

A Comprehensive Review of Analytical Methodologies for Cefoperazone Sodium: From Spectrophotometric to Advanced Chromatographic and Electrochemical Technique

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Abstract—Cefoperazone sodium is a semisynthetic third-generation cephalosporin antibiotic widely used against serious Gram-negative and selected Gram-positive bacterial infections. Its broad antimicrobial coverage, favourable safety profile, and frequent clinical combination with the β -lactamase inhibitor sulbactam have sustained its importance in antimicrobial therapy despite growing concerns over bacterial resistance and formulation stability. Ensuring the quality, safety, and efficacy of cefoperazone-containing formulations therefore depends on robust analytical methodology. This review consolidates current knowledge on the chemistry, structural features, mechanism of action, pharmacokinetics, and physicochemical properties of cefoperazone sodium, and critically summarises the principal analytical techniques used for its determination in pharmaceutical formulations and biological samples. These include UV-Visible spectrophotometry, Liquid chromatography–mass spectrometry (LC-MS/MS), reverse-phase high-performance liquid chromatography (RP-HPLC), high-performance thin-layer chromatography (HPTLC), and adsorptive cathodic stripping voltammetry. Reported validation parameters including linearity, accuracy, precision, limit of detection (LOD), and limit of quantification (LOQ), are compared across methods to highlight their relative sensitivity, selectivity, cost, and suitability for routine quality control versus bioanalytical applications. The review is intended to guide the selection of appropriate analytical strategies for the continued quality assurance of cefoperazone sodium.

Index Terms—Cefoperazone sodium, RP-HPLC, HPTLC, LC-MS/MS, UV spectrophotometry, Voltammetry.

I. INTRODUCTION

Cefoperazone sodium is a semisynthetic third-generation cephalosporin antibiotic that is widely used to manage serious bacterial infections, particularly those caused by Gram-negative microorganisms [1]. Cephalosporins are a large and clinically important class of β -lactam antibiotics derived from cephalosporin C, which was originally isolated from the fungus *Acremonium* (formerly *Cephalosporium*) [2]. They exert bactericidal activity by inhibiting bacterial cell wall synthesis through binding to penicillin-binding proteins, leading to cell lysis and death [2]. The third generation exhibits expanded activity against Gram-negative pathogens and resistant bacterial strains [2]. Owing to their broad spectrum of activity, favourable safety profile, and clinical efficacy, cephalosporins are widely used in the treatment of respiratory tract infections, urinary tract infections, skin and soft tissue infections, septicemia, meningitis, and other serious bacterial diseases [2]. Cefoperazone sodium produces its antibacterial effect by interfering with bacterial cell wall synthesis, which ultimately leads to destruction of the bacterial cell [1]. Owing to its broad-spectrum activity and strong

therapeutic efficacy, cefoperazone sodium has become an important drug in modern antimicrobial therapy.

Chemically, cefoperazone sodium possesses a complex cephalosporin nucleus with structural modifications that enhance its antibacterial activity and stability against several β -lactamase enzymes [1]. These structural characteristics contribute to its effectiveness against a wide variety of pathogenic bacteria. The drug demonstrates significant activity against clinically important organisms such as *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* [1]. Because of this broad antimicrobial coverage, cefoperazone sodium is commonly prescribed for respiratory tract infections, urinary tract infections, septicemia, skin and soft tissue infections, intra-abdominal infections, and gynaecological infections [1].

Cefoperazone sodium is generally administered through intravenous or intramuscular routes due to its poor oral absorption [3]. In clinical practice, it is frequently combined with sulbactam, a β -lactamase inhibitor, to improve its activity against resistant bacterial strains [3]. This combination therapy has shown enhanced effectiveness against organisms belonging to the Enterobacteriaceae family as well as anaerobic bacteria such as *Bacteroides* species [3]. The increasing prevalence of multidrug-resistant pathogens has further increased the clinical importance of cefoperazone-based therapies.

Although cefoperazone sodium is considered highly effective, prolonged and widespread use of antibiotics has raised concerns regarding bacterial resistance, adverse drug reactions, and stability-related issues [1]. Some studies have also indicated that cefoperazone may affect metabolic enzymes including glutathione S-transferase and acetylcholinesterase, highlighting the importance of proper therapeutic monitoring and dosage adjustment in certain patient populations [1]. Therefore, maintaining the quality, safety, and efficacy of cefoperazone-containing formulations is essential in pharmaceutical practice.

To ensure accurate drug estimation and quality control, several analytical techniques have been developed for the determination of cefoperazone sodium in pharmaceutical formulations and biological samples [3]. These methods include spectrophotometric analysis, high-performance thin-layer chromatography (HPTLC), flow injection

analysis, liquid chromatography–mass spectrometry (LC-MS/MS), ultra-performance liquid chromatography (UPLC-MS/MS), and reverse-phase high-performance liquid chromatography (RP-HPLC) [1,3]. These analytical methods showed satisfactory precision, low detection limits, and suitability for routine pharmaceutical quality control [3].

In pharmaceutical industries, validated analytical methods are essential for ensuring product consistency, regulatory compliance, and patient safety [1,3]. Parameters such as accuracy, precision, specificity, robustness, linearity, limit of detection (LOD), and limit of quantification (LOQ) are evaluated according to International Conference on Harmonization (ICH) guidelines to confirm the reliability of analytical procedures [1]. Consequently, continuous improvement in analytical methodologies for cefoperazone sodium remains an important area of pharmaceutical and biomedical research.

This review article aims to present a detailed overview of cefoperazone sodium, including its chemical characteristics, pharmacological importance, therapeutic applications, and analytical determination methods. The review also highlights current challenges and future perspectives related to its pharmaceutical quality control and analytical assessment.

II. CEFOPERAZONE: CHEMISTRY AND PHARMACOLOGICAL PROFILE

Cefoperazone is a third-generation cephalosporin antibiotic belonging to the β -lactam class. It is a semisynthetic, broad-spectrum antibiotic used to treat bacterial infections such as urinary and respiratory tract infections and skin infections, and it acts strongly against *Pseudomonas* species. This section focuses on the structure, structural modifications, mechanism of action, pharmacodynamics, pharmacokinetics, and pharmaceutical properties of cefoperazone. [4]

2.1. Chemical Structure

Cefoperazone exists in two forms, namely cefoperazone sodium and cefoperazone in combination with sulbactam. Cefoperazone–sulbactam is more frequently used in clinical practice. The cefoperazone molecule consists of a β -lactam ring fused to a dihydrothiazine ring [5] (Figure 1).

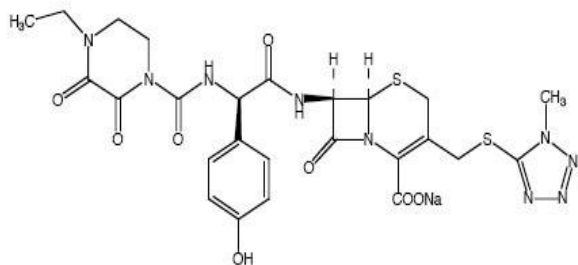


Figure 1. Chemical structure of cefoperazone sodium, showing the β -lactam ring fused to the dihydrothiazine ring, the C7 piperazine-derived side chain responsible for anti-pseudomonal activity, and the C3 methyl-tetrazole-thiomethyl (MTT) side chain.

2.2. Structural Modifications

2.2.1. C7 Side Chain

Modification of the piperazine ring at the C7 side chain is responsible for anti-pseudomonal activity.

2.2.2. C3 Side Chain

The C3 side chain carries an MTT (5-methyl-1,3,4-thiadiazole-2-thiol / methyl-tetrazole-thiomethyl) chain, which improves activity but may cause bleeding or coagulopathy. [5]

2.3. Mechanism of Action

Cefoperazone is a broad-spectrum third-generation cephalosporin antibiotic that is effective against the Gram-negative bacterium *Pseudomonas aeruginosa* and certain Gram-positive bacteria. It acts by inhibiting cell wall synthesis through binding to penicillin-binding proteins (PBPs). After binding to PBPs, it blocks the transpeptidation reaction, which halts cell wall formation. The resulting weakened cell wall renders the bacterial cell sensitive to changes in osmotic pressure, causing the cell wall to swell, rupture, and ultimately leading to bacterial death. [5] Cefoperazone sodium exhibits bactericidal activity by inhibiting bacterial cell wall synthesis through binding to penicillin-binding proteins (PBPs), resulting in bacterial cell lysis.

2.4. Pharmacokinetics and Pharmacodynamics

Cefoperazone is administered via intravenous or intramuscular injection and is poorly absorbed following oral administration. It reaches a wide range of body tissues and fluids; during meningeal inflammation, higher concentrations of the drug are

found in the cerebrospinal fluid. It is widely distributed in the lungs, liver, bile, and kidney, undergoes minimal hepatic metabolism, and is primarily excreted in bile. Its half-life is approximately 1.6 to 2.4 hours.

Cefoperazone has very poor oral bioavailability, whereas after intravenous administration it exhibits approximately 100% bioavailability. The pKa value of cefoperazone is approximately 2.5–3.0 for the carboxylic acid group and 4.5–5.0 for the amino/piperazine functional group, although it does not possess a single defined pKa value. The pKa value influences the solubility, ionization, drug stability, and distribution of the drug in biological fluids.

Cefoperazone sodium exhibits bactericidal activity by inhibiting bacterial cell wall synthesis through binding to penicillin-binding proteins (PBPs), resulting in bacterial cell lysis.[6]

2.5. Physicochemical Properties

Cefoperazone sodium is a white to yellowish-white crystalline powder that is slightly characteristic in odor or odorless, and hygroscopic in nature. It is freely soluble in water and methyl alcohol, slightly soluble in dehydrated alcohol, and insoluble in acetone, ether, and ethyl acetate. Its molecular formula is $C_{25}H_{27}N_9O_8S_2$. [5,7]

A 25% aqueous preparation of cefoperazone sodium is slightly acidic, with a pH of 4.5–6.5. Its molecular weight is 645.7 g/mol, and its melting point is 160–170 °C. Protein binding of cefoperazone is 80–90%. [6,7]

III. ANALYTICAL METHODS FOR DETERMINATION OF CEFOPERAZONE SODIUM

3.1. UV-Visible Spectrophotometric Methods

UV-Visible spectroscopy is based on the absorption of ultraviolet or visible radiation by molecules containing chromophore groups. When cefoperazone sodium absorbs electromagnetic radiation within the UV region, electrons are promoted from lower energy states to higher excited states. The amount of absorbed radiation is proportional to the concentration of the analyte according to the Beer-Lambert law. [8]. The absorbance of cefoperazone sodium is generally measured near its maximum absorption wavelength (λ_{max}), which provides enhanced analytical

sensitivity and accuracy. UV spectrophotometric methods are widely used for routine assay analysis because they require minimal sample preparation and provide rapid results. [8].

3.1.1. Important Analytical Parameters

The key parameters evaluated in UV spectrophotometric analysis of cefoperazone sodium are summarised in Table 1.

Table 1. Important analytical parameters in UV analysis of cefoperazone sodium.

Parameter	Significance
λ_{max}	Provides maximum sensitivity
Linearity	Indicates proportionality between concentration and absorbance
Accuracy	Closeness to true value
Precision	Reproducibility of results
LOD	Lowest detectable concentration
LOQ	Lowest quantifiable concentration

Careful optimization of solvent composition, pH, concentration range, and temperature improves analytical reliability and minimizes experimental errors. [8,9]

3.2. LC-MS Methods

Liquid chromatography–mass spectrometry combines chromatographic separation with mass-based detection. In this technique, cefoperazone sodium is first separated from other components by liquid chromatography and subsequently detected by the mass spectrometer based on its mass-to-charge ratio (m/z). [10] LC-MS provides highly sensitive and selective analysis and is particularly useful for biological samples such as plasma and serum. The technique is extensively applied in pharmacokinetic investigations, bioavailability studies, therapeutic drug monitoring, and impurity profiling. [10,12]. An LC-MS system for cefoperazone sodium analysis contains the major components summarised in Table 2. Electrospray ionization (ESI) is commonly used for cefoperazone sodium because it efficiently ionizes polar compounds in solution. [10,12]

Table 2. Major components of an LC-MS system used for cefoperazone sodium analysis.

Component	Function
Solvent Reservoir	Stores mobile phase
Pump	Delivers mobile phase at constant pressure
Injector	Introduces sample into system
Chromatographic Column	Separates analytes
Ionization Source	Converts analyte into ions
Mass Analyzer	Separates ions according to m/z ratio
Detector	Detects separated ions
Data System	Processes chromatographic and mass spectral data

3.2.1. Chromatographic Conditions

Several chromatographic parameters influence LC-MS analysis of cefoperazone sodium, as summarised in Table 3. Mixtures of water with acetonitrile or methanol containing formic acid or ammonium acetate are frequently used as mobile phases. [8,10]

Table 3. Chromatographic parameters influencing LC-MS analysis of cefoperazone sodium.

Parameter	Role
Mobile Phase Composition	Influences separation and ionization
pH of Mobile Phase	Affects analyte stability and retention
Flow Rate	Controls chromatographic resolution
Column Type	Determines separation efficiency
Ionization Mode	Enhances detection sensitivity

3.3. Comparative Evaluation of UV and LC-MS Methods

UV-Visible spectroscopy and LC-MS are important analytical techniques used for the determination of

cefoperazone sodium in pharmaceutical and biological samples. UV spectrophotometric methods are widely preferred for routine quality control because of their simplicity, low cost, and rapid analysis. However, LC-MS offers significantly greater sensitivity and selectivity, making it more suitable for pharmacokinetic investigations, bioanalytical applications, and therapeutic drug monitoring, [9] as summarised in Table 4.

Table 4. Comparative evaluation of UV spectroscopy and LC-MS for cefoperazone sodium analysis.

Parameter	UV Spectroscopy	LC-MS
Sensitivity	Moderate	Very high
Selectivity	Limited	Excellent
Cost	Low	High
Sample Preparation	Simple	More complex
Biological Sample Analysis	Limited	Highly suitable
Analysis Time	Short	Moderate
Quantification Ability	Good	Excellent
Trace-Level Detection	Difficult	Highly effective

The choice between UV spectroscopy and LC-MS depends on the analytical objective, sample complexity, required sensitivity, and available laboratory facilities. Continuous advancements in analytical instrumentation and data-processing technologies are further enhancing the reliability and efficiency of both methods. [8,10,11,12]

3.4. Voltammetric Determination of Cefoperazone

The electrochemical behaviour of cefoperazone was investigated by cyclic voltammetry in Britton-Robinson buffers over the pH range 3–6. The optimized conditions for adsorptive cathodic stripping voltammetry included an accumulation potential of -0.3 V and an accumulation time of 100–120 s. Differential pulse adsorptive cathodic stripping voltammetry (DP-AdCSV) and square-wave

adsorptive cathodic stripping voltammetry (SW-AdCSV) were applied for quantitative analysis.[13]

Optimization of instrumental variables such as accumulation time, pulse amplitude, pulse time, voltage step, and frequency was achieved using a Central Composite Face experimental design with Modde 9.1 software. Experimental runs were randomized to minimize systematic errors, and response surface methodology was used to determine the optimum analytical conditions.[13]

3.4.1. Validation Parameters

The validation parameters for the DP-AdCSV and SW-AdCSV methods for the determination of cefoperazone sodium are summarized in Table 5. The obtained data demonstrate excellent linearity, sensitivity, precision, and recovery, confirming the reliability of both analytical techniques for pharmaceutical dosage forms and spiked human urine samples.[13]

Table 5. Validation parameters for DP-AdCSV and SW-AdCSV methods for cefoperazone sodium.

Parameter	DP-AdCSV	SW-AdCSV
Linearity Range	0.01–0.06 $\mu\text{g/mL}$ (pharmaceuticals); 0.01–0.07 $\mu\text{g/mL}$ (urine)	0.01–0.06 $\mu\text{g/mL}$ (pharmaceuticals); 0.01–0.07 $\mu\text{g/mL}$ (urine)
Regression (R^2)	0.999	0.999
LOD	Not specifically stated	Not specifically stated
LOQ / LLOQ	0.01 $\mu\text{g/mL}$	0.01 $\mu\text{g/mL}$
Repeatability Level	0.03 $\mu\text{g/mL}$	0.03 $\mu\text{g/mL}$
Precision (%RSD)	0.5–3.3%	0.5–2.1%
Mean Recovery (%)	99–101%	99–101%
Accuracy in Urine Samples	92.3–102.0%	94.8–102.0%

Parameter	DP-AdCSV	SW-AdCSV
Selectivity	No interference from sulbactam or urine matrix	No interference from sulbactam or urine matrix
Robustness	Robust against small changes in pH, accumulation time, and buffer concentration	Robust against small changes in pH, accumulation time, and buffer concentration

3.4.2. Main Parameters of Method Validation

Table 6. Main parameters of the voltammetric method validation for cefoperazone.

Item	Description
Analytical Technique	Differential Pulse Adsorptive Cathodic Stripping Voltammetry (DP-AdCSV) and Square Wave Adsorptive Cathodic Stripping Voltammetry (SW-AdCSV)
Electrode Used	Hanging Mercury Drop Electrode (HMDE)
Electrode Composition	Conventional mercury electrode system
Main Objective	Quantitative determination of cefoperazone in pharmaceutical formulations and urine samples
Supporting Electrolyte	Britton–Robinson buffer (pH 4.0)
Nanotechnology Involvement	No nanomaterial modification
Sensitivity Enhancement	Achieved through adsorptive accumulation step
Sample Analysis	Pharmaceutical dosage forms and human urine
Optimization Method	Central Composite Face experimental design
Detection Principle	Adsorptive cathodic stripping response

Item	Description
Key Findings	High precision, accuracy, and successful application to biological samples
Major Limitation	Use of mercury electrode may pose toxicity concerns

The electro-reduction mechanism of cefoperazone at the hanging mercury drop electrode (HMDE) was successfully elucidated using Britton-Robinson buffer (0.004 M, pH 4.0) as the supporting electrolyte for the DP-AdCSV and SW-AdCSV methods for the determination of cefoperazone in bulk powder, pharmaceutical dosage forms, and spiked human urine samples, without the need for extraction, separation, or adsorption procedures. The obtained voltammetric results were statistically comparable with the official United States Pharmacopoeia (USP) HPLC method, indicating that the developed methods were accurate and precise, and exhibited acceptable sensitivity and reliability for the analysis of cefoperazone in spiked human urine samples. [13]

3.5. RP-HPLC and HPTLC Methodologies

3.5.1. Introduction to Cefoperazone Analysis by Chromatographic Methods

Cefoperazone sodium is utilized extensively for its broad-spectrum antimicrobial activity. In pharmaceutical manufacturing and clinical settings, the development of rigorous analytical protocols is required to quantify cefoperazone sodium in various dosage forms, notably Peracef (cefoperazone) and Peractam (a combination of cefoperazone and sulbactam) vials.[1]

A primary objective of analytical monitoring is the detection of specific process-related impurities, such as 7-aminocephalosporanic acid (7-ACA) and 5-mercapto-1-methyl-tetrazole (5-MER), to ensure product purity. Beyond chemical quantification, the clinical efficacy of the drug is evaluated through microbiological assays. In vitro studies using the conventional broth micro-dilution tube method against a standard strain of Burkholderia cepacia (ATCC 25416), a Gram-negative bacterium, have established a Minimum Inhibitory Concentration (MIC) of 250 µg/mL and a Minimum Bactericidal Concentration (MBC) of 125 µg/mL.[1]

3.5.2. RP-HPLC Methodology and Chromatographic Conditions

Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) provides high linearity, sensitivity, and selectivity for the analysis of cefoperazone.[14] Different chromatographic setups have been optimized to address specific analytical requirements, ranging from standard assaying to stability-indicating profiles.

- **Method 1 – Standard Assay:** This configuration utilizes an ODS column (150 mm × 4.6 mm, 5 µm) protected by a guard column to enhance stationary-phase longevity. The mobile phase consists of a mixture of KH₂PO₄ buffer and acetonitrile (80:20 v/v), operated at a flow rate of 1.0 mL/min with an injection volume of 20 µL. Detection is performed at 230 nm at room temperature. This method is noted for its efficiency and reliance on standard reagents.[1]
- **Method 2 – Impurity Separation:** To achieve resolution of cefoperazone from its impurity mixture (7-ACA and 5-MER), a C₈ column (250 mm × 4.6 mm, 5 µm particle size) is employed. The mobile phase comprises methanol and 0.05 M KH₂PO₄ buffer (22.5:77.5 v/v) adjusted to pH 7.5. Detection is shifted to 254 nm to optimize the response for the three distinct components (cefoperazone and the two impurities).[14]
- **Method 3 – Stability-Indicating Assay:** This method utilizes an Appurassil C-18 column (250

mm × 4.6 mm, 5 µm). The mobile phase consists of a buffer:methanol mixture (5:2 v/v) maintained at pH 6.8.[15] With a flow rate of 1.0 mL/min and detection at 254 nm, cefoperazone sodium exhibits a retention time of 2.67 minutes. This setup is specifically designed to isolate the drug from its degradation products.

3.5.3. HPTLC Methodology and Chromatographic Conditions

High-Performance Thin-Layer Chromatography (HPTLC) was evaluated as a comparative technique, particularly for its sensitivity in separating cefoperazone from reported impurities. The stationary phase consists of silica gel HPTLC F254 plates.[14] The mobile phase is a quaternary system composed of acetone:methanol:ethyl acetate:sodium lauryl sulfate:glacial acetic acid (3:2:3:0.8:0.2 by volume). Following development, detection and quantification are performed at 254 nm. While the method provides a distinct alternative to liquid chromatography, its primary advantage lies in its sensitivity for trace detection.[14]

3.5.4. Comparative Validation Parameters

The validation parameters for the primary RP-HPLC methods and the HPTLC methodology are summarized in Table 7. The data highlight the high degree of accuracy and precision achieved across both platforms. [14,15]

Table 7. Comparative validation parameters for RP-HPLC and HPTLC methods for cefoperazone.

Parameter	RP-HPLC (Standard)	RP-HPLC (Stability-Indicating)	HPTLC
Linearity Range	10–90 µg/mL	1–10 µg/mL	1–10 µg/band
Regression (R ²)	0.993	0.9899	Not specified
LOD	4.04 µg/mL	0.2 µg/mL	Not specified
LOQ	12.24 µg/mL	0.4 µg/mL	Not specified
Repeatability Level	20 & 80 µg/mL	Not specified	2 & 7 µg/band
Precision (%RSD)	0.34–0.92%	0.49–0.7451%	Not specified
Mean Recovery (%)	99.67% (SD 1.465)	95–106%	95.1–99.0% (SD 1.335)

3.5.5. Practical Applications in Quality Control and Stability Testing

- **Quality Control (QC):** Shorter analysis times make the RP-HPLC methods highly valuable for

the high-throughput quantification of commercial cefoperazone sodium in Peracef and Peractam vials. The low detection limits also facilitate cleaning validation by identifying the smallest

traces of cephalosporins on production machinery. [1]

- **Stability-Indicating Ability:** The Appurassil C-18 RP-HPLC method is a proven stability-indicating assay that effectively separates cefoperazone from its degradation products, allowing accurate quantitative estimation in injection formulations, with validation confirming no interference from excipients. [15]
- **Microbiological Context:** The analytical validation of these methods supports the broader evaluation of the drug's potency. The established MIC (250 µg/mL) and MBC (125 µg/mL) values for *Burkholderia cepacia* serve as critical benchmarks for verifying that chemical stability measured by chromatography correlates with biological efficacy. [1]

3.6. Summary of Reported Analytical Methods

Table. 8 summarises representative analytical methods reported in the literature for the determination of cefoperazone sodium, alone or in combination with sulbactam or other cephalosporins, together with the instruments, conditions, validated parameters, and key results of each method. UV-Visible spectroscopy and LC-MS are both important analytical techniques for the determination of cefoperazone sodium in pharmaceutical and biological samples. UV spectrophotometric methods are widely preferred for routine quality control because of their simplicity, low cost, and rapid analysis, whereas LC-MS offers significantly greater sensitivity and selectivity, making it more suitable for pharmacokinetic investigations, bioanalytical applications, and therapeutic drug monitoring.

Table 8. Summary of analytical methods reported for the determination of cefoperazone sodium.

S.N o.	Drug Name	Work Type	Method	Instrument Used	Conditions	Parameters	Results	Re f.
1	Cefoperazone	Stability and antimicrobial activity	Rapid RP-HPLC	RP-HPLC	Column: ODS (150 mm × 4.6 mm × 5 µm); Mobile phase: KH ₂ PO ₄ solution:acetonitrile (80:20); Flow rate: 1.0 mL/min	Range, linearity, LOD & LOQ, repeatability, precision, robustness, accuracy, ruggedness, specificity	Determined MIC at 250 µg/mL and MBC at 125 µg/mL of Cfz against the standard strain of <i>Burkholderia cepacia</i> (B. cepacia) [1]	

The electro-reduction mechanism of cefoperazone at the hanging mercury drop electrode has been elucidated, and the resulting DP-AdCSV and SW-AdCSV methods have been shown to be accurate, precise, and statistically comparable with the official USP HPLC method, without requiring extraction, separation, or adsorption procedures. These validated voltammetric methods can therefore be effectively applied for routine quality control analysis and pharmacokinetic studies of cefoperazone, although the use of a mercury electrode remains a limitation from a toxicity standpoint.

Both RP-HPLC and HPTLC are reliable, cost-effective, and robust techniques for the routine analysis of cefoperazone sodium. HPTLC demonstrates superior sensitivity for specific trace-level applications, while RP-HPLC provides more reproducible results and significantly reduces analysis time. Both methodologies adhere to international validation guidelines regarding robustness and ruggedness and require no specialized chemical reagents, making them well suited to standard laboratory quality control and stability monitoring. Overall, the choice among UV spectroscopy, LC-MS, voltammetry, RP-HPLC, and HPTLC depends on the analytical objective, sample complexity, required sensitivity, and available laboratory facilities. Continuous advancements in analytical instrumentation and data-processing technologies are expected to further enhance the reliability and efficiency of these methods, collectively supporting the safe and effective pharmaceutical use of cefoperazone sodium.

S.N o.	Drug Name	Work Type	Method	Instrument Used	Conditions	Parameters	Results	Re f.
						& selectivity, system suitability		
2	Cefoperaz one Sodium	Development and validation	HPLC method	Shimadzu HPLC	Column: Waters Xterra RP-18 column (5 μ m, 250 $\times$ 4.6 mm); Mobile phase: Acetonitrile:0.05M ammonium acetate buffer (70:30); Flow rate: 1.0 mL/min	Linearity, specificity, precision, accuracy, robustness, ruggedness	Determined quality control analysis	[2]
3	Cefoperaz one Sodium	Determination	Spectroscopy (colorimetry)	Shimadzu-1601 UV/Vis spectrophotometer	Sodium carbonate (20% w/v), Folin-Ciocalteu's phenol reagent and water (1:2); Stock solution (100 μ g/mL); Detection: 668 nm	Accuracy, precision, reproducibility	Estimated concentration of cefoperazone sodium	[3]
4	Cefoperaz one Sodium, Cefazolin Sodium and Ceftriaxone Sodium	Kinetic spectrophotometric determination	Spectroscopic method	Shimadzu UV-1700 PC, UV-Visible spectrophotometer	Stock solution (2 mg/mL); N-bromosuccinimide, Quercetin dihydrate; Detection: 510 nm	Accuracy, precision, robustness, selectivity	Determined quality control analysis of active drug	[4]
5	Cefoperaz one Sodium and Sulbactam Sodium	Simultaneous determination	LC-MS/MS method	2690 HPLC system with Thermo Finnigan TSQ Quantum triple quadrupole mass spectrometer with ESI	Column: Waters Xterra C18 column (5 μ m, 2.1 mm $\times$ 50 mm); Mobile phase: methanol:ammonium formate solution (30:70); Flow rate: 0.2 mL/min; Injection volume: 5 μ L; Run time: 3.5 min	Accuracy, precision, LLOQ, linearity, selectivity, stability, matrix effect, recovery	Quantitative analysis of two analytes in plasma of HAP patients	[5]
6	Cefoperaz one and Sulbactam	Therapeutic drug monitoring in children (simultaneous determination)	HPLC-MS/MS method	HPLC system with API 4000 triple quadrupole mass	Column: Shim-pack XR-ODS C18 column (100 mm $\times$ 3 mm, 2.6 μ m); Mobile phase:	Selectivity, linearity, detection limits, matrix effects,	Determined cefoperazone and sulbactam concentrations in children	[6]

S.N o.	Drug Name	Work Type	Method	Instrument Used	Conditions	Parameters	Results	Re f.
				spectrometer with ESI	water:acetonitrile; Flow rate: 0.3 mL/min	accuracy, precision, recovery, stability		
7	Cefoperaz one Sodium	Development and validation	HPLC method	HPLC (Agilent 1260 Infinity)	Column: C8 column (5 µm, 250 mm×4.6 mm); Mobile phase: Methanol:0.05M KH ₂ PO ₄ buffer (22.5:77.5); Flow rate: 2 mL/min; Injection volume: 20 µL; Run time: 12 min; Detection: 254 nm	Linearity, range, accuracy, precision, specificity, LOD and LOQ, robustness, system suitability	Quantitative determination of cefoperazone (CEF) in the presence of impurities 7- aminocephalospo ranic acid (7- ACA) and 5- mercapto-1- methyl-tetrazole (5-MER)	[7]
8	Cefoperaz one Sodium	Development and validation	HPTLC method	HPTLC- Camag TLC scanner	Stationary phase: HPTLC aluminum plates (20×20 cm) coated with 0.25 mm silica gel 60 F254; Mobile phase: Acetone:methanol: ethyl acetate:2% sodium lauryl sulfate:glacial acetic acid (3:2:3:0.8:0.2); Scan: 254 nm; Scanning speed: 20 mm/s	Linearity, range, accuracy, precision, specificity, LOD and LOQ, robustness, system suitability	Quantitative determination of cefoperazone (CEF) in the presence of impurities 7-ACA and 5-MER	[7]

IV. CONCLUSIONS

Cefoperazone sodium remains a clinically important third-generation cephalosporin, and the continued assurance of its pharmaceutical quality depends on the availability of reliable, validated analytical methods. UV spectroscopy, LC-MS, voltammetry, RP-HPLC, and HPTLC provide reliable approaches for the analysis of cefoperazone sodium in pharmaceutical and biological samples. UV spectroscopy offers simplicity and rapid routine quality control, whereas LC-MS provides superior sensitivity and selectivity for bioanalytical and pharmacokinetic applications. Voltammetric methods offer accurate and precise alternatives for routine analysis, although mercury

electrodes present toxicity concerns. RP-HPLC provides robust and reproducible analysis, while HPTLC offers enhanced sensitivity for trace-level applications. The selection of an analytical technique depends on sample complexity, sensitivity requirements, analytical purpose, and available instrumentation. Collectively, these methods contribute to effective quality control, stability assessment, and safe pharmaceutical use of cefoperazone sodium.

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