: 0.1% Formic acid in H_2O (A) – 0,1% formic acid in Acetonitrile (B), gradient program (A: B; v/v): 80:20 at 0 min, 5:95 4 min, 5:95 7 min, 80:20 7.1 min, 80:20 10 min, flow rate 300 μL/min.	MS-MS	LOD 0.8 ng/g; LOQ 2.7 ng/gRecovery > 63.1%; Precision < 17.3%

cephalosporins are mainly under their ionic form, hence, in the pH range of 3–8, their chromatographic retention will significantly depend on the dissociation capacity of the carboxylic group that is partly ionized [18]. On the other hand, UV absorbance is commonly used for the quantitation of cephalosporins. Most of the solvents used in HPLC have wide windows in the UV–visible region, making them compatible with UV detectors even at short wavelengths. For instance, acetonitrile is a solvent that is frequently used, in particular, at wavelength below 195 nm [23,24,27].

As cephalosporins are among the most widely prescribed of all antibiotics because of their safety and effectiveness as broad spectrum bactericidal antibiotic active ingredients, their determination in biological samples is essential [23,24]. Generally, recoveries were successfully maintained up to 80%. Regarding CV and RSD (%), were maintained below the 20% accepted, confirming an adequate choice of analytic method [19,24]. Finally, the LOQs and LODs reported were on tens of ng/mL; hence, exhibiting acceptable results for trace quantities in biological samples or prescribed antibiotics [19,23,24].

c) Monobactams: No information about monobactams was found on the literature.

d) Carbapenems: Carbapenems exhibit a structure similar to that of penicillins. The main characteristics that differentiate them, is that in their ring it has a carbon atom in position 1, replacing the sulphur atom that most penicillins and cephalosporins commonly have. The predominant choice in this group of antibiotics for their determination is a reversed-phase liquid chromatography, C18 column, using predominantly as mobile phases MeOH. Moreover, UV detection was performed at 300 nm, as well as penicillins, they do not contain strong chromophore or luminophore moieties [33].

An adequate empirical antibiotic dose selection has to be taken into account due to their broad spectrum of activity against gram-negative bacteria. Adequate values of trueness (>90%) and precision (RSD < 15%) LODs and LOQs were < 10 ng/mL; hence, it has been an adequate analytical method to determine trace cephalosporins [33].

3.1.2. Glycopeptides

An excellent selectivity can be obtained for polar hydrophilic compounds like glycopeptides using HILIC. The presence of a high organic-solvent content in mobile phase leads to a rapid evaporation of the solvent during electrospray ionization (ESI), predominant negative mode [34]. This type of antibiotics can also be successfully determined by HPLC, using C18 columns and polar mobile phases containing water and polar organic solvents, like acetonitrile [35], methanol [36] or a mixture of both [37]. They were also analyzed natively or after fluorescent labelling, mostly with MS or fluorescence detection, complemented with diode array detectors, at wavelengths below 400 nm [29,37], evaporative light scattering detector [36] or mass spectrometry in ESI mode [35]. They have also been determined using UPLC-MS/MS in ESI + mode, using a BEH-C18 column and a 0.1 formic acid/methanol mobile phase [38].

These analytical procedures exhibited CV below 15% and then, according to the comparison of RSD(%) and precision for the literature, they are reliable methods to determinate glycopeptides in biological applications. Otherwise, trueness stands in the range 70–110%, assuring a right separation and determination of these samples. Finally, LODs and LOQs exhibit orders of μg/mL; hence, describing adequate methods in order to determine glycopeptides in biological samples and food products.

3.1.3. Aminoglycosides

Aminoglycoside antibiotics are strongly polar and present in polyionic form in aqueous solutions. Therefore, they are not effectively resolved by common reverse phase C18 columns because hydrophilic compounds are barely retained. In order to separate hydrophilic compounds by LC, ion-pair chromatography (IPC) or hydrophilic interaction liquid chromatography (HILIC) are usually employed [39]. The analysis of aminoglycosides (AGs) is challenging due to the lack of a chromophore, which prevent direct determination by UV absorption, even though some articles were found where this technique has been used [40]. Advancement in the detection technologies for liquid chromatography (LC) such as time-of-flight mass spectrometry (TOF) [41,42], evaporative light-scattering detection (ELSD) [13] and tandem mass spectrometry (MS/MS) made their determination possible to some extent [40,43–45]. Some of them use ESI detection, generally in positive mode [41,42,45]. In fact, the main analysis methods obtained for aminoglycosides by the literature has been the usage of C18 columns in HPLC, with temperature of 20–30 °C and ESI + detectors as named previously, fluorescence [37,46] or UV detectors with wavelengths below 400 nm [40].

The analysis of AGs is required in a significant number of applications, like residue analysis in food of animal origin (food safety) and, because of its frequent use in veterinary applications, in environmental samples like water and soil. In addition, the determination of AGs and their related products is important in drug formulations and in therapeutic drug monitoring (TDM) in body fluids and tissues. Generally, the determination of aminoglycosides in biological samples by the literature has been precise and accurate, with values of RSD < 15% and CV < 20%. On the other hand, recoveries with analytical methods like HPLC-ESI-MS

detection have been lower [41,45] than UV/fluorescence detection [37,46]. Finally, adequate LODs and LOQs have been obtained tens of μg/mL, assuring a correct analysis of AGs and related products in biological samples.

3.1.4. Macrolides

The most used technique for purity assessment of macrolides is liquid chromatography with UV detection at wavelengths below 285 nm [47–50]. The selection of organic eluent proved to be an important factor for the successful separation of target macrolides while using C18 columns generally, because peak shapes considerably improved when acetonitrile was employed instead of MeOH or using a second mobile phase with MeOH, whereas part of these separations have had a total run below 10 min [47–51]. The other macrolides, similar to azithromycin, which contain additional nitrogen in the lactone ring, were more strongly retained on the sorbent, probably due to the stronger ionic interactions with the cation exchanger [51].

Macrolide antibiotics are a prominent group of emerging contaminants frequently found in wastewater effluents (mainly from pharmaceutical industry) and wastewater-impacted aquatic environments, as well as trace compounds found in food, and that is why it is very important to find an optimized method for their determination [48–51]. Generally, recoveries have been maintained>80% and the analytical methods used have been adequate for the determination of these compounds, obtaining RSD < 20%, CV < 10%. Reported LODs and LOQs fall within the range of μg/mL or ng/mL; hence, optimal analytical methods at the literature are described for biological samples.

3.1.5. Quinolones

The most commonly used techniques to determine quinolones are liquid chromatography with UV detection due to its chromophore structure [42,52–55], mass spectrometry (MS) [18,47,56,57], fluorescence [6–11] or luminescence detection [58]. Wavelengths selected for UV detection were generally below 400 nm, as well as ESI has been selected in positive mode. Preferred chromatographic conditions for quinolones resolution are hydro organic-RP-HPLC using C18 [47,52,53,57,58] or C8 [18,54] columns combined with mobile phases containing acetonitrile or methanol. RP-HPLC using secondary equilibria, like ion-pairing [55] and micellar liquid chromatography [6–11] have also been employed.

Precision of these analytical procedures has been obtained with RSD < 20%, assuming that they are validated methods to determine quinolones, as well as recoveries of the literature were over > 60%. Moreover, LODs and LOQs exhibit orders of ng/mL, describing optimal analytical methods in order to analyse and separate this type of antibiotics.

3.1.6. Tetracyclines

Their determination is basically done by the literature using HPLC, C18 columns [25,26,57,59–63] followed by UV–visible spectrophotometer detection with wavelengths that do not exceed 400 nm [26,60–62]. Another type of detection is less used, ESI interface in positive mode [25,63]. Typical mobile phases for this type of chromatography are acetonitrile, MeOH and aqueous formic acids with flow rates are approximately 1.0 mL/min.

Recoveries for this type of antibiotics are>65% and RSD < 20%, assuming that they are precise analytical methods to rely on in order to determine tetracyclines. LODs and LOQs are generally in order of ng/L; therefore, it means that the determination of the chromatographic peaks of our analytes are being correct.

3.1.7. Discussion

The analytical methods reviewed for the determination of antibiotics have generally used RP-C18 columns in order to separate the analytes, except for glycopeptides, that mainly used HILIC columns. Another type of chromatographic analyses was used in less proportion, such as C8, cianopropyl, phenyl and PLRP-S columns.

On the other hand, HILIC uses hydrophilic stationary phases, recovered with simple or diol-linked silica (anionic), aminophenols (cationic), and amides or zwitterions (neutral), with reverse phase-type eluents such as acetonitrile and water. Ammonium acetate/formate is typically added to the mobile phase to adjust the pH and the ionic strength of the mobile phase [34]. When a mobile phase with a high proportion of water flows through an HILIC column, the water generates a thin layer around the hydrophilic stationary phase. Water-soluble analytes migrate into the water layer. The proportion of the non-polar solvent in the mobile phase is gradually increased and the analytes detach sequentially from the thin water layer, depending on their hydrophilicities.

Water, methanol and acetonitrile with formic acid have been the solvents preferred for mobile phases in the determination of antibiotics, exhibiting excellent mass spectral performance, namely symmetrical peak shapes, higher peak intensities, and minimal tailing.

As retention is directly influenced by column temperature, this parameter should remain constant during elution. Unstable column temperatures can give rise to retention-time shifting and transitions in the order of elution. In particular, if the temperature distribution in the column is not uniform, unsymmetrical peaks are typically obtained. Column temperatures used for the detection of antibiotics here mostly vary between 15 and 45 °C, although optimal values are between 30 and 40 °C. Otherwise, taking into account total run times, the average found on the literature accords to 20–30 min, but it has been found that the analysis for macrolides has been with lower total run times, to 10 min.

The most used detectors are UV–Visible (single wavelength or photodiode array) detector, fluorescence detector (FLD), and mass spectrometer, and are selected depending on the chemical properties of the target analytes. In this case, UV detection has been the optimal option for every type of antibiotics. [17,21,24]. But, although UV detectors and FLDs are relatively simple and inexpensive, they are not sufficiently sensitive to quantify trace levels of antibiotics in environmental samples. In addition, these detectors cannot detect glycopeptides since they do not contain chromophores. Therefore, tandem mass spectrometry (MS/MS) is usually chosen for the analysis of this type of antibiotics. In ESI, ionization is performed in positive or negative mode and precursor ions are typically produced in their $[M + H]^+$ or $[M-H]^-$ forms. ESI is applicable to both polar and non-polar compounds and is also very useful for the ionization of heat sensitive substances [43,45]. Cephalosporins, carbapenems and macrolides have been frequently detected with UV detectors at wavelengths below 300 nm, as well as penicillins, quinolones, tetracyclines and tyrosine kinase inhibitors have been detected below 400 nm. Without doubt, MS detection mode provide far better analytical results, even though its high acquisition and maintenance cost impairs its use in many laboratories. Otherwise, methods are developed to determine only antibiotics belonging to the same categories, and a limited number in the same run. This could be a limitation for far-reaching studies. The use of MS detection also favours the development of multiresidue methods.

Method validation is a critical step in the development of reliable analytical methods [64]. The analytical methods reviewed here have been validated by studying their recoveries, trueness values, precisions, limits of detection (LODs), and limits of quantification (LOQs). The precision of an analytical method, either as repeatability (intra-day precision) or as reproducibility (intra-day precision) can be expressed as coefficient of variation; acceptable CV values are < 20%. In general, bias describes the recovery level of an analyte obtained after all the analytical steps, including pre-treatment and instrumental analysis, and is used to evaluate the trueness of an analytical method. For environmental and biological samples in the literature, values of recovery were obtained from 65 to 100% (acceptable values are 80–120 %). Therefore, some antibiotics were quantified with a trueness under the acceptable limits. Finally, most of the methods reported in the literature exhibited LOQs at the ng/L level; hence the sensitivity is enough to detect even trace amounts of antibiotics.

Table 3
Summary of the determination conditions and analytical performances for each antibiotic for environmental samples.

Analyzed substances (matrix) [Reference]	Separation conditions	Detection conditions	Run time and Validation Data
AMO, CFL, cephradine(Water and milk samples) [24]	RP-C18, Vinj = 20 μL, mobile phase: MeOH – H_2O (63:37, v/v), run time 20 min. Flow rate 1 mL/min.	UV detection at 220 nm.	LOQ 4–10 ng/mL; LOD 1.5–3 ng/mLPrecision: 10.82%;Trueness 91.31–102.9%
VCM, AMO, CTM, DOC, LFX, PNV, PIP(Wastewater samples) [29]	SPE-HPLC, HILIC column, 40 °C, Vinj = 20 μL, mobile phase: A (3/97/0.05, v/v/v) – B (95/5/0.05, v/v/v), mixture of Acetonitrile: NH_4Ac(2 mM): Formic acid, flow rate 0.4 mL/min.	MS/MS	LOQ 0.8–241.5 ng/L; LOD 0.2–73.5 ng/L; Trueness −9.3 – 10.6 %Precision < 13.7%
FLE, CIP, GAT, NOR (Waste water) [48]	C18, 40 °C, Vinj = 20 μL, mobile phase: MeOH – 0.025 M aq. Phosphoric acid sol. (20:80, v/v, pH = 3.2), flow rate at 1 mL/min.	DAD detector at 285 nm.	LOD < 5.50 ng/mLRecovery > 95.47%Precision: < 4.44%
Erythromycin, clarithromycin, azithromycin (Agricultural soil) [49]	C18, mobile phase: 0.1% formic acid in H_2O (A) – Acetonitrile (B), gradient program; 88%A-12%B to 53:47 for 9 min, 90%B 5 min, 2 min, initial conditions 2 min, held 7 min, flow rate of 0.3 mL/min.	UV detector at 205 nm.	Recovery > 63% Precision < 18.34%
Fluoroquinolones, quinolones(Soil samples) [53]	C18, Vinj = 100 μL, gradient elution: 96% A (formic acid, pH 2.5, 3.16 Mm) – B (Acetonitrile) to 50% A – 50% B in 17 min, to initial conditions in 3 min.	Fluorescence; λem = 260/280 nm	Precision < 12% Recovery > 84.3% LOQ 0.15–0.25 μg/g
OTC, florfenicol, FLUME(Marine samples) [57]	C18, 40 °C, Vinj = 100 μL, 0.1% formic acid in H_2O (A) – Methanol (B), gradient program: 5%B 1 min; 100%B 11 min until 13 min, flow rate 0.4 mL/min.	TOF/MS	Concentration range: 0.5–250 ng/mLLOQ > 1 μg/L; Recovery 63–120%LOD > 0.3 μg/L; Precision < 20%

3.2. Sample treatment

Sample treatment to determine antibiotics in food, biological and environmental samples by HPLC-based methods almost always include extraction/purification steps. Nowadays, solid-phase extraction techniques are the most used ones, for they are faster, less laborious, consume less volume of solvents and have better reproducibility and higher selectivity, compared to the traditional liquid–liquid extraction

Table 4
Analytical treatment methods applied to different biological samples to analysis antibiotics by HPLC.

Compounds [Reference]	Matrix	Sample treatment (number of analytes) / Components of the extraction system / Eluent / Conditions
Tetracyclines: TCN, OTC, CTC [86]	Urine	SM-LPME (3) / Fatty acids: hexanoic acid, nonanoic acid, pivalic acid and oleic acid / MeOH / 100 μL sodium hexanoate solution 20 μL HCl – pH 4.0
Tetracyclines: OTC, TCN, DOC and CTC [82]	Urine, blood plasma and blood serum	HLLME (3) / extraction with n-octylamine and isopropanol/ MeOH
Beta-lactam: PNG-G, CTX, CIP, CFI and CLO [73]	Urine	MSPE (5) / Cryo–SIPN with polyaniline and polypyrrole / MeOH
Glycopeptides: VCM, TCP, TLV, OVC and DVC [38]	Blood and urine	SPE (5) / Oasis HLB and MCX Cartridge / 3 mL MeOH
*Quinolones:*CIP, LEV, ENR [77]	human sputum	microextraction by packed sorbent (3) / removable needle containing a C18stationary phase / MeOH
macrolide antibiotics, penicillins, benzimidazoles, imidazoles, polyether antibiotics, sulfonamides, quinolones and other drugs [96]	Urine and blood of livestock and poultry	QuEChERS (160)
Sulfadiazine [98]	Fish Plasma	Direct injection: stand in ACN/water (15:85, v/v) and centrifugation (1) / On-Line Column-Switching
Tazobactam and Piperacillin [99]	Human fatty tissues	Mixed with 50 mM sodium dihydrogenphosphate buffer (pH 5.0) / homogenization / centrifugation /
	Human plasma	Dilution with 50 mM sodium dihydrogenphosphate buffer (pH 5.0) / HPLC integrated extraction

procedures (LLE). The main variants are cartridge (SPE) [36,38,65–70], dispersive (d-SPE) [71,72], microextraction in a miniaturized cartridge (μ or MSPE) [73,74,75], magnetic stir cake sorptive extraction (MSCSE) [76], microextraction by packed sorbent [77], molecular imprinted polymer (MISPE) [74,75,78], and immunoaffinity clean-up columns (IAC) [79]. However, the extraction parameters, as the type of solvent extraction, the volume of sample and solvent extraction, pH, addition of salts or modifiers to sample and/or extraction solvent, type of sorbent-support, conditioning of the sorbent and reconstitution depend on the properties of the target analytes. Hence, these parameters must be optimized for each particular analysis. Another alternative is liquid–liquid microextraction techniques, which also use low volume of organic solvents, and do not require specific devices or sorbents. However, an accurate selection of the extraction conditions (nature and volume of extraction and sample, duration, addition of salts or modifiers, pH) are required to maximize the recovery, while avoiding the formation of emulsions and solvent evaporation [80–88]. LLE using non-conventional solvents, such as ionic liquids, has become an interesting alternative [89].

Nevertheless, before to apply these analytical treatment methods sometimes an additional pretreatment step is required to prepare the sample, such as, solid-to-liquid extraction [79,90,91], derivatization [92], protein precipitation [78,86], filtration to eliminate possible particles [85] or acidification with different acids, such as glacial acetic acid [69], formic acid [36]. In fact, it has been demonstrated that the acidity of extraction solutions affects the liberation of polypeptides from their matrix because of the interaction between polypeptide antibiotics and proteins in sample [36].

Table 5
Analytical treatment methods applied to different food samples to analysis antibiotics by HPLC.

Compounds [Reference]	Matrix	Sample treatment (number of analytes) / Components of the extraction system / Eluent / Conditions
Tetracyclines: OTC, TCN, TCT, DC [71]	Honey	d-SPE (4) / 3MOFs: MIL-101 (Cr), MIL-100 (Fe) and MIL-53 (Al) / MeOH / 5 mL Na_2EDTA-McIlvaine buffer – pH 4.0
OTC and AMO [81]	Bovine milk	USA-DLLME-SFO (3) / Oasis HLB Cartridge/ ACN / 20 mL Na2EDTA-McIlvaine buffer – pH 4.0 (pH 3.4 for AMO)
Tetracyclines:OLA, OTC, CTC [90]	Feed animal samples	Liquid-to-solid extraction (3) / mixture of acetonitrile and 0.1 mol/L ethylenediamine tetraacetic acid disodium-McIlvaine buffer (1:4, v/v)
Tetracyclines: OTC, TCN,CTC, DC [76]	Milk, egg, chicken muscle and chicken kidney	MSCSE (4) / Fe_3O_4@$Cu_3(btc)_2$-embedded polymerized high internal phase emulsion (Fe_3O_4@HKUST-1-polyHIPE) monolithic cake/ ethanol–formic acid–water /pH 8.0
Tetracyclines: OTC, TCN,CTC, DC [68]	chicken tissue	SPE (1) / electrospun graphene oxide–doped poly (acrylonitrile-co-maleic acid) nanofibers / methanol:formic acid:dichloromethane, 40:20:40, (v/v/v) / 5 mL formic acid-ammonia buffer solution - pH 2.0
Tetracyclines: OTC, DC, PNG-GMacrolide: CAP [87]	Milk	salt induced–homogenous liquid–liquid extraction (4) / acetonitrile, followed by ternary deep eutectic solvent–based dispersive liquid–liquid microextraction / PChCl:DCA:dodecanoic acid
Beta-lactam: PNG-G, AMP,AMO [80]	Chicken meat, egg, and honey	USA-DLLME-SFO (3) / HP-DES: Benzyl triethylammonium chloride and decanoic acid / ACN / buffer solution – pH 5.5
Beta-lactam: PNG-G, CIP, CFI, CTX, CLO [73]	Honey	SPME (5) / Cryo–SIPN with polyaniline and polypyrrole / MeOH
Glycopeptides: VCM, POL-B1, POL-B2, POL-E, TCP, BAC-A, DAP, VIR [36]	Piglet premix, pig feed additive, poultry complete feed, pig complete feed and fattening pig premix	SPE (8) / Oasis HLB Cartridge / 5 mL of 2% formic acid in methanol
Glycopeptides: TLV, TCP, OVC, VCM, DVC [38]	egg, chicken meat, and milk	SPE (5) / Oasis HLB and MCX Cartridge / 3 mL methanol
Aminoglycosides: PARO, SPC, TOB, GEN, KAN, HYG, APRA, STR, DHSTR and AMK[65]	Aquatic feeds (fish, prawn, and crab)	SPE (3) / C18 Cartridge, Oasis HLB Cartridge, Oasis WCX Cartridge, Oasis MCX Cartridge / ACN
Polypeptides: gramicidin S, bacitracin, polymyxin B, and polymyxin E [66]	Milk powder	SPE (4) / Oasis HLB Cartridge / 0.1 Formic acid-MeOH
Chloramphenicol [67]	Honey	SPE (1) / Oasis HLB Cartridge / MeOH
Chloramphenicol [88]	Honey	USA-DLLME (1) / 800 μL of ACN (dispersive solvent) and 300 μL of $CHCl_3$ (extraction solvent)
Chloramphenicol [79]	Proh, fish and liver	Solid-to-liquid extraction (1) / digestion with β-glucuronidase/sulfatase – extraction with ethyl acetate-diethyl ether (9:1, v/v) – drynees – residue with 2 mL of 50% acetonitrile solution – 1 mL filtrate diluted to 10 mL with PBS – clean up with immunoaffinity column
Chloramphenicol [83]	milk, egg, and shrimp	LLE-ATPS (1) / ethylene glycol-ran-propylene glycol (80%, w/w) and K2HPO4 (55%, w/w)
Quinolones: CIP, ENR, SAR, OXO, NAD, FLUME [70]	Shrimp tissue	SPE (6) / Lichrolut RP-18B Cartridge / 1.5 mL of acetonitrile and 0.5 mL of citric acid solution
Quinolones: ENR [74]	Fish	MSPE (1) / imprinted polymer (h-MIP) consisting of $K_2Ti_4O_9$ / ACN
Quinolones: MARBO, CIP, DAN, ENR, SAR, DIF, FLUME, OXO [72]	Honey, royal jelly and propolis	d-SPE (8) / Agilent SampliQ EN QuEChERS extraction kit / 1 mL of H_2O:ACN:formic acid (88:10:2)
Macrolide: FLO, TAP, CAP [84]	Beef, sausage, pork, wieners and liver	DLLME (3) / QuEChERS composed by 0.9 g of $MgSO_4$, and 0.15 g of each ofBondesil_PSA and C_{18} per 5 g of a sample (dispersive solvent) and 450 μL of CH_2Cl_2 (extraction solvent)
Macrolide: Erythrom, OLE, AZI, TM, CLA, ROX, CAP, TAP, *Quinolones*: CIP, SPFX [75]	Pork, shrimp and fish	MSPE (10) / imprinted polymer (h-MIP) consisting of ethromycin (template molecule) –Fe_3O_4 nanoparticles (support substrate) / 10 mL MeOH:50 mM KH_2PO_4 (pH 8)(8:2, v/v)
Ceftiofur sodium [78]	milk and animal-origin food	molecularly imprinted solid-phase extraction (1) / acetonitrile/0.2% acetic acid (30/70)
Quinolones: enoxacin, DAN, LOM, ENR, DIF, OXO*Sulfanilamides*: sulfanilamide, sulfadiazine, sulfapyridine, sulfamerazine, sulfachloropyridazine, sulfadimethoxine, sulfaquinoxaline*Amphenicols*: chloramphenicol, florfenicol, thiamphenicol [93]	Chicken meat, pork, beef, cheese, ham, beef liver, milk, honey, Egg	QuEChERS (16)
Macrolide antibiotics and metabolites [94]	Milk	QuEChERS (20)
Sulfonamides, fluoroquinolones, macrolides, nitroimidazoles and tetracyclines [95]	Honey and royal jelly	QuEChERS (42)
Semicarbazide [91]	Bread, Fish	Solid-to-liquid extraction (1) / 1% HCl at 50 °C for 3 h / methanolDerivatization step (on-line pre-column): Fluorenylmethyloxycarbonyl chloride in borate buffer (1 M, pH 8.0)
Sulfadiazine [98]	Fish Muscle	Direct injection: vortex-mixed and centrifugation (1) / On-Line Column-Switching
Tetracyclines: TC, OTC, CTC and DOX [100]	Eggs	Homogeneization with acetonitrile (4) / On-line MISPE-HPLC-DAD
Tetracyclines: OTC, TC, CTC [101]	Milk	Dilution with McIlvane/EDTA solution pH 2.9 (3) / On-line SPE preconcentration with

(*continued on next page*)

Table 5 (*continued*)

Compounds [Reference]	Matrix	Sample treatment (number of analytes) / Components of the extraction system / Eluent / Conditions
Quinolones: Enrofloxacin and gatifloxacin [102]	Milk	Zeolite imidazolate framework-8 as sorbents Centrifudation and direct injection / On-line SPE-HPLC with restricted access material with hybrid poly(glycerol mono-methacrylate) and cross-linked bovine serum albumin as hydrophilic out layers as sorbent

Table 6
Analytical treatment methods applied to different environmental samples to analysis antibiotics by HPLC.

Compounds [Reference]	Matrix	Sample treatment (number of analytes) / Components of the extraction system / Eluent / Conditions
Beta-lactam: PNG-G, CTX, CIP, CFI and CLO [73]	Wastewater	MSPE (5) / Cryo–SIPN with polyaniline and polypyrrole / MeOH
Quinolones: CIP, NOR and PEF [85]	Soll and water	LLE (3) / polyoxyethylene cetyl ether (POELE20)–NaH2PO4
Mix: AMO, CIP, tylosin, ERY, sulfamethoxazole and CTC [69]	Municipal wastewater	SPE (6) / Oasis HLB Cartridge/ ACN:MeOH:acetic acid (40:40:20 v/v) / pH 3.0
Macrolide: CAP [89]	Lake water and feed water	ILATPF (1) / midazolium ionic liquid (1-butyl-3-methylimidazolium chloride, [C_4mim]Cl) and inorganic salt (K_2HPO_4) with solvent sublation
Kanamycin [92]	Wastewater and Soil	Solidification of Floating Dispersive Liquid-phase Microextraction (1) / ethanol (dispersive solvent) / dodecanol (extraction solvent)
Tetracyclines: OTC, TCN, TCT, doxycycline [97]	Cosmetics	field-assisted extraction (FAE), micro-solid-phase extraction (μ-SPE) (4) / acetonitrile and water containing 0.2% acetic acid (pH 2.7)
Tetracyclines: OTC, TC, CTC [101]	Water	Direct injection (3)/ On-line SPE preconcentration with Zeolite imidazolate framework-8

Moreover, it has been reported that the use of QuEChERS (quick, easy, cheap, effective, rugged, and safe) extraction method can be useful to perform fast multicomponent analysis of a wide variety of drugs in different matrices [72,93–96].

Sample pretreatment is usually the most time-consuming step of the analytical method, due to this, some authors have developed automated methods or strategies to perform the analysis by direct injection. Furthermore, an additional advantage is miniaturized the pretreatment system, which is translated in less volume consuming of solvents, and consequently less waste production being more environmentally friendly. L. Xia et al. designed a total online device based on field-assisted extraction (FAE) and micro-solid-phase extraction (μ-SPE) using a monolithic column to determine polycyclic aromatic hydrocarbons (PAHs) in foods and tetracycline antibiotics (TCAs) in cosmetic samples. Compared with offline methods, this total online FAE-μ-SPE-HPLC method not only simplifies the operation process, but also increases the precision and accuracy [97].

Other authors have combined an online precolumn derivatization with High Performance Liquid Chromatography (HPLC) to determine Semicarbazide in fish and bread samples [91]. This method allows working without requiring no expensive analytical instruments, as for example tandem mass spectrometry, yielding similar results.

Another procedure to automatize the sample processing and connect this with the chromatographic system is to connect this step directly with the chromatograph by column-switching technique. A pre-column packed with polystyrene-divinylbenzene copolymer (PS/DVB) has been used for determination of SDZ in fish plasma and muscle [98]. Also, R. Tritller et al. used a NH_2 –precolumn to determine tazobactam and piperacillin in fatty tissue and serum by connecting it directly to the chromatograph [99]. Furthermore, another way to achieve an online coupling LC method for a specific target compound is to develop some reagents for the SPE. T. Jing *et al.* developed a molecularly imprinted polymer based on oxytetracycline and chlortetracycline as sorbent for the SPE for the determination of trace tetracycline antibiotics (TCs) in egg samples [100], X.Q. Yang et al. prepared a SPE column by packing a zeolite imidazolate framework-8 (ZIF-8) into a stainless-steel column (3 cm long × 4.6 mm i.d.) and mounted on the HPLC injector valve to replace the sample loop for on-line SPE of tetracyclines [101]. Finally, W. Huang *et al.* employed a novel restricted access material (RAM) through combination of the hydrophilic polymer poly(glycerol mono-methacrylate) and cross-linking bovine serum albumin (BSA) for direct biological analysis, specifically, for the analysis of enrofloxacin and gatifloxacin in milk samples [102]. In the material preparation, the poly(styrene-co-divinylbenzene) and poly(glycerol mono-methacrylate) were grafted on silica successively by atom transfer radical polymerization. Then the BSA was adsorbed on the material and cross-linked through an in-column process. These approaches allow the simplification of the sample treatment: an analyte is taken from the sample by a simple solid-to-liquid extraction for solid samples, while liquid samples are directly injected after dilution.

4. Conclusions

Public agencies and governments are concerned by the impact of antibiotic pollution in human health and environment, and then require bioanalytical methods to monitor antibiotics in the main sources of exposition: biological, food and environmental samples. This review describes and compares analytical methods to determine several groups of drugs belonging to the category of antibiotics in these samples. Nowadays, although analytical techniques for simultaneous detection and quantification of almost all prescribed antibiotics have been developed, their optimization remains difficult and challenging taking into account all their diverse properties, especially for environmental samples.

The process of sample control to evaluate the contamination level by antibiotics has to be improved in the future. The most urgent challenge is the enhancing of the analytical performances, especially that of trueness, which is unacceptable for some antibiotics, as well as the construction of multiresidue bioanalytical methods. It would be also interesting the development of new automatized on-line methods (sample treatment coupled to chromatographic separation), and to determine unknown metabolites, the transformation products of antibiotics and new antibiotics. For that, we need high-flying trained manpower and versatile instrumentation, able to adapt to the needs of the hospitals, public agencies and society; the development of is also required. Finally, the utilization of MS detection would be extended among the laboratories, what requires the development of the required instrumentation at lower prices.

5. List of abbreviations

1. Beta-lactam: Penicillins (AMO, Amoxicillin; AMP Ampicillin; CLO, Cloxacillin; DCL, Dicloxacillin; FLU, Flucloxacillin; NAF, Nafcillin; PEV, Phenoxymethylpenicillin; PIP, Piperacillin; PNG, Penicillin G; OXA, Oxacillin; TAZ, Tazobactam); Cephalosporins (CDX, Cefadroxil; CEF, Cephuroxime; CFL, Cephazolin; CFP, Cephepime; CFT, Ceftazidime;

CFX, Cephalexin; CTX, Cefotaxime); Carbapenem (IMP, Imipenem; MER, Meropenem); CFI, Cefixime; CLO, cloxacillin;

2. Glycopeptides: DEX, Dexamethasone; DVC, Dalbavancin; OVC, Oritavancin; TCP, Teicoplanin; TLV, Telavancin; VCM, Vancomycin; POL, polymyxin; BAC, bacitracin; DAP, daptomycin; VIR, virginiamycin

3. Aminoglycosides: AMK Amykacin; APRA, Apramycin; DHST,R, Dihydrostreptomycin; GEN, Gentamycin; HYG – Hygromycin B; KAN, Kanamycin; NEO, Neomycin; PARO, Paromomycin; RIB, Ribostamycin; SPC, Spectinomycin; STR, Streptomycin; TOB, Tobramycin

4. Macrolides: CAP, Chloramphenicol; TAP, Thiamphenicol; FLO, Florfenicol; OLE, oleandomycin phosphate dihydrate, AZI, azithromycin dihydrate; TM, tylmicosin; CLA, clarithromycin; ROX, roxithromycin; ERY, Erythromycin.

5. Quinolones: CIP, Ciprofloxacin; DAN, Danofloxacin; ENR, Enrofloxacin; FLE, Fleroxacin; FLUME, Flumequine; GAT, Gatifloxacin; LOM, Lomefloxacin; MARBO, Marbofloxacin; NOR, Norfloxacin; OFL, Ofloxacin; ORB, Orbifloxacin; OXO - Oxolinic acid; SAR – Sarafloxacin; PEF, Pefloxacin, MOX, Moxifloxacin; NAD, Nalidixic acid: LEV, Levofloxacin; DIF, Difloxacin; SPFX, sparfloxacin.

6. Tetracyclines: CTC, Chlortetracycline; DOC, Doxytetracycline; OTC, Oxytetracycline; TCN, Tetracycline; DC, doxycycline; OLA, Olaquindox.

7. Analgesic: DPR, Dipyrone; PAR, Paracetamol

8. Diuretic: FUR, Furosemide

9. Azole Antifungals: FZ, Fluconazole

10. Nonsteroidal anti-inflammatory drug: KET – Ketoprofen

11. Corticosteroid: PRE, Prednisolone

12. Reagents: ACN, acetonitrile; MeOH – Methanol; HAc – Acetic acid; IPA, Isopropanol; EDTA, Ethylenediaminetetra-acetic acid; HFBA, Heptafluorobutiric acid; PFPA, Pentafluoropropionic acid; TFA, Trifluoroacetic acid; TEA, Triethylamine; SDS, Sodium docecyl sulfate

13. Validation parameters: RSD, Relative standard deviation; CV, Coefficient of variation; LOD, Limit of detection; LOQ, Limit of quantification.

14. Treatment sample concepts: SM-LPME, stir membrane liquid phase microextraction; USA-DLLME-SFO, -assisted dispersive liquid–liquid microextraction based on solidification of floating organic drop; HP-DES, hydrophobic deep eutectic solvent; HLLME, Homogenous liquid–liquid microextraction; Cryo–SIPN, cryogel–based semi–interpenetrating polymer network; MSCSE, magnetic stir cake sorptive extraction; μ- or M−SPE, micro solid phase extraction; ATPS, aqueous two-phase systems; ILATPF, Ionic liquid–salt aqueous two-phase flotation; MOFs, metal organic frameworks; MIL, magnetic ionic liquid; LLE, liquid liquid extraction.

CRediT authorship contribution statement

J. Peris-Vicente: Methodology, Validation, Investigation, Writing – original draft, Writing – review & editing, Funding acquisition. **Ester Peris-García:** Software, Formal analysis, Investigation, Data curation, Writing – review & editing. **Jaume Albiol-Chiva:** Software, Formal analysis, Data curation, Writing – original draft. **Abhilasha Durgbanshi:** Data curation, Methodology, Supervision, Resources. **Enrique Ochoa-Aranda:** Validation, Data curation, Visualization, Supervision. **Samuel Carda-Broch:** Methodology, Validation, Resources, Conceptualization, Supervision. **Devasish Bose:** Conceptualization, Writing – review & editing, Project administration, Funding acquisition. **Josep Esteve-Romero:** Conceptualization, Methodology, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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