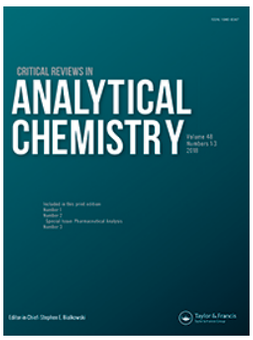

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A Critical Review of Analytical Methods for Determination of Ceftriaxone Sodium

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ABSTRACT

Ceftriaxone sodium is a third-generation semi-synthetic antibiotic belonging to the class of cephalosporins. Is administered only by parenteral route and has the ability to cross the blood-brain barrier. It has bactericidal action; its main activity is related to the Gram-negative bacteria, being also able to act against Gram-negative bacilli resistant to the first- and second-generation cephalosporins. The present study presents a survey of the characteristics, properties and analytical methods used for the determination of ceftriaxone sodium, for the gathering of data searches were carried out in scientific articles in the world literature, as well as in the official compendia. It is necessary to create awareness about the importance of developing effective and reliable analytical methods for quality control and consequently for conducting pharmacokinetic, bioavailability, bioequivalence studies as well as for the therapeutic monitoring of this drug. Most of the methods found use high-performance liquid chromatography, but also methods that use absorption spectroscopy ultraviolet, infrared spectroscopy, spectrofluorimetry and microbiological methods have been presented. A discussion was presented highlighting the need to develop new ecological methods using less toxic solvents, rapid analysis and miniaturization of the samples.

KEYWORDS

Analytical methods; ceftriaxone sodium; quality control; review

Introduction

Natural antibiotics and their semi-synthetic derivatives comprise the majority of antibiotics in clinical use; the class of β-lactams constitutes the first class of derivatives of natural products used in the therapeutic treatment of bacterial infections.[1]

Since 1970, cephalosporins are among the most potent and widely used anti-infective agentes.[2] They are the second largest class of β-lactam antibiotics which have a broad spectrum of antibacterial activity, clinical efficacy and excellent safety profile, acting on the enzyme transpeptidase, which is unique in bactéria which confers the action in impediment of synthesis of the wall bacterial.[1] Cephalosporins are classified into generations according to general characteristics of antimicrobial activity. Currently, there are five generations of cephalosporins. They differ in relation to the action spectrum, stability to β-lactamase, pharmacokinetics, stability and collateral reactions.[2–5]

Ceftriaxone sodium is a third-generation semi-synthetic cephalosporin, derived from a fermentation product, for parenteral use, being this group of extreme importance because they are able to overcome the blood-brain barrier, since previous generations do not have this capacity.[1,6,7]

It acts on Gram-positive and Gram-negative bacteria, the activity against Gram-positive is noticeably smaller in relation to the first-generation cephalosporins. Its major activity is related to Gram-negative bacteria, and it is also capable of acting against Gram-negative bacilli resistant to the first- and second-generation cephalosporins.[2,7,8,9]

Ceftriaxone is presented in the form of single-ingredient preparations in the USA, United Kingdom, Japan and Canada as Rocephin™; in Brazil as Rocefin™, Ceftriax™, Celltriaxon™, Keftron™, Triaxin™, Amplospec™, Ceftriona™, Triaxton™; in China as Ansailong™, Cefin™, Dezhi™, Likang Kesong™, Livzonphin™, Locekin™, Oframax™, Rocephin™, Xianqin™; in Germany as Cefotrix™, Rocephin™; in Italy as Axobat™, Bixon™, Cefrag™, Davixon™, Daytrix™, Deixim™, Diaxone™, Eftry™, Eraxitron™, Fidato™, Frieng™, Kocefan™, Monoxar™, Nilson™, Panatrix™, Pantoxon™, Ragex™, Rocefin™, Setriox™, Sirtap™, Valexime™.[10–12]

It is indicated for cases of septicemia, meningitis, disseminated Lyme borreliosis (early and late stages of the disease) (Lyme disease), intra-abdominal infections (peritonitis, gastrointestinal and biliary tract infections), bone, joint, soft tissue, skin and wound infections, infections in immunocompromised patients, kidney and urinary tract infections; infections of the respiratory tract, particularly pneumonia andotolaryngological infections, genital infections, including gonorrhea, perioperative prophylaxis of infections.[10,11,13]

The development of effective and reliable analytical methods is extremely important for quality control of marketed drugs, being this a multidisciplinary task. The need to demonstrate such efficacy and trust is increasingly recognized and demanded. Therefore, the validation process of the analysis is fundamental to guarantee the analytical quality, providing reliability in the obtained results.[3,4,14,15]

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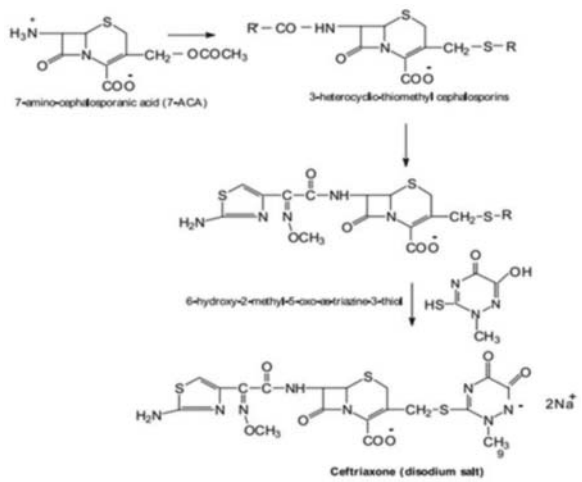

Figure 1. Synthesis of ceftriaxone sodium.

Due to the importance of this information, the present study presents a review of the characteristics of ceftriaxone sodium, its properties and the analytical methods used for its identification and quantification.

Ceftriaxone sodium

Structural modification

Ceftriaxone sodium was synthesized through the precursor 7-amino-cephalosporanic acid (7-ACA). Synthesis occurred by the addition of an acyl molecule at the 7-amino position and the displacement of the acetoxy group by thio-substituent heterocyclic at the 3-methyl position. Then, the substitution of the R-alkyl group was determined by the addition of 6-hydroxy-2-methyl-5-oxythiadiazine-3-thiol, the RO-alkyl group was substituted by 2- (2-amino-4-thiazolyl) -2-amino- [(Z) -methoxylamino] acetyl completing the synthesis of ceftriaxone sodium. The model for the synthesis of ceftriaxone sodium is shown in Figure 1.[16]

Structural forms

Ceftriaxone sodium is present in disodium hemieptahydrate form, its molecular structure is observed in Figure 2.[17–22]

Action mechanism

Ceftriaxone sodium has a bactericidal action, through the inhibition of cell wall synthesis. It is highly stable in the most β-lactamases, shows greater activity against Gram-negative bacteria and is also capable of acting against Gram-negative bacilli resistant to the first- and second-generation cephalosporins, it is effective against the enterobacteria *Haemophilus influenzae* and *Streptococcus pneumoniae*, as well as *Citrobacter, Serratia marcescens* and *Providencia*. It has synergistic action with the aminoglycosides.[8,23,24]

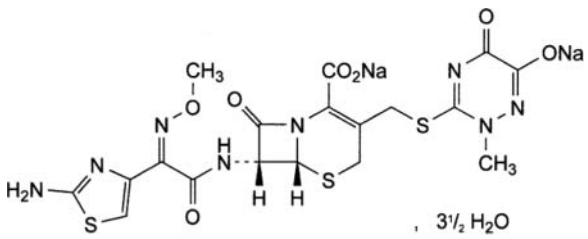

Figure 2. Chemical structure of ceftriaxone disodium hemieptahydrate (CAS 104376-79-6).[17]

Pharmacokinetics

Ceftriaxone sodium is administered parenteral route and is not absorbed by the oral route. The daily dose of 1 g is satisfactory for most serious infections, it is recommended to administer 4 g once daily in the treatment of meningitis. It has a half-life between 6 and 9 hours and may be prolonged in neonates. This cephalosporin can be injected every 24 hours at a dose of 15–50 mg/kg/day, it has satisfactory penetration of body fluids and tissues, it reaches sufficient levels in the cerebrospinal fluid to inhibit most pathogens except *Pseudomonas*, it is more active against pneumococci resistant to penicillin. About 85 to 95% is bound to plasma proteins. Crosses the placenta and low concentrations have been detected in breast milk; ceftriaxone is excreted unchanged in the urine (40 to 65%), the remainder is excreted in the biliary tract and there is no need for dose adjustment in renal insufficiency.[10,23,24,25]

Physicochemical properties

Ceftriaxone sodium is a semi-synthetic antibiotic derived from a fermentation product chemically designated asdisodium (6*R*,7*R*)-7-[[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl] amino]-3-[[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 3.5 hydrate.[17]

It has the molecular formula $C_{18}H_{16}N_8Na_2O_7S_3$, $3^1/_2H_2O$, with molecular weight of 661.60 g/mol and for the anhydrous form ($C_{18}H_{18}N_8O_7S_3$) 598.56 g/mol.[22]

Ceftriaxone sodium is in the form of a crystalline powder, almost white or yellowish, slightly hygroscopic, very soluble in water, poorly soluble in methanol, very sparingly soluble in ethanol. It has at least 905 μg (potency) and not more than 935 μg/mg calculated on the anhydrous basis.[17–19] It shows melting point > 155°C, logP −1.7 with pka 3.19 (acid) and 4.17 (alkaline).[26]

Analytical methods for determining the ceftriaxone sodium

The analytical methods for ceftriaxone evaluation were researched in the literature through scientific articles, as well as in official compendium (Portuguese Pharmacopoeia, 2005; SP, 2007; JP, 2011; BP, 2013; EP, 2013; USP, 2016). The sites used during a survey were: http://www.sciencedirect.com/, http://www.scopus.com/ and http://www.ncbi.nlm.nih.gov/pubmed/. Key words were used: ceftriaxone sodium, analytical methods and green chemistry. The research was carried out from July to September 2017.

Quantitation of the ceftriaxone sodium is of the utmost importance for conducting pharmacokinetic studies of bioavailability and bioequivalence therefore for the therapeutic

Table 1. Chromatographic analytical methods described in the literature for the determination of ceftriaxone sodium.

Method	Conditions	Detection system	Matrices	Reference
HPLC-UV	Column C18 (250 mm × 4.6 mm; 5 μm). Mobile phase: dissolve 2 g of tetradecyl ammonium bromide and 2 g of tetraheptyl ammonium bromide in a mixture of 440 mL of water, 55 mL phosphate buffer pH 7, 5.0 mL citrate buffer pH 5 and 500 mL of acetonitrile; flow rate 1.5 mL/min; injection volume 20 μL.	254 nm	Standard	[17–22]
HPLC-UV	Column hypersil gold C18 (100 mm × 4.6 mm; 10 μm); at ambient temperature. Mobile phase: methanol: 0.025 M monopotassium phosphate adjusted to pH 7.5 using triethylamine (16:84, v/v); flow rate 1 mL/min; injection volume 10 μL.	254 nm	Standard and pharmaceutical form	[29]
HPLC-UV	Column ODS hypersil C18 (250 mm × 4.6 mm; 5 μm). Mobile phase: 50 mM ammonium phosphate buffer and methanol (90:10% v/v) adjusted to pH 7.0 with triethylamine; flow rate 1 mL/min; injection volume 20 μL.	230 nm	Parenteral formulation	[36]
HPLC-UV	Column waters × Terra RP-18 (250 mm × 4.6 mm; 5 μm). Mobile phase: 0.1 M triethylammonium acetate and acetonitrile (60:40 v/v); flow rate 1 mL/min; injection volume 20 μL.	240 nm	Standard and pharmaceutical form	[25]
HPLC-UV	Column shimpack GLC-ODS (150 mm × 6 mm; 5 μm); at ambient temperature. Mobile phase: acetonitrile and 0.1 M ammonium acetate solution (10:90 v/v), pH 7.5 using ammonium solution; for alkaline degradation was used phosphate buffer (pH 10) with heating; flow rate 1.5 mL/min; injection volume 50 μL.	270 nm	Powder for injectable solutions and their degradation products	[43]
HPLC-UV	Analytical column Spherisorb ODS C18 (250 mm × 4.6 mm; 10 μm). Mobile phase: monopotassiumphosphate buffer pH 2.5 and methanol (70:30 v/v); flow rate 1 mL/min; injection volume 10 μL.	254 nm	Standard	[40]
HPLC-UV	Column sphere-Image 80–5 ODS 2 (250 mm), at 30°C. Mobile phase: acetonitrile and aqueous 0.1 M citrate buffer with 5 mM ammonium perchlorate and 2 mM tetrabutylammoniumhydrogen sulfate (11:89 v/v).	265 nm	Plasma and bone	[27]
HPLC-UV	Column waters × bridge C18 BEH (50 mm × 3 mm; 2.5 μm), at 40°C. Mobile phase: 100 mM *o*-phosphoricacid and/or sodium dihydrogen-phosphate with NaOH pH 2.55 and acetonitrile (100:12 v/v).	260 nm	Plasma	[28]
HPLC-UV	Column C18 (250 mm × 4.6 mm; 5 μm); at ambient temperature. Mobile phase: acetonitrile, methanol and triethylamine (TEA) buffer (pH 7) (1:1:2 v/v), flow rate 0.6 mL/min, injection volume 20 μL.	240 nm	Biological sample	[30]
HPLC-UV	Column Kromasil C18 (250 mm × 4.6 mm; 5 μm). Mobile phase: 1.5 mM potassium dihydrogen phosphate (adjust the pH to 4.5 with phosphoric acid) with 0.0125% triethylamine – methanol (70:30, v/v); flow rate 1 mL/min; injection volume 20 μL.	247 nm	Human urine	[31]
HPLC-UV	Column C18 (30 mm × 4.6 mm; 2.5 μm) at ambient temperature. Mobile phase: acetonitrile and 50 mM phosphate buffer at pH 2.4 (8:92 v/v); flow rate 1 mL/min; injection volume 25 μL.	260 nm	Human plasma	[32]
HPLC-UV	Column Atlantis T3 (150 mm × 4.6 mm; 5μm) Mobile phase: 10 mM phosphoric acid solution, adjusted to pH 2 with hydrochloric acid, and acetonitrile (gradient elution).	230 nm	Human plasma	[33]
HPLC-UV	Column C18 Atlantis (150 mm × 4.6 mm; 3 μm), at 35°C. Mobile phase: 50 mM monopotassium phosphate and acetonitrile (gradient elution); flow rate 1 mL/min.	274 nm	Bone	[34]
HPLC-UV	Column C18 (30 mm × 4.6 mm; 2.5 μm), at ambient temperature. Mobile phase: acetonitrile and 50 mM phosphate buffer at pH 2.4 (8:92 v/v).	260 nm	Human plasma	[37]
HPLC-UV	Column inertsil ODS-3 (250 mm × 4.6 mm; 5 μm); at ambient temperature. Mobile phase: methanol and 10 mM dipotassium phosphate buffer at pH 6.7 (21:79, v/v); flow rate 1.1 mL/min; injection volume 20 μL.	270 nm	Rat plasma and intervertebral disc	[38]
HPLC-UV	Column × Terra C18 (250 mm × 4.6 mm; 5 μm) at 32°C. Mobile phase: 40 mM phosphate buffer (pH 3.2) and methanol (gradient mode); flow rate 0.85 mL/ min; injection volume 20 μL.	ND	Plasma and amniotic fluid	[39]
HPLC-UV	Column Nova-Pak C18 (100 mm × 8 mm; 4 μm). Mobile phase: 10 Mm of dibasicpotassium phosphate and 10 mM cetyltrimethyl ammonium bromide (pH 6.5) with acetonitrile (73:27 v:v).	274 nm	Plasma	[41]
HPLC-UV	Column C18 Hypersyl (200 mm × 2.1 mm; 5 μm); at ambient temperature. Mobile phase: for the analysis of the drug in the aqueous system, methanol-acetonitrile-phosphate buffer, pH 7.4 (20:20:60, v/v/v); for the plasma and cerebrospinal fluid, (30:40:30, v/v/v); flow rate 0.5 mL/min.	270 nm	Aqueous and rabbit biological samples	[42]
HPLC-UV	Column supelcosil LC-18 (150 mm × 4.6 mm; 3 μm); at ambient temperature. Two analytical mobile phases were used: mobile phase I: methanol –acetonitrile – 0.01 M phosphate buffer (pH 7.0) (20:15:65) and 5 mM tetrabutyl ammonium hydrogensulfate; mobile phase II: acetonitrile was omitted and 30% of methanol was used; flow rate 1 mL/min; injection volume 20 μL.	267 nm	Serum concentrations	[44]

(*Continued on next page*)

Table 1. (*Continued*)

Method	Conditions	Detection system	Matrices	Reference
HPLC-UV	Column p-Bondapak C18. Mobile phase: 56% 0.07 M sodiumacetateand 44% acetonitrile, pH ofthesolutionwasadjustedto 5.7 with acetic cid; flow rate 1 mL/min.	270 nm	Plasma and urine	[45]
HPLC-UV	Column hypersil ODS (250 mm × 4.6 mm; 5 μm), at 50°C. Mobile phase: acetonitrile: water: pH7: pH5 (39–55–5.5–0.5); flow rate 1.5 mL/min; injection volume 20 μL.	254 nm	Residues on stainless steel surface of pharmaceutical manufacturing equipments	[35]
HPLC-MS	Column cosmosil packed HILIC (150 mm × 2.0 mm) at 30°C. Mobile phase: acetonitrile and 10 mMol/L ammonium acetate (7:3), flow rate 0.5 mL/min; injection volume 10 μL.	Electrospray ionization (ESI) operated in negative mode	Powder for injectable solutions	[46]
HPLC-MS	Column 1: DevelosilPhA (150 mm × 0.5 mm; 5 μm) 2: Develosil PhA (30 mm × 0.5 mm; 10 μm). Mobile phase: 1: deionized water, methanol, acetic acid, glycerol pH 3.0 (59:40:0.5:0.5 v/v) 2: deionized water, methanol, acetic acid, diethanolamine pH 3.0 (57:40:2.5:0.5 v/v).	Operated in positive and negative mode	Human serum	[47]
UPLC-UV	Column Acquity UPLC BEH C18 (100 mm × 2.1 mm; 1.7 μm). Mobile phase: Solution A containing potassium dihydrogenphosphate buffer (pH adjusted to 6.5 ± 0.2 with *o*-phosphoric acid), citric acid buffer (pH adjusted to 5.0 ± 0.2 with NaOH solution) and acetonitrile and solution B containing tetradecyl ammonium bromide, tetraheptyl ammonium bromide and acetonitrile. Solution A: Solution B 65:35 (v/v); flow rate 0.3 mL/min.	230 nm	Powder for injectable solutions	[50]
UPLC-UV	Column purospher star C18 (100 mm × 2.1 mm; 2 μm). Mobile phase: 0.05 M sodium dihydrogen *o*-phosphate dihydrate: acetonitrile (86:14 v/v) adjusted to pH 4.5 with 0.1 M *o*-phosphoric or 0.1 M sodium hydroxide; flow rate 0.4 mL/min.	254 nm	Powder for injectable solutions	[51]
UPLC-UV	Column acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 μm). Mobile phase: acetonitrile and 10 mM oxalic acid (gradient elution); flow rate of 0.35 mL/min; injection volume 5 μL.	380 nm (0–0.58 min), 268 nm (0.58–1.01 min), 229 nm (1.01–1.12 min) and 268 nm (1.12–6.00 min)	Residues in milk	[52]
UPLC-MS/MS	Column AcquityUplcBehC18 (50 mm × 2.1 mm; 1.7 μm) at 35°C. Mobile phase: 0.1% formic acid in ultra-pure water and 0.1% formic acid in acetonitrile (gradient mode); flow rate 0.4 mL/min.	Positive electrospray ionization (ESI) using multiple reaction monitoring (MRM)	Waste water	[48]
UPLC-MS/MS	ColumnC_{18} Wwaters acquity T3 (50 mm × 2.1 mm; 1.7 μm). Mobile phase: 0.1% formic acid in water and 0.1% formic acid in acetonitrile (gradient mode); flow rate 0.4 mL/min; injection volume 5 μL.	Positive electrospray ionization (ESI) using multiple reaction monitoring (MRM)	Blood	[49]

HPLC-UV: High-performance liquid chromatography with detection by ultraviolet; HPLC-MS: High-performance liquid chromatography coupled with mass spectrometry detection; UPLC-MS/MS: Ultra-performance liquid chromatography coupled with sequential mass spectrometry; HPLC-MS/MS: High-performance liquid chromatography coupled with sequential mass spectrometry and UPLC-UV: Ultra-performance liquid chromatography with detection by ultraviolet; ND: not declared.

monitoring of the substance. In the analyzed literature, there is a predominance of determination by high-performance liquid chromatography (HPLC), but there are also determinations using ultra-performance liquid chromatography (UPLC), absorption spectroscopy ultravioleta (UV), infrared spectroscopy (IV), spectrofluorimetry and microbiological methods.

Table 2. Spectrometric analytical methods described in the literature for the determination of ceftriaxone sodium.

Method	Conditions	Detection system	Matrices	Reference
Absorption spectroscopy VIS	Dilution in water until the concentration of 2-8 mg mL^{-1} with 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole.	390 nm	Powder for injectable solutions	[53]
Absorption spectroscopy VIS	Dilution of 250 mg of sample in water, after filtration was diluted with distilled water and made up to 100 mL. Using variamine blue for determination.	556 nm	Commercial productcs	[54]
Absorption spectroscopy VIS	Dilutions of the drug with methanol and acetonitrile, using chloranilic acid for determination.	520 nm	Pharmaceutical formulation	[55]
Absorption spectroscopy VIS	Metallic chromium (VI) reagent isoxidized directly by potassium dichromate in the presence of the drug in acid medium forming a ternary complex.	520 nm	Commercial formulation	[6]
Absorption spectroscopy UV	Volumes of 100–300 μL of ceftriaxona solutions (1 mg/mL) were mixed with 50 μL of the alkali-induced degradation product (1 mg/mL) and diluted to 10 mL with acetonitrile-water (10:90 v/v).	265–320 nm	Powder for injectable solutions and their degradation products	[43]
Absorption spectroscopy UV	A portion of powder equivalent to 100 μg of the drug was weighed and transferred into 100 mL volumetric flask, the drug was dissolved by adding 70 mL of distilled water and sonicated for 15 min. The volume was completed with distilled water and filtered.	241 nm	Powder for injection dosage forms	[56]
Spectrofluorimetry	Dilution with water until 20 μg/mL reacting with *o*-phthalaldehyde.	386 and 324 nm	Pharmaceutical formulations and plasma	[57]
Infrared	It was linear over the concentration range of 0.4–1.2 mg with correlation coefficient of 0.9983 and limits of detection and quantification of 0.016 and 0.049 mg	1800 and 1700 cm^{-1}	Powder for injectable solutions	[59]

Table 3. Microbiological analytical methods described in the literature for the determination of ceftriaxone sodium.

Method	Conditions	Incubation time (hour)	Matrices	Reference
Microbiological-diffusion in agar	Plate cylinder method, 3 × 3 using *Staphylococcus aureus* ATCC 6538P.	18	Standard	[7]
Microbiological-diffusion in agar	Samples containing concentrations of 4.0 μg/mL, using phosphate buffer pH 6.0 as diluent; plates containing 21 mL of medium for antibiotic assay as base layer and 4 mL of the same medium inoculated with *Bacillus subtilis* (ATCC 6633) in a proportion of 0.5%; and incubation at 37 ± 1°C for 18 hours.	18	Commercial productcs	[9]
Microbiological-diffusion in agar	Six plates were used for each assay with *Bacillus subtilis* ATCC 9371 IAL 1027 as test microorganism. The plates were incubated at 35°C aerobically for 18 hours. The diameter of the growth inhibition zone (mm) was carefully measured with a digital caliper.	18	Powder for Injectable Solution	[58]

Tables 1–3 present the chromatographic, spectrometric and microbiological analytical methods, respectively, described in the literature for the determination of ceftriaxone sodium in pharmaceutical formulations, standards and various biological matrices.

Figure 3 shows graphically the percentage of different methods used for the analysis of ceftriaxone sodium, the HPLC technique was the most used in the found methods, being a fast, precise and specific technique but uses organic solvents (acetonitrile, methanol, for example), being toxic waste generators. Many methods use buffer solutions that are non-toxic to the environment and the operator, but can shorten the life of the equipment and accessories, for example, the chromatographic columns, impacting the cost of the analysis.[60–61]

It is necessary to develop methods that use solvents with low toxicity (ethanol and water, for example), as well as to use them in low concentrations. The commitment to using reduced samples through miniaturization, decreasing process steps and pretreatment of samples, are alternatives that directly influence the amount of reagents used, time of analysis, number of materials required and cost involved. On the other hand, work on the recovery of these toxic solvents should be done, as these materials cannot be disposed of directly into the environment.[62–65]

The equipment used should also be considered important, the proposal is to use those that require less solvent, which have less analysis time, generating lower energy consumption and as a consequence lower expenses for the company and lower final product prices.[66–70]

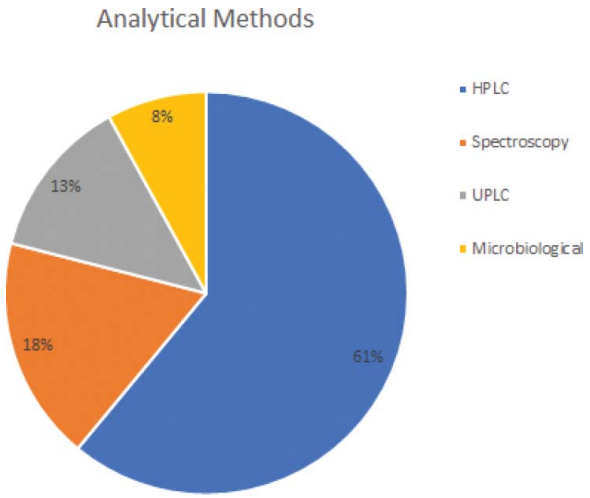

Figure 3. Percentage of various analytical methods used in the ceftriaxone sodium analysis.

The questions tend to focus on the relationship between the new validated methods and their practical uses by chemical and pharmaceutical industries. In discussing the relevant issue, we have to consider how methods can be adopted to routine analysis. This is clearly not an exhaustive list, but it will be very useful for researchers to revise the key concepts and demonstrate the ability of these innovative techniques. The development of these methods should be encouraged more and more, due to their advantages and economic, environmental and social benefits. In this way, universities become reference research centers in the area, helping to achieve this goal.[3,4,15,71–74]

Conclusion

Ceftriaxone sodium is a third-generation antibiotic belonging to a class of cephalosporins, it has a bactericidal action and it shows greater activity against Gram-negative bacteria.

The use of this drug contributes to the development of studies that need to carry out their analytical and bioanalytical quantification. The drug has characteristics, properties and analytical methods well defined. However, it is necessary to encourage and raise awareness for the need to develop and validate innovative analytical methods using green chemistry.

Conflict of interest

The authors declare no conflicts of interest.

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