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Review Paper

Comparison of methods for the determination of beta-lactam drugs using different analytical methods

Maryam Muhson Abd[1], **Elham N. Mezaal**[1*]

[1]Department of Chemistry, College of Education for Pure Sciences (Ibn-Al-Haitham), University of Baghdad, Baghdad, Iraq

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Corresponding author
Elham N. Mezaal
elham.n.m@ihcoedu.uobaghdad.edu.iq

ABSTRACT

Given the increasing global use of antibiotics, it has become necessary to examine and recognize their significance. An antibiotic formulation may contain one or more active components, depending on the antibiotic's type and formulation. Antibiotics act exclusively against bacterial diseases and are ineffective against viral infections such as the common cold and influenza. The purpose of this review is to analyze the existing literature on the determination of antibiotics and to present the methods used for estimating specific antibiotics, including cephalexin, cloxacillin, piperacillin, nafcillin, and cefamandole, in medicinal preparations and biological fluids, such as blood and urine, from humans and animals. Verifying the quality of medications is crucial to ensure the accurate composition of pharmaceutical preparations. Different analytical techniques have been employed to assess antibiotic concentrations, including gas chromatography, high-performance liquid chromatography, spectroscopic and electrochemical methods, and flow injection analysis. These methods are used to analyze antibiotics in various forms, such as tablets, capsules, and other pharmaceutical preparations. This study provides a concise narrative review that examines and compares several analytical techniques used for the determination of antibiotic medications.

Keywords: *Antibiotic, Cefamandole, Cephalexin, Cloxacillin, Piperacillin*

1 INTRODUCTION

Antibiotics are compounds produced by bacteria, other microorganisms, and fungi [1]. They are capable of killing or inhibiting other microbes. Some antibiotics are antimicrobial agents used to manage infectious diseases in both humans and animals [2]. They have also been used to prevent infections during surgery and childbirth, and have undoubtedly contributed to improvements in public health [3]. Antibiotics are ineffective against viral infections such as colds and influenza, as well as most cases of cough, bronchitis, and sore throat, unless a bacterial infection is present. If the cause of the disease is viral, the harm of taking antibiotics may outweigh the benefit. Each time a person takes an antibiotic, the possibility increases that bacteria may develop resistance to that antibiotic [4]. In 1942, Waksman introduced the term "antibiotics" to refer to any chemical generated by microbes that inhibits the growth of other microorganisms in a highly diluted medium. Recently, many antibiotics have become semi-synthetic substances derived from natural compounds, such as beta-lactam antibiotics, including penicillin, which is produced by fungi of the genus Penicillium [5].

2 CLASSIFICATION OF ANTIBIOTICS [6,7]

Antibiotics are classified according to the basis of their biosynthesis into:

1. Antibiotics produced by the chemical breakdown

of amino acids

2. Antibiotics originating from the metabolic breakdown of acetate

3. Antibiotics produced through the process of carbohydrate metabolism

Antibiotics can also be categorized based on their chemical composition into different groups:

1. beta-lactam antibiotics

2. amino glycosides

3. macrolides

4. lincomycin

5. polypeptides.

2.1 beta-lactam antibiotics

Beta-lactam antibiotics are a broad class of chemically diverse compounds commonly used in clinical settings and administered orally or by injection. Beta-lactam antibiotics have become an important therapeutic class of antimicrobials because of their broad-spectrum activity against bacteria. They act by inhibiting bacterial cell wall biosynthesis [8]. They are among the most widely available antibiotics used to treat bacterial infections. Penicillin is a beta-lactam antibiotic and is considered one of the most important medications. Therefore, beta-lactam antibiotics can be regarded as among the most important antibiotics ever discovered [9]. A wide range of bacteria can be eliminated by beta-lactam antibiotics, and their toxicity is low. Therefore, resistance to beta-lactam antibiotics represents a serious threat to the treatment of bacterial and other microbial infections [10].

2.1.1 Cephalexin

Cephalexin is a semisynthetic, broad-spectrum cephalosporin antibiotic with antibacterial activity. It acts by inhibiting bacterial cell wall synthesis [11]. This action produces bactericidal effects and may contribute to the development of bacterial resistance when the antibiotic is misused [12]. Cephalexin is administered orally to treat infections caused by Streptococcus pneumoniae and Streptococcus pyogenes [13]. It is used to treat a range of bacterial infections, including skin, middle ear, and respiratory tract infections, as well as scarlet fever. It is also used to treat various infectious diseases. Because of its improved oral activity, it has been used in selected clinical conditions [14, 15]. According to IUPAC nomenclature, cephalexin is known as 7-[(amino-phenylacetyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, with a molar mass of 347.4 g/mol [16]. The chemical structure of cephalexin is shown in Figure 1.

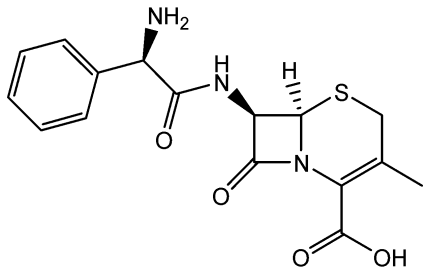

Fig. 1 Chemical composition of cephalexin

2.1.2 Cloxacillin

Cloxacillin is an antibiotic medication that belongs to the penicillin family. It is frequently used to treat infections caused by Gram-positive bacteria, specifically methicillin-sensitive Staphylococcus aureus, particularly in catheter-related infections [17]. Its mechanism of action involves inhibiting bacterial growth. It is used to treat skin, bone, heart valve, bloodstream, lung, sinusitis, pharyngitis, and tonsillitis [18]. According to IUPAC nomenclature, cloxacillin is known as (2S,5R,6R)-6-[[3-(2-chlorophenyl)-5-methyl-1,2-oxazole-4-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, with the empirical formula C19H18ClN3O5S and a molar mass of 435.9 g/mol [19]. Figure 2 shows the chemical structure of cloxacillin.

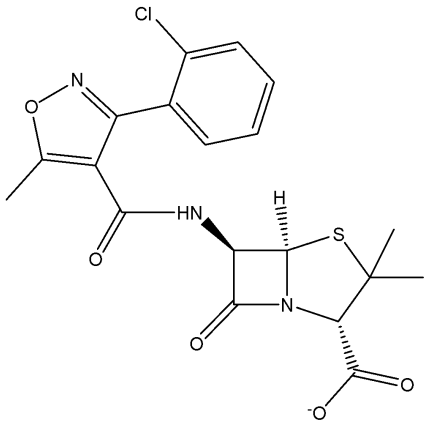

Fig. 2 Chemical composition of cloxacillin

2.1.3 Piperacillin

Piperacillin is a broad-spectrum β-lactam antibiotic that belongs to the penicillin class [20]. Its chemical structure inhibits bacterial cell wall formation [21]. Piperacillin exhibits antibacterial activity against both anaerobic and aerobic bacteria, including Gram-positive and Gram-negative bacteria [22]. Piperacillin is a member of the penicillin class and is used to treat infections caused by susceptible microorganisms [23]. It is very useful in treating hospital-acquired and polymicrobial infections. According to IUPAC nomenclature, piperacillin is known as [(2S,5R,6R)-6-[(2R)-2-[(4-ethyl-2,3-dioxopiperazine-1-carbonyl)amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, with the chemical formula C23H27N5O7S and a molar mass of 517.6 g/mol [24]. Figure 3 shows the chemical structure of piperacillin.

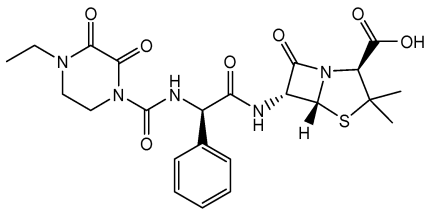

Fig. 3 Chemical composition of piperacillin

2.1.4 Nafcillin

Nafcillin is a narrow-spectrum beta-lactam antibiotic classified under the penicillin group. It is derived from 6-aminopenicillanic acid, and its molecular structure contains a naphthalene ring [25]. It is used to treat infections caused by Gram-positive bacteria, particularly staphylococcal infections resistant to other penicillins. One study reported higher incidences of hypokalemia and severe renal damage in individuals treated with nafcillin compared with individuals treated with oxacillin [26, 27]. According to IUPAC nomenclature, nafcillin is known as (2S,5R,6R)-6-[(2-ethoxynaphthalene-1-carbonyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, with the empirical formula C21H22N2O5S and a molar mass of 414.5 g/mol [28]. Figure 4 shows the chemical structure of nafcillin.

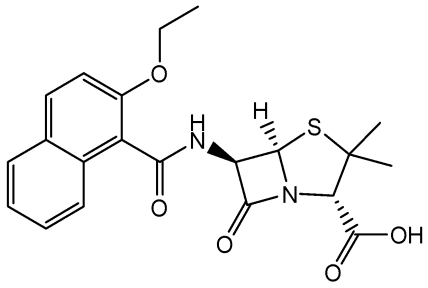

Fig. 4 Chemical composition of nafcillin

2.1.5 Cefamandole

Cefamandole is a second-generation cephalosporin antibiotic administered intravenously or intramuscularly to treat various bacterial infections. It is mainly indicated for the treatment of bacterial infections, particularly those affecting the respiratory tract, and is especially effective against Gram-negative cocci and Haemophilus species. It is also used to treat urinary tract infections and biliary tract infections. Cefamandole nafate, a formate ester of cefamandole, is used medically as an injectable administered intravenously and rapidly hydrolyzes to cefamandole in the body [29]. According to IUPAC nomenclature, cefamandole is known as (6R,7R)-7-[(2R)-2-hydroxy-2-phenylacetyl]amino-3-[(1-methyltetrazol-5-yl)sulfanylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, with the empirical formula C18H18N6O5S2 and a molar mass of 462.50 g/mol [30]. Figure 5 illustrates the chemical structure of cefamandole.

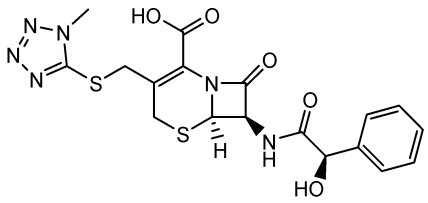

Fig. 5 chemical composition of cefamandole

2.2 The methods used in the determination of antibiotics

Many methods have been used to determine antibiotics, including high-performance liquid chromatography (HPLC), liquid chromatography (LC), gas chromatography (GC), flow injection analysis (FIA), voltammetry, and ultraviolet-visible spectroscopy (UV). These are analytical techniques used in chemical analysis.

2.2.1 Ultraviolet–visible spectroscopy (UV–Vis)

UV-Vis spectroscopy is a type of absorption spectroscopy that occurs in the ultraviolet and visible regions of the electromagnetic spectrum [31, 32]. This technique uses visible light, the near-ultraviolet region, and part of the near-infrared region [33, 34]. It concerns the analysis of electronic transitions from the lowest energy state to a higher energy state [35, 36]. In this technique, molecules are exposed to electromagnetic radiation in the visible and ultraviolet regions, thereby exciting valence electrons. These electrons gain energy, and electronic transitions occur between molecular energy levels [37].

Spectroscopic analysis can be automated using sampling devices and control software. It can also be interfaced with other techniques, especially chromatographic separation, via specialized interfaces that efficiently transfer the separated components to the spectroscopic detector [38, 39]. It may also be combined with flow injection analysis [40]. Spectroscopic techniques are used to determine drugs, including medications for heart failure and hypertension. Spectroscopic methods are common and widely used in the determination of drugs, including beta-lactam antibiotics [32].

Advantages of spectroscopic methods in the determination of beta-lactam drugs [31, 35]:

1. Accuracy and sensitivity: Many spectroscopic techniques provide highly accurate and sensitive results, allowing the determination of very low drug concentrations.

2. Speed and efficiency: Spectroscopic analyses are often rapid, allowing the analysis of large numbers of samples in a short time.

3. Ease of operation: Some techniques, such as ultraviolet–visible (UV-Vis) absorption spectroscopy, are relatively simple to operate and do not require highly sophisticated equipment.

4. Non-destructive nature: Some spectroscopic methods can be used to analyze samples without destroying them.

5. Wide applications: Spectroscopic analysis can be applied to various dosage forms, including tablets, capsules, injections, and solutions, as well as different raw materials.

6. Qualitative and quantitative determination: Spectra can be used to determine the presence of a particular compound qualitatively and estimate its quantity quantitatively.

Disadvantages of spectroscopic methods for the quantification of beta-lactam drugs [32, 34]:

1. Interferences: Other substances present in the sample, such as excipients, impurities, and degradation byproducts, may interfere with the light absorption of the target drug, affecting the accuracy of the results.

2. Requirement for a pure sample or pre-separation: In many cases, spectroscopic methods may require a pure drug sample or pre-separation steps, such as extraction or chromatography, to remove interfering substances and obtain accurate results.

3. Inability to distinguish between chemical analogs: It may be difficult to differentiate between compounds with very similar chemical structures and similar absorption spectra, requiring more advanced spectroscopic techniques or complex separation techniques.

4. Cost of some techniques: Some advanced spectroscopic techniques, such as chromatography coupled with mass spectrometry or nuclear magnetic resonance spectroscopy, can be expensive in terms of instrument purchase and maintenance.

5. Effect of experimental conditions: Spectral readings can be affected by factors such as temperature, pH, and the solvents used, requiring careful control of these conditions to ensure repeatability and accuracy.

6. Degradation challenges: Beta-lactam drugs are known for their active beta-lactam rings, which can easily degrade under certain conditions, such as heat, humidity, and extreme pH. This can lead to the formation of degradation products with their own absorption spectra, complicating the analysis and requiring special attention during method development.

2.2.2 High-performance liquid chromatography (HPLC)

HPLC is a highly effective analytical method widely used across scientific and industrial fields for separation and chemical analysis. HPLC systems are designed to separate, identify, and quantify the components of complex mixtures with high accuracy and sensitivity. An HPLC system consists of several basic components, including the mobile phase, the column (stationary phase), the sample injection system, the pump, the detector, and the data system for producing chromatograms. The mobile phase is usually a liquid solvent, while the column is packed with stationary-phase particles. The choice of stationary phase depends on the required separation conditions, such as reversed-phase, normal-phase, or ion-exchange chromatography [41]. Chromatographic methods can be coupled with spectroscopic detection and flow injection analysis. These methods are used to analyze medications for hypertension, epilepsy, and neuropathic pain, as well as drugs used for respiratory disorders, diarrhea, and gastrointestinal inflammation [42, 43].

Advantages of chromatographic analysis in the determination of beta-lactam drugs [40, 44]:

1. High separation power: This is the most prominent advantage of chromatography. It enables the separation of various components in a sample with high accuracy, including the target drug, impurities, degradation products, and additives in the pharmaceutical formulation. This is critical for beta-lactam drugs because they are highly susceptible to degradation.

2. Sensitivity and accuracy: Chromatographic methods, particularly HPLC with sensitive detectors such as UV-Vis or MS, offer high sensitivity, allowing the determination of very low drug concentrations. They also provide excellent accuracy in quantitative measurement.

3. Qualitative and quantitative analysis: Chromatography can be used to determine the presence of a particular compound through retention time and its quantity through peak area or peak height.

4. Versatility of detectors: Chromatographic systems can be coupled with a wide range of detectors, such as UV-Vis detectors, diode array detectors (DAD), refractive index detectors (RI), and mass spectrometry (MS), increasing their analytical capacity.

5. Reliability and reproducibility: Once a suitable chromatographic method is developed and validated, it provides reliable and reproducible results.

6. Suitability for complex matrices: Because of its separation capability, chromatography is ideal for analyzing beta-lactam drugs in complex pharmaceutical formulations or biological samples containing multiple components.

7. Degradation product and impurity profiling: Chromatography allows the identification and quantification of impurities and degradation products, which is vital for assessing the stability and quality of beta-lactam drugs.

Disadvantages of chromatographic analysis for the determination of beta-lactam drugs [41, 42]:

1. High cost: The purchase and maintenance of chromatographic equipment, especially HPLC-MS systems, are expensive compared with some other analytical techniques.

2. Requirement for pure samples or complex sample preparation: Despite their separation capability, many samples require careful pretreatment, such as extraction or purification, before injection into the instrument to avoid column contamination or interference with the analysis.

3. Analysis time: Some chromatographic analyses require a long time to complete separation, ranging from minutes to hours, which may limit the number of samples analyzed per day compared with direct spectroscopic techniques.

4. Requirement for technical expertise: Operation, method development, and maintenance of chromatographic equipment require significant technical expertise.

5. Use of organic solvents: Many chromatographic methods rely on large quantities of toxic or flammable organic solvents, raising environmental and health concerns and requiring proper disposal.

6. Column degradation and contamination: Chromatographic columns are delicate and may become damaged or contaminated over time if they are not properly maintained or if unclean samples are injected, affecting separation performance.

7. Beta-lactam instability: Although chromatography separates degradation products, the sensitivity of beta-lactam drugs to degradation during sample preparation or under certain system conditions can affect the results if factors such as temperature and pH are not carefully controlled.

2.2.3 Gas chromatography (GC)

GC is a chromatographic technique in which the mobile phase consists of a carrier gas, often an inert gas such as helium or nitrogen [43]. The stationary phase is contained within a narrow tube called a column, in which a thin layer of liquid is coated onto an inert solid support or bonded to the column's inner wall. GC is a chemical analytical technique used to separate and identify chemical substances in a sample [45]. The analyte is introduced into the system, and the sample's chemical components are separated as they pass through the column at different rates, depending on their chemical composition and physical properties. After leaving the column, the compounds are electronically detected and differentiated. The column separates and concentrates the sample's components to improve the detected signal. GC can be coupled with detectors such as an electron-capture detector [43, 46].

Gas chromatography is a powerful analytical technique; however, its use in quantifying beta-lactam drugs is very limited compared with high-performance liquid chromatography (HPLC). This is mainly due to the chemical properties of beta-lactam drugs.

Advantages of gas chromatography (GC) [43, 45]:

Although GC is not the first choice for beta-lactam drugs, it has general advantages that make it useful for other types of compounds:

1. High separation efficiency: GC has excellent separation capacity, allowing accurate separation of complex components in a mixture.

2. High sensitivity: The detectors used in GC, such as FID, ECD, and MS, can be highly sensitive, allowing the detection of very small amounts of substances.

3. Speed of analysis: GC analyses are often rapid, with results obtained within a few minutes. Detector versatility: GC can be coupled with a wide range of detectors, including mass spectrometry (GC-MS), providing strong qualitative and quantitative information.

4. Operational cost-effectiveness: After instrument purchase, GC operating costs may be relatively lower than those of HPLC in terms of solvent consumption.

Disadvantages of gas chromatography (GC) in the determination of beta-lactam drugs [44, 45]:

The disadvantages of GC are particularly evident when it is applied to beta-lactam drugs:

1. Requirement for volatility and thermal stability: This is the main disadvantage. For a compound to be analyzed by GC, it must be volatile and thermally stable enough to withstand the high temperatures of the injector and column without decomposition.

2. Requirement for chemical derivatization: To overcome non-volatility or thermal instability, beta-lactam drugs may require chemical derivatization before GC analysis. This process involves reacting the drug with a reagent to produce a more volatile and thermally stable derivative.

3. Difficulty in analyzing polar compounds: Many beta-lactam drugs are polar compounds and may not interact well with the non-polar stationary phases commonly used in GC without chemical conversion.

4. Initial cost: Although operating costs may be lower, the initial cost of purchasing GC equipment, especially advanced systems such as GC-MS, remains high.

5. Requirement for expertise: Method development, GC operation, and maintenance require technical expertise.

2.2.4 Flow injection analysis (FIA)

FIA was developed as a highly efficient technique for automated sample analysis [47, 48]. It allows rapid sequential analysis of a large number of samples [49, 50]. FIA is one example of continuous flow analysis [51]. In this technique, samples are sequentially injected at uniform intervals into a liquid carrier stream, which transports them to the detector [52]. Flow injection analysis is a powerful and effective tool for analyzing beta-lactam drugs, especially in applications requiring high speed, automation, and low material consumption. However, its limitations, particularly interferences and lack of separation, must be considered, and the method

must be carefully selected according to the nature of the sample and the specific analytical requirements. Flow injection analysis is not only an efficient analytical method but also an environmentally friendly approach that aligns with the main goals of green chemistry by reducing the environmental impact of chemical processes. It is known for low sample consumption, speed, and efficiency. This technique can be considered a sequential analytical system from sample introduction to result generation [53]. It can be coupled with optical spectroscopy, fluorescence spectroscopy, photochemical detection, and chromatography [40,49]. It is used in the analysis of anti-inflammatory drugs and medications for allergy, hypertension, and myocardial infarction [47, 49]. It can also be coupled with optical spectroscopy [47] and chemiluminescence detection [54].

Advantages of flow injection analysis (FIA) for the analysis of beta-lactam drugs [52, 53]:

1. Analysis speed: FIA is characterized by high speed, enabling the analysis of large numbers of samples in a short time. This is particularly important in applications requiring high throughput, such as quality control in the pharmaceutical industry.

2. High automation: The entire analysis process can be automated, from sample injection to reagent addition and signal measurement. This reduces human error and increases the accuracy and reproducibility of results.

3. Low reagent and sample consumption: FIA systems typically require very small quantities of reagents and samples, reducing costs and making them more environmentally friendly.

4. Flexibility and versatility: FIA systems can be adapted to a wide range of reagents and detection methods, such as colorimetric, fluorescence, electrochemical, and photochemical methods, making them suitable for the analysis of different beta-lactam drugs based on their chemical properties.

5. Ease of operation and maintenance: Compared with some more complex analytical techniques, FIA systems are relatively simple to operate and maintain. FIA systems can also be directly connected to various detection systems, providing flexibility in analytical design.

6. Good accuracy and sensitivity: FIA can provide high accuracy and sensitivity in the analysis of beta-lactam drugs, making it suitable for detecting low concentrations.

Disadvantages of flow injection analysis (FIA) for the analysis of beta-lactam drugs [47, 48]:

1. Lack of separation: In its basic form, FIA does not provide a method for separating different components in the sample. Therefore, if the sample contains compounds that may interfere with beta-lactam measurement, sample pretreatment steps or selective reagents may be required.

2. Interferences: Interferences from other matrix components in the sample may occur, affecting measurement accuracy. For example, some compounds may react with the reagents used to detect beta-lactams, leading to erroneous results.

3. Requirement for careful calibration: To obtain accurate and reliable results, FIA systems require careful and regular calibration using known standards of beta-lactam drugs.

4. Limited suitability for some analyses: Despite its flexibility, FIA may not be ideal for all beta-lactam analyses, especially those requiring high separation of very similar compounds or compounds present at very low concentrations in complex matrices. In such cases, techniques such as HPLC or GC-MS may be more appropriate.

5. Requirement for stable reagents: Some FIA detection methods rely on chemical reactions, which require stable reagents to ensure measurement accuracy over time.

2.2.5 Electrochemical analysis

Electrochemical analysis is a group of techniques that use electrical signals to study chemical reactions at the surface of a sample or in solution. The rates of oxidation and reduction reactions are controlled and measured using a single device connected to electrodes immersed in an electrolyte [55]. This type of analysis is used in corrosion studies, in which a material decomposes because of chemical or electrochemical reactions. Test conditions can vary according to the environment, including temperature, electrolyte composition, and oxygen exclusion [56]. Electrochemical analysis is useful

for selecting materials during the design phase or for predicting failure mechanisms and service life during operation [57]. It can be performed using voltammetric and potentiometric techniques [58, 59].

Electroanalytical methods are important techniques for analyzing beta-lactam drugs. They rely on measuring the electrochemical reactions of the analyte at the electrode surface. These methods include voltammetry, amperometry, conductometry, and other related techniques. The following is a review of the advantages and disadvantages of using these methods for analyzing beta-lactam drugs.

Advantages of electroanalytical methods for analyzing beta-lactam drugs [55]:

1. High sensitivity: Electroanalytical methods are characterized by high sensitivity, allowing the detection of very low concentrations of beta-lactam drugs, even at trace levels. This is important in the analysis of biological samples and environmental water, where these drugs may be present in trace concentrations.

2. Low cost: The equipment required for electroanalytical methods is typically less expensive than that required for more complex analytical techniques, such as high-performance liquid chromatography (HPLC) or mass spectrometry (MS).

3. Analysis speed: Electroanalytical methods can be very fast, allowing results to be obtained within a relatively short time, which is beneficial in applications requiring rapid analysis.

4. Operational simplicity: Many electroanalytical methods are simple to operate and maintain, making them suitable for use in various laboratories.

5. Ability to directly analyze complex samples: In some cases, electroanalytical methods can be used to analyze beta-lactam drugs directly in complex samples, such as biological fluids, including urine and serum, without the need for complex pretreatment steps.

6. Selectivity: Good selectivity can be achieved by selecting an appropriate electrode type, adjusting the analysis conditions, such as solution pH, or using electrodes modified with nanomaterials or molecularly imprinted polymers to increase discrimination between beta-lactams and interfering compounds.

7. Miniaturization and automation potential: The nature of electroanalytical methods allows the development of small, portable point-of-care devices that can be used for on-site analysis or for automation of analytical processes.

8. Information on chemical interactions: Electroanalytical methods can provide valuable information about the electrochemical behavior of beta-lactam drugs, such as their redox potentials and reaction mechanisms, helping to clarify their stability and interactions in biological and environmental systems.

Disadvantages of electroanalytical methods for analyzing beta-lactam drugs [56, 57]:

1. Interferences: Interferences are a major challenge in electroanalytical methods. The presence of other compounds in the sample with redox potentials similar to those of beta-lactams can affect measurement accuracy. For example, some metabolites or other compounds present in biological fluids may undergo electrochemical reactions, resulting in positive or negative interferences.

2. Electrode sensitivity to contamination: Electrode surfaces can be affected by contamination from the sample or reagents, reducing measurement sensitivity and accuracy and requiring regular cleaning or renewal of the electrodes.

3. Inability to separate highly similar compounds: If beta-lactam drugs are very similar in chemical structure and have close electrochemical potentials, it may be difficult to distinguish and separate them using electroanalytical methods alone. In such cases, combination with separation techniques such as HPLC may be necessary.

4. Need for specific method development: Each beta-lactam drug or group of beta-lactams often requires the development of a specific electroanalytical method tailored to its electrochemical properties.

5. Limited applicability in some complex matrices: Although direct analysis is possible, some highly

complex matrices may not be suitable for direct analysis using electroanalytical methods because of high interference rates.

Cephalexin: A very sensitive, precise, and rapid FIA method was proposed for quantifying cefotaxime, cefuroxime, ceftriaxone, cefaclor, cefixime, ceftizoxime, and cephalexin (Figure 6). Each cephalosporin was analyzed in aliquots for 15 min at 80 °C using 0.1 M NaOH. The cephalosporins were then oxidized with Fe(III) in a sulfuric acid medium to yield Fe(II), with maximum absorbance at 510 nm. Variables such as acidity, reagent concentrations, reagent residence time, and other flow injection factors were optimized. The method was successfully applied to the analysis of medicinal formulations. There was strong agreement between the results of the proposed method and those of approved methods [57].

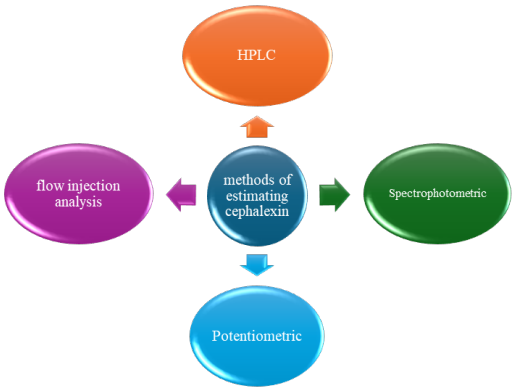

Fig. 6 Methods of determination of cephalexin

Using first- and second-derivative modes, a novel spectrophotometric method was presented for the simultaneous and individual determination of cefixime and cephalexin. The first- and second-derivative spectra of the compounds allowed simultaneous and individual determination of cefixime and cephalexin within a concentration range of 4–24 µg/mL. This was achieved by calculating the area under the peak at specific spectral intervals and the peak-to-baseline amplitude. The procedures demonstrated acceptable precision and accuracy and were used to identify cefixime and cephalexin in two different medicinal formulations [40].

A simple, accurate, indirect spectrophotometric method was used to determine cephalexin in pure form and pharmaceutical products. The method was based on a complexation reaction and depended on the oxidation of cephalexin in an acidic medium with Fe(III). At 510 nm, the concentration range was 0.4–10 µg/mL. The LOD and LOQ were 0.065 µg/mL and 0.218 µg/mL, respectively, with a strong correlation coefficient of 0.992. The method showed an RSD of 6.26% (n = 6). Recoveries ranged from 95.47% to 103.87%, whereas recoveries for commercial formulations ranged from 98.62% to 103.35%. The method was successfully used to determine cephalexin in commercial formulations and bulk powder [60].

This study used RP-HPLC to determine cephalexin (CEP) and aspirin (ASP) in both pure and pharmaceutical forms. The method was accurate, efficient, and repeatable. A pharmaceutical mixture was separated as a standard material and in tablet formulations. A mixture of water (H_2O) and acetonitrile (ACN) was used as the mobile phase at a 60:40 (v/v) ratio, and acetic acid was used to adjust the pH to 4. The flow rate of the mobile phase was 0.8 mL/min. The drugs were separated within 4 min using a UV-Vis detector at 270 nm. The retention times were 1.981 and 3.072 min for ASP and CEP, respectively. The concentration range was 1–50 µg/mL. The R^2 values ranged from 0.9993 to 0.9996, while the mean recovery values for ASP and CEP ranged from 99.77% to 100.16%. The LOD for CEP and ASP was 0.05 µg/mL, and the LOQ for both ASP and CEP was 0.165 µg/mL [61].

This article describes two spectrophotometric procedures that can directly determine the concentration of cephalexin in pure and pharmaceutical forms. In this study, the area under the curve was calculated over the range 260–266 nm, while the zero-order method showed optimal absorption at 263 nm. Both methods exhibited linearity within the range of 10–60 µg/mL. The LOD of the area under the curve method was 0.781, while that of the zero-order method was 0.808. These techniques are suitable for determining the presence of cephalexin in pharmaceutical dosage forms [38].

This study focused on the development of a rapid, specific, highly sensitive, and reliable technique for the simultaneous determination of cephalosporins, including cephalexin (CLN) and cefadroxil (CFL), in biological fluids and tablet samples. A poly(resorcinol)-modified glassy carbon electrode, poly(reso)/GCE, was fabricated using potentiodynamic methods. The peak current observed at the poly(reso)/GCE electrode showed a linear relationship with CLN and CFL concentrations within the ranges of 0.1–300 µM and 0.5–300 µM, respectively, with LOD values of 3.12 and 8.7 nM, respectively. The levels of CFL in two tablet forms and CLN in four selected tablet brands ranged from 91.00% to 103.65% and

from 97.7% to 98.83%, respectively. In pharmaceutical samples, the recovery values ranged from 99.00% to 100.67% for CLN and from 97.9% to 99.75% for CFL. In blood serum and urine samples, the recovery values were 99.55%–100.55% and 99.33%–100.34% for CLN, respectively, and 97.13%–100.60% and 96.73%–102.50% for CFL, respectively [62].

A chromatographic method was used to determine cephalexin and cefixime residues. At a wavelength of 254 nm, a mobile phase composed of acidified water and acetonitrile (85:15, v/v) at pH 4.5, adjusted with phosphoric acid, and a flow rate of 2.0 mL/min was used to assess the effects of three independent factors: pH, organic content, and flow rate, on resolution and retention time. A correlation coefficient of >0.9998 and recovery values of 99%–99.5% were achieved. The spectra of the drugs were successfully resolved at 261 nm for cephalexin and 298 nm for cefixime, with good linearity for the proposed HPLC and MCR methods. The concentration ranges were 0.05–10 ppm and 5–30 ppm, with LOQ values of 0.008, 0.013, 0.79, and 0.68 ppm and LOD values of 0.003, 0.004, 0.26, and 0.23 ppm, respectively [58].

A rapid, simple, and precise method was proposed for determining ciprofloxacin in the presence of cephalexin, and vice versa. The proposed H-point standard addition method proved effective for estimating ciprofloxacin at concentrations of 4–18 µg/mL in the presence of cephalexin, which overlaps with the λmax values of 240–272.3 nm. It was also effective for estimating cephalexin in a combined mixture at concentrations of 6–18 µg/mL in the presence of ciprofloxacin, which interferes at λmax values of 262–285.7 nm. The RSD was less than 2%. The LOD values for cephalexin and ciprofloxacin were 0.1732 and 0.1732 µg/mL, respectively. The method was successfully used to identify the two medications in selected pharmaceutical formulations without overlap or negative interference between them. The proposed method was effective in estimating the combined dosage of cephalexin and ciprofloxacin without causing interactions between the two medications [34].

Cloxacillin: The purpose of that study was to develop a validated HPLC method for quantifying dicloxacillin, cloxacillin, and oxacillin residues in milk, beef, and cheese samples. The substances examined were extracted from the samples using an acidic sodium tungstate solution (Figure 7). At 345 nm, the separated compounds were identified by linear gradient elution. The LOD values were below the maximum residue limits (MRLs), and the recoveries exceeded 80% [39].

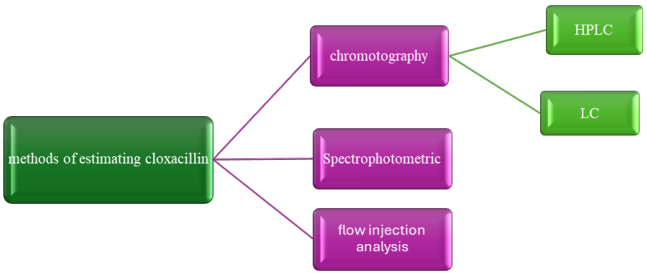

Fig. 7 Methods of estimating cloxacillin

An HPLC method was used for the determination of five types of penicillins: dicloxacillin, oxacillin, cloxacillin, phenoxymethylpenicillin, and benzylpenicillin, in milk samples. Ethyl acetate was used for the extraction, purification, and concentration of the analytes. Then, 1,2,4-triazole and mercury(II) chloride solution at pH 8 were added, and the reaction was allowed to proceed for 10 min at 65 °C. Using acetonitrile and phosphate buffer containing sodium thiosulfate and tetrabutylammonium hydrogen sulfate as an ion-pairing reagent, the derivatized compounds were eluted from a C2 column. The LODs were 4 µg/L for benzylpenicillin in milk and 10 µg/L for the other compounds [63].

A simple and rapid LC technique was developed to directly determine cloxacillin in human plasma. The effects of pH and ionic strength of the washing solution, as well as the addition of an organic modifier to the washing solutions, were investigated to achieve high recovery of cloxacillin and effective sample clean-up. Octadecyl silica was used as the stationary phase for separation, while the mobile phase consisted of acetonitrile and a 25 mM phosphate buffer at pH 4.0 in a 72:28 (v/v) ratio. UV detection was carried out at 215 nm. The official validation phase then involved assessment of these criteria. The LOQ was 50 ng/mL. In addition, the method's accuracy, precision, analyte recovery, linearity, and trueness were confirmed. Finally, the method was successfully used to analyze plasma samples collected from patients who had orally received 500 mg of cloxacillin [64].

In a 50% (v/v) aqueous ethanol solution, cloxacillin sodium was shown to form charge-transfer (CT) complexes with several electron acceptors in a 1:1 ratio. The vertical ionization potential of the cloxacillin sodium molecule was determined to be 7.89 eV based on the observed patterns in the CT absorption bands. The enthalpy and entropy values for the formation of these

complexes were also determined. The current study of complex formation equilibria was made possible by the complete inhibition of the reduction of o-chloranil by hydroethanol in the presence of cloxacillin sodium [65].

Five penicillins were identified in bovine muscle using an HPLC method: penicillin G (PENG), penicillin V (PENV), oxacillin (OX), cloxacillin (CLO), and dicloxacillin (DICLO). The investigated penicillins were separated using a C8 column. The mobile phase consisted of 0.1% TFA/ACN at 50:50 (v/v), delivered isocratically at a flow rate of 1.1 mL/min. The analytes were monitored at 240 nm. The method was validated by assessing specificity, stability, detection capability, accuracy, and precision. The LOQ values obtained using this method were 46 µg/kg for PENV, 16 µg/kg for OX, 43 µg/kg for DICLO, and 54 µg/kg for PENG and DICLO. The detection capabilities (CCβ) for PENG, PENV, OX, CLO, and DICLO were 73.6 µg/kg, 29.1 µg/kg, 350.6 µg/kg, and 379.9 µg/kg, respectively. Using photodiode array (PDA) detection, two penicillins were detected and quantified [66].

This study presents a rapid and accurate HPLC-UV method for analyzing beta-lactam drugs in microsamples of human plasma. The drugs included ticarcillin, amoxicillin, piperacillin, penicillin G, cefepime, cefotaxime, ceftazidime, ceftriaxone, imipenem, meropenem, and oxacillin. Acetonitrile was used to precipitate proteins during the extraction process. The detection wavelength was 210, 230, or 298 nm, depending on the compound, and the pH was 2. This precise and repeatable method allowed quantification of beta-lactam plasma levels from 5 to 250 µg/mL, with a coefficient of variation (CV) of <8%, without interference from other commonly used medications. This technique is simple to use for routine therapeutic monitoring of beta-lactam antibiotics [67].

A simple, reliable, and accurate visible spectrophotometric technique was developed to quantify ampicillin and cloxacillin in solid dosage forms. The technique uses charge-transfer complexes formed between 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and antibacterial agents to identify drug constituents in pharmaceutical samples. The effects of various variables on the formation and stability of the complexes were investigated and optimized. Beer's law was followed. The target analytes in different brands of fixed-dose pharmaceutical formulations were successfully determined using this method [68].

A simple and precise FIA-CL method was used to measure cloxacillin sodium in pharmaceutical preparations and environmental water samples. The technique was based on the enhancing effect of cloxacillin sodium on the luminol–H_2O_2–CuO nanosheet system in a basic solution during the CL reaction. Green sonochemical synthesis was used to prepare the CuO nanosheets. The effects of several experimental variables, including the concentrations of CuO nanosheets, H_2O_2, NaOH, and luminol, were investigated. Under optimal conditions, the enhanced CL intensity showed a linear correlation with cloxacillin sodium concentration in the range of 0.05–30.00 mg/L, with a correlation coefficient of 0.995. The corresponding LOD (3σ) was determined to be 0.026 mg/L. The RSD of the developed method was 2.21%, based on 11 replicate measurements of 4 mg/L cloxacillin sodium. In addition, the total analysis time for each sample was 30 s. The analytical suitability of the proposed CL system was evaluated by quantifying cloxacillin sodium in pharmaceutical preparations and spiked environmental water samples [69].

A new chemiluminescence (CL) system was presented based on the acidic oxidation of carminic acid by $KMnO_4$. CdS quantum dots (QDs) were prepared using a simple hydrothermal technique, and they effectively increased the intensity of the CL system. The $KMnO_4$–carminic acid–CdS QD system exhibited emission quenching in the presence of trace concentrations of cloxacillin. This quenching effect led to the development of a novel and accurate flow injection chemiluminescence method. Under optimal experimental conditions, a strong linear relationship was observed between cloxacillin concentration (0.008–22.0 mg/L) and decreased CL intensity. The LOD was 5.8 µg/L. By examining samples containing 4.0 mg/L cloxacillin, the method's accuracy was assessed, yielding an RSD of 2.08%. The method was also shown to be feasible for estimating cloxacillin in environmental aqueous samples and medicinal formulations [70].

Piperacillin: A study was conducted on the S-oxidation reaction of piperacillin sodium in aqueous solutions using potassium hydrogen peroxomonosulfate (Figure 8). For the analysis, a powder mixture containing piperacillin 4 g and tazobactam 0.5 g was used in vials for piperacillin injection solution. The triple salt potassium $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, with "extra pure" quality, was used as the oxidant. The results showed an RSD of 1.5% and δ of +0.2%. It is evident that piperacillin can be determined in a stepwise manner with high precision and consistency [71].

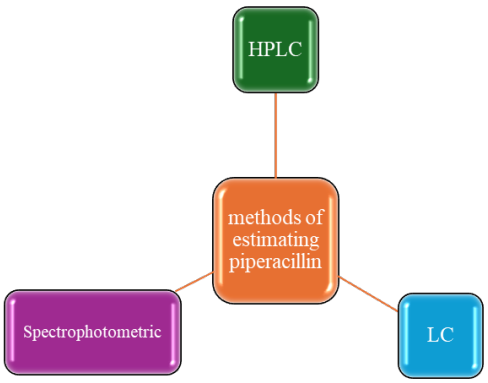

Fig. 8 Methods of estimating piperacillin

A straightforward, validated visible spectrophotometric technique was developed for determining piperacillin in both bulk and pharmaceutical formulations. The proposed procedure involves forming a colored ion-pair complex between the tropaeolin anion and the piperacillin cation, which can then be extracted into chloroform. A doubly charged cation is formed when the two secondary amide groups of piperacillin are protonated. Maximum absorption was measured at 529 nm, and the concentration range was 4–24 µg/mL. Several parameters, such as precision, accuracy, LOD, and LOQ, were evaluated for validation in accordance with current ICH guidelines. The RSD values were low (<2%), and regression analysis showed r = 0.9999, indicating that the proposed method is accurate, precise, and repeatable. The proposed technique was extended to assay piperacillin powder for injectable formulations [72].

FT-IR is one of the most widely used analytical techniques worldwide. It is strongly associated with user-friendly instrumentation, rapid analysis, and reliable outcomes. Using the film-formation method, two active pharmaceutical ingredients in a piperacillin and tazobactam preparation were analyzed simultaneously in this study, both qualitatively and quantitatively. This process requires forming a film on the ATR crystal after evaporating the solvent from a small amount of the liquid sample. Both APIs exhibited optimal adhesion between the film surface and the crystal, despite the low tazobactam content in the formulation. One calibration curve was used, with a correlation coefficient of 0.999 [73].

This work aimed to provide an analytical approach to identify and quantify intravenous (IV) medications prior to administration. It describes the use of Raman spectroscopy to analyze an IV formulation of piperacillin and tazobactam. The simultaneous analysis of the two active pharmaceutical ingredients (APIs) in the same formulation was conducted in three sequential phases: immediately after reconstitution, before administration, and either online after introduction of the liquid medication into the infusion set or at-line after transferring a small quantity from the IV bag to a Raman optical cell. In addition to successful identification of the APIs in all cases, quantification was performed using calibration curves, which showed correlation coefficients for PIP and TAZ of 0.953-0.999 and 0.965-0.997, respectively. Conventional protocols may be more complex, costly, time-consuming, and environmentally unfriendly. This technique has the potential to reduce the gap between experimental design and practical clinical application [74].

A novel LC technique based on a mixed micellar mobile phase was developed, and its parameters were examined. The main goal of this method was to eliminate the use of organic solvents in routine analyses. Combinations of tazobactam (TZB) with piperacillin (PPC) or cefepime (CFM) are frequently used as potent antimicrobial treatments, particularly against resistant strains. A mobile phase free of organic solvents was used to separate and quantify the three medications. The mixed micellar mobile phase, adjusted to pH 3.5, contained 15 mM Brij-35 and 38 mM SDS. Separation was performed by HPLC at a flow rate of 1 mL/min and a detection wavelength of 210 nm. Precision and accuracy were evaluated over the ranges of 5–100 µg/mL for PPC and CFM, and 0.625–12.5 µg/mL for TZB, indicating the method's validity and applicability. Finally, the greenness of the innovative technique was assessed using the Green Analytical Procedure Index and compared with the most environmentally friendly reported approach [24].

The simultaneous determination of piperacillin and tazobactam in pharmaceutical preparations was achieved by developing and validating a straightforward, accurate, and precise RP-HPLC method. Separation was performed on a C18 column using acetonitrile and potassium dihydrogen orthophosphate buffer at pH 3.5 in a 60:40 (v/v) ratio as the mobile phase, at a flow rate of 1 mL/min. The λmax was 226 nm. Piperacillin and tazobactam had retention times of approximately 2.5 and 4.3 min, respectively. The method was validated in accordance with ICH criteria, including linearity, accuracy, precision, LOD, LOQ, robustness, and ruggedness. For piperacillin and tazobactam, the concentration ranges were 5–15 µg/mL and 10–30 µg/mL, respectively, with correlation coefficients greater than 0.996. Accuracy ranged from

98% to 102%, expressed as a recovery percentage. The developed technique proved suitable for routine quality-control analysis of piperacillin and tazobactam in pharmaceutical dosage forms [75].

An accurate and direct HPLC technique was developed and validated to simultaneously measure piperacillin and tazobactam levels in human plasma. 0.3 mL samples were deproteinized with acetonitrile. After evaporation, the supernatant was reconstituted and injected into the HPLC system. The analysis was conducted using a C18 column with gradient elution and a mobile-phase mixture of acetonitrile and water containing 0.1% trifluoroacetic acid. A UV detector set at 218 nm was used, and the flow rate was 0.8 mL/min. For piperacillin and tazobactam, the concentration ranges were 0.5–400 µg/mL and 1–100 µg/mL, respectively, with acceptable linearity throughout the method ($r^2 > 0.99$). The technique produced results with sufficient stability and acceptable precision and accuracy within ±20%. In summary, the developed method is simple and highly sensitive, employing direct, uncomplicated procedures for sample preparation and elution, making it suitable and valuable for piperacillin/tazobactam therapeutic drug monitoring [76].

Nafcillin: A highly sensitive and specific approach for determining nafcillin in medicinal solutions is room-temperature phosphorescence (Figure 9).

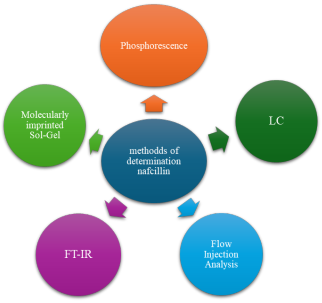

Fig. 9 Methods of estimating nafcillin

To achieve high sensitivity and sufficient selectivity, the phosphorescent properties of sodium dodecyl sulfate, thallium(I) nitrate, and sodium sulfite were thoroughly examined and shown to be highly effective. The determination was carried out using a solution containing 0.092 M sodium dodecyl sulfate, 0.023 M thallium nitrate, and 0.01 M sodium sulfite. A pH of 7.2 was determined to be sufficient to produce phosphorescence. After 15 min, the phosphorescence was fully developed, and its intensity was measured at λex = 284 nm and λem = 540 nm. The concentration range was 0.2–1.5 mg/L, and the response was linear. Error propagation theory indicated that the LOD was 0.18 mg/L. The procedure was validated using HPLC and a fluorometric technique. The results were compared with certified values obtained using turbidimetry and HPLC, and all three techniques showed excellent agreement [77].

A multiresidue analytical technique was used to simultaneously quantify benzylpenicillin (PCG), phenoxymethylpenicillin (PCV), oxacillin (MPIPC), cloxacillin (MCIPC), nafcillin (NFPC), and dicloxacillin (MDIPC) in bovine liver and kidney. Ion-exchange cartridges were used for sample clean-up, followed by ion-pair HPLC with UV detection. The coefficients of variation for the recoveries of PCG, PCV, MPIPC, MCIPC, NFPC, and MDIPC from bovine liver samples spiked at concentrations of 0.5 mg/kg and 0.1 mg/kg were in the ranges of 1.4%–4.2% and 3.4%–8.7%, respectively. The recoveries were within the ranges of 73%–91% and 83%–96%, respectively. In bovine kidney samples spiked at concentrations of 0.5 mg/kg and 0.1 mg/kg, the compounds yielded recoveries of 79%–92% and 82%–92%, with RSD values of 1.8%–5.9% and 2.7%–7.8%, respectively. The LOD values of the six penicillins in bovine liver and kidney were 0.02–0.05 mg/kg [78].

The β-lactam antibiotic nafcillin was examined using non-protected room-temperature phosphorescence (NP-RTP) in a solution system without an organized medium. Batch and flow injection methods were examined and compared. An RSD of less than 2.1% was obtained for both approaches. The limit of detection (LOD) was 7.7×10^{-8} M for the batch system and 3.6×10^{-7} M for the flow-through system. The method was described and applied to the determination of nafcillin in milk samples [79].

Using a room-temperature phosphorescent flow system, the analytical application of a nafcillin-imprinted sol–gel was studied for the direct determination of this β-lactam antibiotic in spiked milk samples. The findings indicated that the imprinted sol–gel optical sensing system can be a useful tool for real-sample analysis. The LOD values for skimmed and aqueous milk were 5.8×10^{-6} and 3.3×10^{-5} mol/L, respectively, and both matrices showed RSD values of less than 5%. Statistical analysis of variance showed no significant differences in the detection performance of the imprinted material across various commercial skim milk products. This indicates that the proposed analytical system is robust and supports

external real-matrix calibration. The application of this technique to the analysis of nafcillin in additional milk-based samples was also described [80].

A novel composite material based on core–shell molecularly imprinted polymers (MIPs) was prepared by combining the surface imprinting approach with a sol–gel method using silica-coated carbon nanotubes (CNTs). The morphology and structure of the carbon nanotubes and Nafion-based molecularly imprinted polymers were analyzed using transmission electron microscopy (TEM) and Fourier-transform infrared spectroscopy (FT-IR). The adsorption characteristics of carbon nanotubes and Nafion-based molecularly imprinted polymers (Naf-MIPs) were evaluated using equilibrium binding experiments and Langmuir analysis. For CNTs and Naf-MIPs, the maximum adsorption capacity and dissociation constant were 9.5 mg/g and 56.6 mL/mg, respectively. The CNTs and Naf-MIPs reached equilibrium within 30 min because of their rapid binding dynamics. The efficiency of detecting nafcillin in real samples was demonstrated using the imprinted polymer as the adsorption medium, with spiked egg samples containing concentrations of 5 and 10 µg/kg. With good precision, nafcillin recoveries ranged from 61.3% to 84.3%. The MIPs provide a rapid and simple method for determining nafcillin in egg samples [81].

Cefamandole: Cefamandole concentrations were measured in the anterior chamber aqueous humor of the eyes of 15 patients undergoing cataract extraction and 10 rabbits (Figure 10).

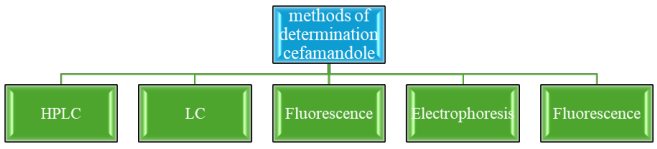

Fig. 10 Methods of estimating Cefamandole

Human patients received an intravenous infusion of 2 g of cefamandole before surgery, while rabbits received 50 mg/kg body weight through the ear vein. The detected concentrations were several times greater than the minimum inhibitory concentrations (MICs) for the bacteria that most frequently cause ocular infections [82].

A novel HPLC method using column switching was developed for the simultaneous quantification of cefamandole and cefamandole nafate in plasma and urine. Methanol and tetrabutylammonium bromide (45:55, v/v) were used as the mobile phase on a reversed-phase C8 column to separate the concentrated drugs after desorption in back-flush mode. With an LOD of 0.5 pg/mL, the method demonstrated high precision, excellent sensitivity, and rapid analysis. The mean coefficients of variation for both intra- and inter-assay measurements were below 4.9%, and the total analysis time per sample was less than 30 min. The technique was successfully applied to plasma and urine samples obtained from human volunteers following intravenous cefamandole nafate administration [83].

A technique was developed to assess unbound cefamandole in rat blood. After intravenous administration of 50 mg/kg cefamandole, a microdialysis probe was placed in the right atrium and jugular vein of male rats to measure unbound cefamandole in blood. The dialysates were directly introduced into a liquid chromatographic system. A mobile phase composed of acetonitrile, methanol, and 100 mM monosodium phosphate, 15:20:65 (v/v/v), at pH 5.0 was used for separation. Detection was performed at a UV wavelength of 270 nm. The in vivo microdialysis recovery in rat blood was 55.44% at a perfusate concentration of 1 mg/mL cefamandole. The intra-assay precision and accuracy were within 10% over the range of 0.1–10 mg/mL. Recovery-corrected dialysate concentration–time data for cefamandole were used to calculate pharmacokinetic parameters. The elimination half-life, $t_1/_2\beta$, was 21.6 ± 1.6 min. The findings suggest that a two-compartment model best describes the pharmacokinetics of unbound cefamandole in blood after administration of 50 mg/kg cefamandole [84].

Cephapirin, cefamandole, and cefmetazole were quantified using the cathodic stripping voltammetric approach. This involved adsorptive accumulation on a hanging mercury drop electrode (HMDE) in phosphate buffer solutions at pH 5.5 and 7.0. Three separate cathodic peaks were observed at potentials of -1.46, -0.98, and -1.00 V versus an Ag/AgCl reference electrode for cefamandole, cefmetazole, and cephapirin, respectively. For the drugs under investigation, the effects of several factors were examined, including pH, accumulation time, deposition potential, supporting electrolyte, potential interferences, and other variables. Excellent linearity was achieved. The proposed technique was successfully used to analyze the studied pharmaceuticals in both biological samples (serum and urine) and commercial formulations [85].

The study examined the efficacy of capillary zone electrophoresis for measuring cefamandole and probenecid in body fluids, using salicylic acid as an internal standard. The running buffer consisted of 10 mM disodium

tetraborate at pH 8.0, and the analytes were monitored at a separation voltage of 18 kV using UV detection at 230 nm. Within 6 min, the standard curves of cefamandole and probenecid demonstrated strong linearity over the ranges of 10–200 and 5–110 µg/mL, respectively, with correlation coefficients r ≤ 0.999. The LOD values for cefamandole and probenecid were 2.7 and 1.1 µg/mL, respectively. Both the peak area and migration time of the two drugs exhibited RSD values of less than 2%. Recoveries at three spiking levels of probenecid and cefamandole from urine and blood serum samples ranged from 96.23% to 105.1%, with RSD values of 0.55%–2.36%. The proposed method was successfully used in a clinical setting to simultaneously determine cefamandole and probenecid levels in human urine and serum [59].

Fluorescence quenching of bovine serum albumin (BSA) was used as a novel technique for detecting cefamandole in pharmaceutical preparations. Tyrosine and tryptophan residues in BSA provide strong intrinsic fluorescence. Cefamandole (CEF) solution alone did not produce fluorescence; however, when cefamandole was combined with BSA, the fluorescence intensity of BSA decreased. A novel technique was developed to detect cefamandole in pharmaceutical preparations based on the finding that, within a specific range, the fluorescence quenching of BSA at λex = 340 nm showed a strong linear correlation with cefamandole concentration. The maximum fluorescence value of the BSA–cefamandole conjugate was observed at 340 nm. The decrease in fluorescence intensity at 340 nm was proportional to cefamandole concentration, with a correlation coefficient of 0.9969. The average sample recovery ranged from 94.67% to 98.43%, the RSD was 0.16%, and the LOD was 1.02991 x 10^{-6} mol/L. The technique was rapid and yielded good results for detecting trace amounts of cefamandole in pharmaceutical preparations [86].

Table 1 Selected analytical methods for the determination of beta-lactam drugs.

Antibiotic	Methods	Matrix	LOD/LOQ	Range	RSD	Recovery	Ref.
Cephalexin	Flow injection analysis	Medicinal formulations	30 /100 µg/mL	0.04–0.50 (mg/mL)	1.8	99.5	[57]
	Spectrophotometric	Medicinal formulations	0.0654 µg/mL	4-24 µg/mL	less than 0.405	98.5	[40]
	Spectrophotometric	Commercial formulations, bulk powder	0.065/0.218 µg/mL	0.4-10 µg/mL	6.26	95.47-103.87	[60]
	RP-HPLC	Pure and formulation form	0.05/0.165 µg/mL	1-50 µg/mL	≤ 2.0	99.77-100.16	[61]
	Spectrophotometric	Pure pharmaceutical form	0.808 mg/L	10-60 mg/L	0.189	98.85	[38]
	Potentiometric	Biological fluid and tablet samples	3.12	0.1-300 µM	2.28	99-100.6 and 99.55-100.55	[62]
	HPLC	Pharmaceutical formulation	0.003/0.008 ppm	0.05-10 ppm	2>	99-99.5	[58]
	H-point	Pharmaceutical formulation	0.4620 µg/mL	6-18 µg/mL	less than 2	99.30-104.42	[34]
	HPLC	Samples of milk, beef, and cheese	5 ng/g	5-1500 ng/mL	less than 2	85-93	[39]
	HPLC	Milk samples	4µg/L	4 -80 µg/L	less than 2	85.2	[63]
Cloxacillin	LC	Human plasma	15/50 ng/mL	50–5000 ng/mL	0.3-1.5	92.8-98.5	[64]
	HPLC	Cow muscles	14/43 µg/kg	0.5-10 ng/µL	5.1-8.1	89.1-96.1	[65]
	HPLC	Human plasma	2/5 µg/mL	5-250 µg/mL	less than 8	102.9-103.3	[67]
	Spectrophotometric	Bulk and dosage form	0.59/3 mol/dm	1.05×10^{-3}-10.5×10^{-3} mol/dm	less than 1.6	93.1-97.2	[68]
	FIA-CL	Pharmaceutical preparation and water sample	0.026 mg/L	0.5-30 mg/L	2.21	96-102.2 And 99.31-102.54	[69]

Table 1 (continued)

Antibiotic	Method	Matrix	LOD/LOQ	Range	RSD	Recovery	Ref.
Piperacillin	CL	Environmental aquatic samples and medical preparations	5.8 mg/L	0.008-22 mg/L	2.08	101.86-102.30	[70]
	Spectrophotometric	Bulk and tablet formulations	0.15/0.50 μg/mL	4-24 μg/mL	<2	99.50-99.85	[71]
	LC	Pharmaceutical preparation	1.6/4.9 μg/mL	5-100 μg/mL	less than 1.5	99.37-101.14	[72]
	RP-HPLC	Pharmaceutical form	0.81/2.46 μg/mL	5-15 μg/mL	<2	98-102	[75]
Nafcillin	HPLC	Human plasma	0.08/0.5 μg/mL	0.5-400 μg/mL	0.004528	86.13-90.64	[76]
	Phosphorescence	Pharmaceutical solutions	0.18 mg/L	0.2-1.5 mg/L	less than 2	100.9	[77]
	LC	Liver and kidney of cows	0.02 mg/kg	0.005–1 μg/mL	less than 4	84 and 89	[78]
	Flow Injection Analysis	Milk sample	7.7×10^{-8} 3.6×10^{-7} M	0.01 and 0.25 M	<2.1	94.3-102.1	[79]
	Molecularly imprinted Sol-Gel	Milk samples	5.8×10^{-6} and 3.3×10^{-5} /1×10^{-4} mol/L	5×10^{-6} -6×10^{-5} mol/L	<5	95-105	[80]
	FT-IR	Egg sample	-------	5 and 10 μg/kg	<7.8	61.3-84.3	[81]
Cefamandole	HPLC	Plasma and urine	0.5 pg/mL	0.5-100 μg/mL	less than 4	90.9-91.5	[83]
	LC	Rat blood	0.05 μg/mL	0.1-50 μg/mL	10	99-103.3	[84]
	Voltammetric	Human serum	1×10^{-8} mol/dm	3×10^{-5}-5×10^{-4} mol/dm	0.36	97.3-101.2	[85]
	Electrophoresis	Body fluids	2.7/8.9 μg/mL	10-200, 5-110 μg/mL	<2	96.23-105.1	[59]
	Fluorescence	Cow serum	1.0299×10^{-6} mol/L	0.4×10^{-6} - 2×10^{-6} mol/L	0.16	92.8	[86]

3 CONCLUSION

This article discusses several methods for determining beta-lactam antibiotics, including FIA, HPLC, UV-Vis spectroscopy, GC, and electrochemical methods. Given the importance and wide use of antibiotics, it is essential to conduct research on analytical methods that can precisely quantify their concentrations. This is important for ensuring the quality of commercial products and promoting public health. There is a growing need to develop reliable, precise, and accurate analytical techniques. Therefore, the objective of this review is to examine recent studies that have provided significant insights.

This review discusses the determination of antibiotics in pharmaceutical preparations using various approaches, including high-performance liquid chromatography, gas chromatography, spectroscopic methods, flow injection analysis, and electrochemical methods. Chromatographic procedures, particularly HPLC, were the most commonly used techniques because of HPLC's high sensitivity and its ability to perform both determination and separation. This method is highly precise and can effectively resolve problems arising from interactions in most pharmaceutical formulations.

FIA is regarded as a green chemistry approach because it uses fewer chemicals and, because it is performed in a closed system, reduces the possibility of researcher exposure to material vapors or reaction products. In conclusion, this review shows that antibiotics can be measured in various matrices using precise analytical techniques, which can be integrated with instruments such as flow injection systems and spectrophotometers. Furthermore, each method has distinct advantages depending on the sample type and the precision of the obtained results. Researchers can use these methods to determine the quantity and quality of pharmaceuticals in a given sample. Figure 11 shows the techniques used for determining beta-lactam antibiotics. Depending on the sample type, each technique applied by researchers for antibiotic determination was successful.

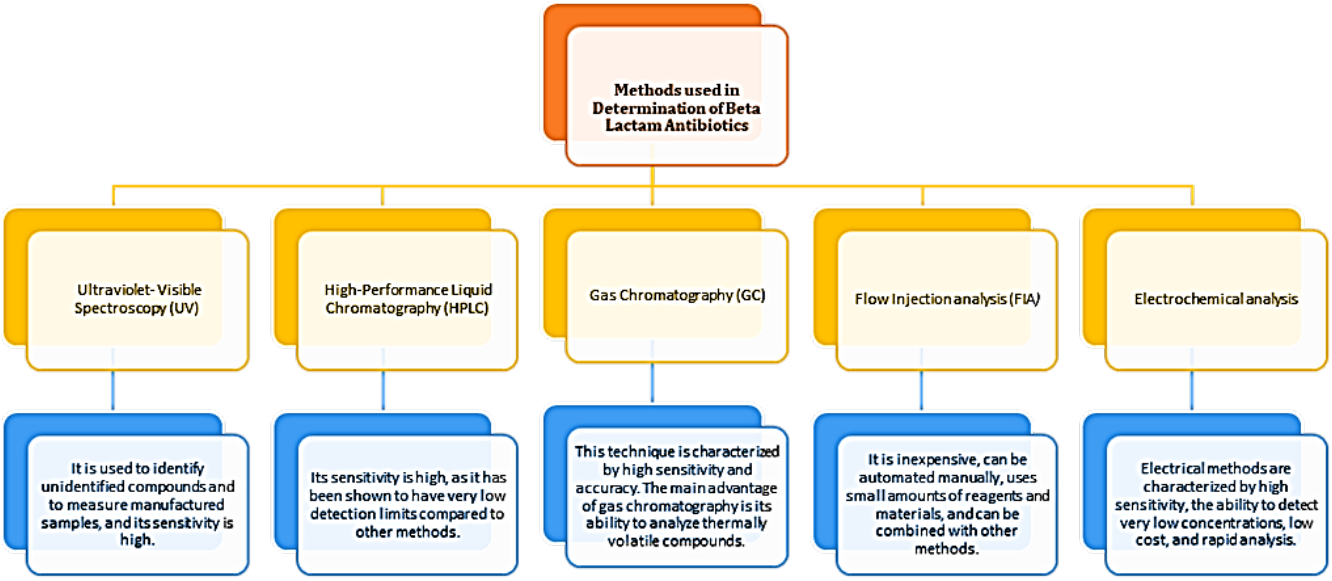

Fig. 11 Methods of Estimating Drugs

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