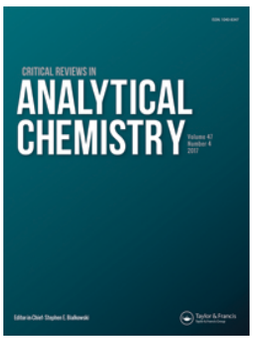

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A Critical Review of Analytical Methods for Quantification of Cefotaxime

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ABSTRACT

Bacterial resistance to antibiotics is a growing phenomenon in the world. Considering the relevance of antimicrobials for population and the reduction in the registration of new antimicrobials by regulatory, proper quality control is required in order to minimize the spread of bacterial resistance and ensure the effectiveness of a treatment, as well as safety for the patient. Among the antimicrobials is cefotaxime, a drug belonging to third-generation cephalosporins, which is highly active against Gram-negative bactéria and is used to treat central nervous system infections such as meningitis and septicemia. Due to the critical importance of quality control in regard to drugs and pharmaceutical products, combined with bacterial resistance to antibiotics, this study aims to conduct a detailed review of analytical methods for cefotaxime. Using a critical review of literature, this paper describes the analytical methods published to quantify cefotaxime in different matrices; a large number of methods by HPLC and spectrophotometry were observed. Despite the advantages of the techniques, most methods reported have large environment and occupational impact, which enfatizes the need to adopt green procedures in quantifying cefotaxime.

KEYWORDS

Analytical methods; cefotaxime; HPLC; quality control; review

Introduction

Bacterial resistance to antimicrobial agents is a phenomenon that occurs following extensive contact of bacteria with antibiotics and their presence in the environment. Until the twentieth century, bacterial resistance was usually restricted to hospitals; however, it can now be identified in different environments where it can affect even healthy individuals (Guimarães et al., 2010).

Faced with the high rate of bacterial resistance to antibiotics, as well as a reduction in the number of drugs approved by the FDA in recent years, it is necessary to develop new drugs, adopt new therapeutic strategies and incorporate cultural changes – educating professionals and population (Guimarães et al., 2010; Brooks and Brooks, 2014; Oldifield and Feng, 2014). Antimicrobials have great relevance in the health field since bacterial infections are one of the leading causes of mortality globally (Brito and Cordeiro, 2012).

Among the antibiotics are the cephalosporins, the second-largest class of β-lactam antibiotics (Guimarães et al., 2010). Acting to prevent bacterial cell wall synthesis, cephalosporins are considered safe and low-toxicity antimicrobials (Tortora et al., 2012). The existing cephalosporins are classified in five generations according to the action spectrum, stability to β-lactamases, pharmacokinetics, chemical stability and side effects (Alessio and Salgado, 2012; Vieira et al., 2012; Fernandes et al., 2013; De Marco and Salgado, 2016).

Cefotaxime sodium is included in the third-generation cephalosporins. The major developments in relation to previous generations of cephalosporins are the presence of amplification in the penetration of drugs in Gram-negative bacteria, which contributes to the expansion of the spectrum of action and the development of higher affinity for the site of action (Patrick, 2009). In addition, third-generation antimicrobials reach the central nervous system in significant concentrations, allowing their use in the treatment of meningitis and sepsis by Gram-negative microorganisms (Fernandes et al., 2013).

Given the importance of antibiotics in the global population, these drugs require accurate and reliable quality control. Analytical methods comprise one of the quality control tools in pharmaceutical industry required by regulatory organizations worldwide to verify the suitability of pharmaceutical ingredients and finished products to the established specifications, which can guarantee satisfactory quality of these products. Confirming the pertinence of the products to the specifications, in other words the correct dosage of the pharmaceutics, with implementation of analytical methods that provide reliable results, the patient will have a more effective and safe treatment, minimizing the chances of developing bacterial resistance (ANVISA, 2010).

Cefotaxime is an important third-generation cephalosporin related to its high resistance to β-lactamases, a bacterial resistance mechanism developed by microorganisms, and for its beneficial activity against numerous aerobic Gram-negative and Gram-positive bacterias when compared to other β-lactam compounds. It is used effectively in the treatment of meningitis and other severe infections (Brunton et al., 2012). Due to its importance of cefotaxime in therapeutics, reliable quality

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control has a high impact in the efficiency of cefotaxime and bacterial resistance in the hospital environment.

Related to the presented facts, we prepared a large search of analytical methods described for the quantification of cefotaxime in both pharmaceutical and general matrices.

Cefotaxime

Sodium cefotaxime (Figure 1) is a third-generation cephalosporin that binds irreversibly to the transpeptidase enzyme, responsible for catalyzing the peptide bonds synthesis of the bacteria wall. Following this binding, the structure is impaired, leading to bacterial cell lysis (Tortora et al., 2012).

In North America and Europe, cefotaxime is commercially available as a lyophilized powder that can be administrated via the intramuscular or intravenous routes, as 1–4g of cefotaxime per day in two or three doses; in case of severe infection, 10–12g per day may be administrated. It is used mainly in the treatment of meningitis caused by *Haemophilus influenzae, Streptococcus pneumoniae* sensitive to penicillin, *Neisseria meningitidis* and other infections of the central nervous system (Korolkovas, 2010). The reference product is Claforan®, which is produced by Sanofi-Aventis LLC (ANVISA, 2016).

When administered intravenously, the plasma half-life of cefotaxime is approximately 1 hour and when administered intramuscularly, it is approximately 1.5 hours. About 25–40% of cefotaxime binds to plasma proteins (Patel et al., 1995; Brunton et al., 2012). Around 90% of the administered dose is excreted by the kidneys, 50% in unchanged form and 20% as desacetylcefotaxime (the main metabolite of cefotaxime) (Kees et al., 1981). Desacetylcefotaxime is less active than the original molecule, but acts synergistically with cefotaxime against several microorganisms (Ko et al., 1991; Jones, 1995).

Cefotaxime sodium, sodium (6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 7^2-(Z)-(O-methyloxime), acetate (ester), is a semisynthetic derivative of a drug fermentation product. Its molecular formula is $C_{16}H_{16}N_5NaO_7S_2$ and its molecular weight is 477.45 g/mol (Infarmed, 2005; Society of Japanese Pharmacopeia, 2011; O'Neil, 2013; The Stationary Office, 2014; Council of Europe, 2014; United States Pharmacopeia Convention, 2014).

It is a white or slightly yellowish crystalline powder, and it is hygroscopic. It is freely soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and practically insoluble in organic solvents; it must be stored in a tightly closed container protected from light, at temperatures below 30°C (Infarmed, 2005; Society of Japanese Pharmacopeia, 2011; O'Neil, 2013; The Stationary Office, 2014; Council of Europe, 2014; United States Pharmacopeia Convention, 2014).

The characteristic chemical grouping of cephalosporin present in cefotaxime is 7-aminocephalosporinic acid, comprising a β-lactam ring and a dihydrothiazine ring. The characteristic chemical structure of cephalosporins is presented in Figure 2; the group attached to carbon 7 of the basic structure differentiates cefotaxime from the others in the class. In addition, the carbon group linked to position 3 ensures good pharmacokinetic properties such as the transfer to the central nervous system in significant concentrations (Patrick, 2009; Fernandes et al., 2013).

Analytical methods

The quality control of active pharmaceutical ingredients (APIs) and pharmaceutical products is an important activity embedded in good manufacturing practices within the pharmaceutical industry (ANVISA, 2010). Therefore, the development and validation of new analytical methods and the improvement of existing methods for proper identification and quantification of drugs and pharmaceutical products are of great importance in the industry and the scientific community, to ensure their safety and effectiveness. Thus, research groups have studied analytical methods for the quantification of drugs and cefotaxime sodium in different biological matrices.

Bioassays are relevant for clinical studies, therapeutic drug monitoring (TDM) and individual dose adjustment. Hydrophilic drugs may present daily variations in the plasma concentrations of critically ill patients. In this scenario, the development of bioanalytical methods is essential for the efficacy and safety of the treatment with cefotaxime.

There are some papers describing analytical methods to quantify cefotaxime in many matrices, such as blood, plasma, serum, peritoneal fluid and urine. In the literature, it is possible to find papers that noticed the importance of the development of practical analytical methods to be used in the TDM of cefalosporins.

Yilmaz and Biryol (1998) developed a method of determining cefotaxime by voltammetry. The analysis conditions were: carbon electrode, platinum wire for dosing and calomel electrode and standard solutions for analysis using 0.2 M phosphoric acid as diluent. Quantification by direct titration was developed by Helaleh et al. (1998), where a lyophilized powder of cefotaxime sodium solution at a concentration of 1 mg/mL

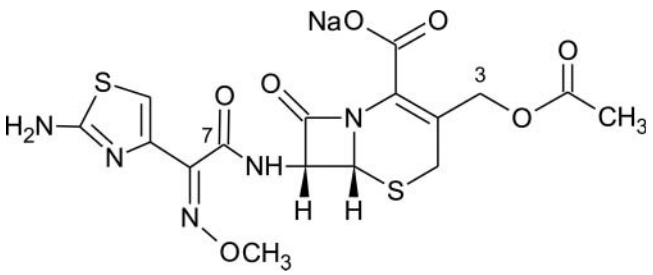

Figure 1. Chemical structure of sodium cefotaxime (CAS 64485-93-4).

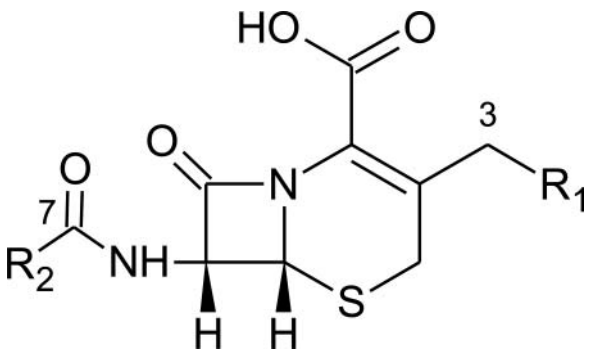

Figure 2. Chemical basic structure of cephalosporins.

was titrated with potassium iodide and end-point detection conducted with the aid of carbon tetrachloride 0.01 M.

Cefotaxime sodium feedstock samples and in pharmaceutical formulations were analyzed by Nassar and collaborators (1996) with the assessment of the utility of N-bromosuccinimide compounds (NBS) and N-chlorosuccinimide (NCS) in determining cefotaxime sodium by colorimetric and titrimetric techniques. The optimal reaction time was 20 minutes and the method had the limit of quantification of 1.5913 mg of cefotaxime.

Methods for determining the assay of cefotaxime sodium and other cephalosporins by capillary electrophoresis are also reported in the literature under different analytical conditions.

Solangi et al. (2007) describe a method of analysis for eight cephalosporins in urine. Fused silica capillary with 57 cm of total length, 50 cm of effective length and 75 μm internal diameter was used. Sodium tetraborate buffer pH 9.0 separates the cephalosporins with a 30 kV of potential. The detector used was a UV detector at 214 nm. The analysis was performed at 25°C.

Gáspár et al. (2002a) developed a method for the analysis and stability study of 14 cephalosporins. The analysis was performed with a fused silica capillary having 64.5 cm of total length, 56 cm of effective length and internal diameter of 50 μm at a temperature of 25°C. The solution used for the separation was a 25 mM phosphate solution of pH 6.8. A potential of 125 kV was applied and a UV detector was used at 260 nm.

A method for detection of cefotaxime and its metabolites in plasma was reported by Penalvo et al. (1997). The analysis was performed with a fused silica capillary having 57 cm of total length, 50 cm effective length and 75 μm internal diameter at a temperature of 5°C. The solution used for the separation was a solution of dihydrated sodium dihydrogen phosphate with pH adjusted to 8.0 and 5 M sodium hydroxide solution containing 165 mM sodium dodecyl sulfate. A 25-kV potential was applied, and the detection was performed with a UV detector at 254 nm.

Mrestani et al. (1997) also described a method for the analysis of cephalosporins, but using a fused sílica capillary of 48.5 cm total length, 40 cm of effective length and 50 μm of internal diameter. The separation was performed with 20 mM phosphate buffer solution of pH 7.2. A potential of 30 kV was used and the detection was performed using the UV detector at 200 nm. The analysis temperature was 25°C.

Gáspár et al. (2002b) published another paper reporting the development of a method for quantification of four cephalosporins in samples obtained after neurosurgeries (fluid drained from injury, cerebrospinal fluid, plasma and urine). The fused silica capillary with 48.5 cm of total length, 40 cm of effective length and 50 μm of internal diameter was used. The separation solution was 25 mM borate buffer solution of pH 9.2. A potential of 25 kV and a UV detector at 270 nm were applied. The analysis temperature was 25°C.

Penalvo et al. (1996) also validated an analytical method for quantification of cefotaxime and its related impurities. A fused silica capillary used had a total length of 57 cm, effective length of 50 cm and internal diameter of 75 μm. The solution of 30 mM sodium dihydrogen phosphate of pH 7.2 containing 165 mM sodium dodecyl sulfate was used for the separation. A potential of 15 kV was applied and a UV detector was used at 254 nm. The analysis was performed at a temperature of 25°C.

Mrestani et al. (1999) published another study for the analysis of nine cephalosporins in urine and bile samples. A fused silica capillary of 57 cm total length, 50 cm of effective length and internal diameter of 50 μm was used. For the separation, 50 mM citrate buffer solution of pH 6 was used. The potential applied for the analysis was 30 kV and the detector used was a UV detector at 214 nm. The temperature of the analysis was 25°C.

Lin et al. (2000) published a study of optimization of the separation and migration of cephalosporins in capillary electrophoresis. The best conditions were the following: fused silica capillary with 57 cm of total length, effective length of 50 cm and internal diameter of 50 μm, separation with citrate buffer and atanosulfonic acid monohydrate buffer solution at various pH's, 30 kV potential, UV detector at 214 nm and temperature of 25°C.

Finally, Wang et al. (2009) published a study of the determination of cefotaxime and its enantiomers. The analysis conditions used were: a fused silica capillary of effective length of 40 cm and internal diameter of 75 μm, separation solution consisting of 75 mM dihydrogen phosphate buffer sodium solution of pH 7, a potential of 20 kV, a UV detector at 280 nm and a temperature of 25°C.

Methods for the determination of cephalosporins and cefotaxime by spectrophotometry with absorption in light ultraviolet and visible on various biological matrices, in APIs and in pharmaceutical formulations were found in the literature and the main analytical conditions for each one are listed in Table 1. The low cost and simplicity of the technique can justify the extensive use of spectrophotometric analysis in quantifying the drug. Despite advantages, it has a limitation regarding selectivity: interfering with a similar absorption spectrum of the drug can give inaccurate results, which can compromises the reliability of the analysis (Moreno and Salgado, 2008; Moreno and Salgado, 2009; Vieira and Salgado, 2011).

High performance liquid chromatography (HPLC) is one of the most used techniques for the analysis of drugs and formulations. In the literature, increased number of analytical methods to quantify cefotaxime sodium using this technique were found, both for quantification of cefotaxime in drugs and biological matrices. According to the significant number of methods available for cefotaxime determination by HPLC, we could conclude it is the most used technique for quantifying cefotaxime. All analytical methods found, as well as the analysis conditions, are presented in Table 2.

United States Pharmacopeia Convention (2014) provides monographs for cefotaxime API, injectable solution and lyophilized powder for injection. The raw material monograph presents a method for determining the content of cefotaxime by HPLC using a C_{18} column in the dimensions 150 × 3.9 mm^2, 5 μm at 30°C. Gradient mode was used by switching the proportions of mobile phases A (0.05 M phosphate buffer solution with pH adjusted to 6.25 with phosphoric acid and methanol 86:14 (V/V)) and B (0.05 M phosphate buffer solution with pH adjusted to 6.25 with phosphoric acid and methanol 60:40 (V/V)), with a flow rate of 1.0 mL/min. The detector used was a UV detector at 235 nm. The determination of the

Table 1. Analytical conditions for methods by spectrophotometry in ultraviolet and visible.

Sample	Sample preparation/wavelength	Concentration range	Reference
Lyophilized powder and plasma	Addition of excess of N-bromosuccinimide to the drug in an acidic medium and determining the excess of N-bromosuccinimide by reaction with methyl orange at 508 nm.	1.2–3.2 μg/mL	Aswani et al. (2011)
API and pharmaceutical formulation	Drug complexation with eriochrome black T in an acid medium, extraction with dichloromethane and organic phase, reading at 510 nm.	30–120 μg/mL	Sayed et al. (2012)
API and pharmaceutical formulation	Hydrolysis of the β-lactam ring of the cephalosporins by reaction with NaOH and iodate releasing iodine in an acid medium, the liberated iodine oxidizes forming a violet blue coloration with maximum absorption at 556 nm. Absorbance was measured in pH range 4.0–4.2.	0.5–5.8 μg/mL	Pasha and Narayana (2008)
API	β-lactam attached to the 2-aminothiazol-4-yl-2-alkoxyiminoacetamido form purple colored complex or cherry red after reacting with sodium nitrite in acid medium. Quantification was performed at 500 nm.	12.5–200 μg/mL	Uri and Jain (1985)
API and pharmaceutical formulation	Reaction with methyl 2-nitrophenylhydrazine in the presence of dicyclohexilcarbodi-imide and pyridine. The resulting violet coloration of hydrazine was quantified at 537 nm.	0.6–3 mmol/10 mL	Korani et al. (1989)
API	Water as a diluent, analysis at 276.8 nm.	0.005–0.080 mg/mL	Nuevas et al. (1998)
API and pharmaceutical formulation	Water and methanol as diluente, analysis at 260nm.	10–30 μg/mL	Bushra et al. (2014)
Lyophilized powder	Hydrolysis of cephalosporins with NaOH to produce sulfide ion which reacts with sulphate N, N-diethyl-p-phenilenadiamine and iron (III) producing a blue color quantified at 670 nm. In method A, the sulfide ion reacts with the dihydrochloride of *p*-phenilenediamine and iron (III) developing violet coloration quantified at 597 nm.	Method A: 95.48–477.4 μg/mL Method B: 0.5–450 μg/mL	Metwally et al. (2001)
API and pharmaceutical formulation	0.1 M NaOH as diluent, analysis at 238 nm.	5–30 μg/mL	Marreddy et al. (2011)
Pharmaceutical formulation	Water and methanol as eluent with 1,2-naphthoquinone-4-sulfonic acid, analysis at 493 nm.	0.2–1.2 μg/mL	Ahmed et al. (2015)
API	Hydrolysis of cephalosporins in alkaline medium at elevated temperature with 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole, developing yellow color, analysis at 390 nm.	5–160 μg/mL	Rageh et al. (2010)
API and pharmaceutical formulation	Reagent metallic chromium (VI) is oxidized directly by potassium dichromate in the presence of drug in acidic medium to form a ternary complex with absorption at 520 nm.	0.2–28 μg/mL	Amin and Ragab (2004)
API	Colored charge transfer complex formed between the drug and 7,7,8,8-tetracyanoquinodimethane (TCNQ) or *p*-chloranilic acid (*p*-CA), analysis at 838 nm for TCNQ and 529 nm for *p*-CA.	TCNQ: 7.6–15.2 μg/mL *p*-CA: 95.0–427.5 μg/mL	Ayad et al. (1999a)
API	Reaction of the drug with 1,2-naphthoquinone-4-sodium sulfonate in 0.1 M NaOH, analysis at 489 nm.	3.8–114.6 mg/mL	Fan et al. (2013)
API and pharmaceutical formulation	Drug oxidation with cerium (IV) 1-chlorobenzotriazole, analysis at 464 nm for the cerium (IV) and 298 nm for 1-chlorobenzotriazole.	CE(IV): 0.5–4.5 μg/mL 1-CTB: 10.0–70.0 μg/mL	Ayad et al. (1999b)
Pharmaceutical formulation	Reaction of drugs with iron (III) nitrate forms iron (II) that reacts with hexacyanoferrate (III) potassium producing a blue complex, analysis at 777 nm.	0.1–8.0 mg/mL	Al-Arfaj (2005)
Pharmaceutical formulation	Hydrolysis of drugs in alkaline medium under heating and oxidation of iron (III) sulfuric acid medium with production of iron (II), that forms complex with *o*-phenanthroline in pH 4.2 citrate buffer solution forming red complex with absorption at 510 nm.	0.20–2.50 mg/mL	Al-Momani (2001)
API and pharmaceutical formulation	Drug oxidation with molibdofosforic acid results in blue color, analysis at 700 nm.	—	Issopoulos (1988)
API and pharmaceutical formulation	Reaction of amino groups in the molecule with ninhydrin produces colouring with maximum absorbance at 568 nm.	10–90 μg/mL	Sayed (2013)
API and pharmaceutical formulation	The paper presents the methods A, B and C. Formation of pink and purple chromogenic obtained by diazotization with nitrous acid of the drugs and the reagents N-(1-naphthyl) etilenodiaminodiclorídrico (method A) diphenylamine (method B) and β naphthol (method C) with maximum absorbance at 555 nm, 510 nm and 542 nm, respectively.	Method A: 5–25 μg/mL Method B: 20–100 μg/mL Method C: 10–50 μg/mL	Mruthyunjayaswamy et al. (2006)
Pharmaceutical formulation	Oxidation with potassium permanganate in alkaline medium, analysis at 610 nm.	Initial time: 5–15 μg/mL Fixed time: 5–25 μg/mL	Omar et al. (2009)
API and pharmaceutical formulation	Drug in alkaline medium with 1, 2-naphthoquinone-4-sulfonic sodium form orange coloration with analysis at 495 nm.	20–140 μg/mL	Kumar et al. (2010)
Pharmaceutical formulation	3 methods were developed: 1. Method of the simultaneous equation; cefotaxime is determined at 233.5 nm. 2. Area under the curve; cefotaxime is determined from 238.5 to 228.5 nm.	1.5–35 μg/mL	Nanda et al., 2010

	3. Method of multicomponent mode; cefotaxime is determined at 233.5 nm.		
API	Cephalosporins complexing with palladium (II) chloride, analysis at 347 nm.	3.99–29.93 μg/mL	Bagheri et al. (2012)
Pharmaceutical formulation	2 methods were developed: 1. Method of the simultaneous equation; cefotaxime is determined at 231 nm. 2. Method of Q absorption; cefotaxime is determined at 234.2 nm.	5–30 μg/mL	
API	3 methods were developed:		Sajeh et al. (2001)
	1. Reaction with iodine σ-acceptor, analysis at 364 nm.	1.6–40 μg/mL	
	2. Reaction with π-acceptor 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ), analysis at 460nm.	2.40–200 μg/mL	
	3. Reaction with π-acceptor 7,7,8,8-tetracyanoquinodimethane (TCNQ), analysis at 843 nm.	3.6–18 μg/mL	
API	Acid hydrolysis of cephalosporins and oxidation with vanadium phosphoric acid, analysis at 516 nm.	0.4–45 μg/mL	Amin and Shama (2000)
Plasma	Analysis at 295 nm.	–	Datta et al. 2003)
API and pharmaceutical formulation	Gelatin complexing with silver, reduction by sulfide ions generated in alkaline hydrolysis of the drugs, with the formation of yellow silver solution, analysis at 352 nm.	24–76 μg/mL	Sayed et al. (2012)

Table 2. Analysis conditions for the methods by high performance liquid chromatography.

Sample	Column	Mobile phase	Flow (mL/min)	Injection volume (μL)	Detection	Retention time (minutes)	Reference
API	Luna C_{18} (250 × 4.6 mm^2, 5μm)	Ammonium acetate buffer 20 mM and acetonitrile (60:40 V/V)	1.0	20	UV 254 nm	3.477	Saranya et al. (2014)
API	C_{18}	Sodium phosphate dibasic 0.05 M at pH 6.25 and methanol	1.0	—	UV 235 nm, 30°C	Between 13 and 30	Zhang et al. (2014)
Honey	Acquity UPLC BEH C_{18}, (100 × 2.1 mm^2, 1.7 μm)	Formic acid 0.1% and acetonitrile 0.1% formic acid (gradient)	0.4	5 (TOF/MS) and 10 (MS/MS)	TOF/MS and MS/MS, 40°C	—	Sporri et al. (2014)
API	Fortis C_{18} (150 × 4.6 mm^2, 5 μm)	Methanol and water pH adjusted to 4.0 with acetic acid (30:70 V/V)	0.8	20	UV 235 nm, 25°C	4.6	Stirbet et al. (2014)
Bovine milk	Acquity UPLC BEH C18 (50 × 2.1 mm^2, 1.7 μm)	Water 0.1% formic acid and acetonitrile 0.1% formic acid (gradient)	0.25	5	MS/MS, 35°C	1.86	Li et al. (2014)
Parenteral nutrition solutions	Supelcosil LC-18-DB (250 × 4.6 mm^2, 5 μm)	Ammonium acetate 25 mM pH adjusted to 4.0 with glacial acetic acid and acetonitrile 50% in methanol (80:20 V/V)	0.9	3	UV 254 nm, 40°C	6.2	Iqbal et al. (2013)
API	Hibar C_{18} (250 × 4.6 mm^2)	Methanol and formic acid 0.05% (55:45 V/V)	1.0	20	UV 260 nm, MS	3.740	Qureshi et al. (2013)
Waste water	Acquity HSS T3 (50 × 2.1 mm^2, 1.8 μm)	Water 0.1% formic acid and acetonitrile (gradient)	0.5	5	MS, 30°C	1.18	Gros et al. (2013)
Human blood	ACE C_{18} (150 × 4.6 mm^2, 5 μm)	Water 0.1% formic acid or ammonium acetate 5 mM and acetonitrile (gradient)	0.4	15	MS	7.06	Szultka et al. (2013)
Cerebrospinal fluid	LiChrospher 100 RP-18 (250 × 4 mm^2, 5 μm)	Acetate buffer at pH 4.8 and methanol (85:15 V/V)	1.5	20	UV 254 nm, 23°C	13.8	Bafeltowska et al. (2002)
Milk	CN-RP (150 × 2.1 mm^2, 5 μm)	Phosphate buffer 0.01 M at pH 5.8 and acetonitrile (60:40 V/V)	1.0	5	UV 220 nm	5.9	Adlnasab et al. (2012)
API	C_{18} (25 × 4.6 mm)	Methanol and potassium phosphate monobasic 40 mM pH adjusted to 3.5 with *o*-phophoric acid (30:70 V/V)	0.85	50	UV 254 nm, 30°C	9.593	Alnahhas et al. (2012)
API	Acclaim C_{18} PAII (150 × 2.1 mm^2, 3 μm)	Water 0.1 % formic acid and acetonitrile 0.1% formic acid (gradient)	0.4	—	MS, 25°C	12.694	Gode et al. (2012)
API	Click-CD (150 × 2.1 mm^2, 5 μm, pore size 10 nm)	Ammonium formate 10 mM at pH 6.8 and acetonitrile + ammonium formate 100 mM 90:10 V/V at pH 6.8 (gradient)	0.2	—	UV 254 nm and MS, 30°C	± 5.0	Liu et al. (2011)
API	C_{18} (250 × 4.6 mm^2, 5 μm)	Acetonitrile and water pH adjusted to 3.0 with hydrochloric acid solution 10%, w/V (15:85 V/V)	0.5	20	UV 254 nm	—	Han et al. (2011)
Serum	Unison UK-C_{18} ODS (50 × 2 mm^2, 3 μm)	Aqueous ammonium formate 10 mM 0.1% formic acid and methanol 0.1% formic acid (gradient)	0.3	20	MS/MS, 30 and 5°C	5.86	Ohmori et al., 2011
Water	Shimpack VP-ODS (150 × 4.6 mm^2, 5 μm)	Water and formic acid 0.1% and methanol (60:40 V/V)	0.5	10	UV 254 nm and 270 nm, 35°C	7.5	Wang et al. (2011)
Humam plasma	Atlantis T3 (150 × 4.6 mm^2, 5 μm)	Phosphoric acid solution 10 mM pH adjusted to 2 with hydrochloric acid and acetonitrile (gradient)	—	20	UV 230 nm	6.8	Verdier et al. (2011)
API	Luna C_{18} (4.6 mm × 150 mm^2, 5.0 μm)	Phosphoric acid 0.007 *M* and acetonitrile (85:15 V/V)	1.3	20	UV 254 nm	—	Manda et al. (2011)
Milk	1: Inertsil ODS-3 (250 × 4 mm^2, 5 μm) 2: Orbit 100 C_{18} (250 × 4 mm^2, 5 μm) 3: Chromolith RP-18 (100 × 4.6 mm)	Acetic acid 0.1% and methanol + acetonitrile (75:25 V/V) (gradient)	1.5	20	UV 265 nm	22.142	Karageoru and Samanidou (2010)
Lyophilized powder	Symmetry ODS (150 × 4.6 mm^2, 5 μm)	Phosphate buffer and methanol/acetonitrile with pH adjusted to 6.0 with phosphoric acid (80:15:5 V/V/V)	1.3	20	UV 254 nm, 25°C	5.8	Tippa and Singh (2010)
Lyophilized powder	SS Wakosil II- C8 (250 × 4.6 mm^2, 5 μm)	Ammonium acetate buffer at pH 6.8 and acetonitrile (85:15 V/V)	0.8	100	UV 252 nm	5.57	Lalitha and Sanjay (2010)
Urine	OptimaPak C_{18} (150 × 4.6 mm^2, 5 μm)	Phosphate buffer 0.005 mol/L and methanol at pH 5.0 (79:21 V/V)	0.7	—	UV 254 nm	18.1	
API		Phosphate buffer 40 mM at pH 3.2 and methanol (gradient)	0.35	100	UV, 32°C	± 16	

	XTerra C_{18} (250 × 4.6 mm^2, 5 μm)						Nemutlu et al. (2009)
Peritoneal fluid	Coluna Atlantis C_{18} (150 × 4.6 mm^2, 5 μm)	Phophoric acid at pH 2 and acetonitrile (gradient)	2.0	—	UV 230 nm	—	Seguin et al. (2009)
Urine	XTerra C_{18} (150 × 3.9 mm^2, 5μm)	Phosphoric acid 0.007 *M* and acetonitrile (85:15 V/V)	1.0	20	UV 262 nm, 25°C	3.822	Aleksic et al. (2008)
Milk	Kromasil 100, C_{18} (250 × 4.0 mm^2, 5 μm)	Acetate buffer at pH 4 and metanol (60:40 V/V)	1.0	20	UV 265 nm	2.514	Samanidou et al. (2008)
Injectable solution of glicose	Zorbax Eclipse XDB-C_8 (150 × 4.6 mm^2, 5 μm)	Methanol and water (gradient)	1.0	20	UV 238 nm, 30°C	2.254	Guo et al. (2007)
API and lyophilized powder	Zorbax ODS (150 × 4.6 mm) Hypersil ODS (125 × 4.5 mm)	Water and acetonitrile (50:50 V/V)	—	—	UV 254 nm and MS	1.732	Sokolova and Chuchalin (2006)
Plasma	C_{18} Aqua (150 × 4.6 mm^2, 5 μm)	Ammonium dihydrogen phosphate buffer 50 mM, acetonitrile and triethylamine (87,8:12:0,2 V/V/V) pH adjusted to 3.0 with phosphoric acid 85%	1.0	100	UV 285 nm	13.21	Rosseel and Vandewoude (2004)
Humam plasma	Hibar Lichrospher 100 RP8 (250 × 4 mm^2, 5 μm)	Dihydrogen phosphate buffer 0.025 mol/L pH adjusted to 2.2 with orthophosphoric acid and methanol (75:25 V/V)	1.2	100	UV 255 and 280 nm, 25°C	7.5	Zendelovska et al. (2003)
Rat plasma and humam plasma	Zorbax SB-C $_{18}$ (250 × 4.6 mm^2, 5 μm)	Ammonium acetate 0,05 *M*, acetonitrile and tetrahydrofuran (87:1:2, V/V) pH adjusted to 5.5 with glacial acetic acid	1.0	20	UV 254 nm	6.3	Ling et al. (2003)
Rat intestine	C_{18} Shim-Pack (CLC-ODS-M) (250 × 4.6 mm^2, 5 μm)	Phosphate buffer at pH 7.0 and methanol (70:30 V/V)	1.0	50	UV 254 nm, 25°C	± 7.5	Sharma et al. (2002)
Milk	Inertsil ODS-3 (250 × 4 mm^2, 5 μm)	Ammonium acetate 0.05 M and acetonitrile	1.4	20	UV 265 nm	22.5	Karageorgou et al. (2012)
Blood and urine	Spherisorb ODS-2 (250 × 34 mm^2, 5 μm)	Acetate buffer at pH 4.0 and methanol (78:22 V/V)	1.2	20	UV 265 nm	4.348	Samanidou et al. (2003)
API	ODS TSK-gel 80TM (150 × 2.0 mm^2, 5 μm)	Water and acetonitrile (20:80 V/V)	1.0	5	MS	—	Horimoto et al. (2002)
Plasma	Econosphere C_{18} (5 μm)	Sodium scetate buffer pH adjusted to 4.8 with glacial acetic acid and methanol (80:20 V/V)	1.0	20	MS	6.0	
Humam plasma and cerebrospinal fluid	Spherisorb ODS2 (150 × 4.6 mm^2, 5 μm)	Phosphate buffer 0.007 *M* and acetonitrile (85:15 V/V)	1.3	20	UV 262 nm	6.8	Scanes et al. (2001)
Bovine milk	Nova-Pak phenil (150 × 3.9 mm^2, 5 μm)	Octanosulphonate acid 0.005 *M* (pH 2.52)+acetonitrile (90:10 V/V) and acetonitrile+methanol (30:15 V/V) (gradient)	1.0	100	UV 270 nm, 20—24°C	—	Sorensen and Snor (2000)
Blood	Microbore C_{18} (150 × 1 mm^2, 5 μm)	Monosodium phosphoric acid 10 mM and methanol at pH 5.5 (75:25 V/V)	0.05	10	UV 254 nm	7	Tsai et al. (2000)
API	Supelcosil ODS (150 × 4.6 mm^2, 5 μm)	Phosphate buffer at pH 7 and methanol (4:6 V/V)	1.0	20	UV 254 nm	4.27	Shalaby (1988)
API	Nova-Pak C_{18} Radial-Pak (100 × 8 mm^2, 4 μm)	Acetate buffer 0.01 M at pH 4.7 + methanol + acetonitrile (87:11:2 V/V/V) and acetate buffer 0.01 M at pH 4.7 + methanol + acetonitrile (87:2:11 V/V/V) (gradient)	1.0	50	Electrochemical, 20 ± 2°C	± 15	Yun et al. (1998)
API	Schimpack GLC-ODS (150 × 6 mm^2, 5 μm)	Ammonium acetate 0.1 *M* and acetonitrile (90:10 V/V) pH adjusted to 7.5 with ammonia	1.5	50	UV 270 nm	5	Abdel-Hamid (1998)
Aqueous humor and plasma	ODS Hypersil C_{18} (300 × 4.6 mm^2, 5 μm)	Sodium phosphate monohydrate 0.01 M + acetonitrile 15% (V/V) e N,N-dimethylformamide + water 6% (V/V) pH adjusted to 3.0 with phosphoric acid 85%	1.0	10	UV 285 nm	6.7	Kraemer et al. (1997)
API	1: Develosil PhA (150 × 0.5 mm^2, 5 μm) 2: Develosil PhA (30 × 0.5 mm^2, 10 μm)	1: Deionized water, methanol, acetic acid and glycerol at pH 3 (59:40:0.5:0.5 V/V) 2: Deionized water, methanol, acetic acid and diethanolamina at pH 3 (57:40:2.5:0.5 V/V)	0.004	500	MS	16.1 and 13.6	Kobayashi et al. (1996)
Plasma e urine	Zorbax SB-C_8 (80 × 4.6 mm^2, 3,5 μm)	Trifluoroacetic acid 0.1% and acetonitrile (82:12 V/V)	1.0	20	UV 254 nm	1.75	Kirkland et al. (1994)

(*Continued on next page*)

Table 2. (*Continued*)

Sample	Column	Mobile phase	Flow (mL/min)	Injection volume (μL)	Detection	Retention time (minutes)	Reference
Bool, serum and ascitic fluid	C_{18}	Sodium acetate buffer 0.1 M at pH 4.1 and sodium bromide 0.01 M (90:10 V/V)	1.8	100	UV	—	Runyon et al. (1991)
Plasma	Partisil ODS-3 (250 × 4 mm)	Acetate buffer 0.02 M at pH 4.3 and acetonitrile (15:85 V/V)	1.0	100	UV 254 nm	8.7	Lee and Lee (1990)
Rat plasma	RP-8 (250 × 4.6 mm^2, 10 μm)	sodium phosphate buffer 20 mM at pH 4.5) and methanol (77:23 V/V)	1.0	20	UV 254 nm, 25°C	14.6	Hakim et al. (1988)
Serum and urine	Hypersil ODS (200 × 4.6 mm^2, 5 μm)	1: Phosphate buffer 0.05 M at pH 2.1 and methanol (80:20 V/V) 2: Acetate buffer 0.1 M at pH 4.1 and methanol (80:20 V/V) 3: Phosphate buffer 0.05 M at pH 7.65 and methanol (83:17 V/V)	1.6	24	UV 254 nm and amperometric	± 18	Fabre et al. (1988)
API	Hypersil ODS (200 × 4.6 mm^2, 5 μm)	Acetate buffer 0.1 M at pH 4.1 and methanol (83:17 V/V) with 0.01 M of NaBr	1.8	24	Electrochemica, +0.4 V with reference electrode Ag/AgCI/KCl and UV 254 nm, 20°C	13.5	Fabre and Kok (1988)
Serum	Resolve (100 × 8 mm^2, 5 μm)	Phosphoric acid 0.1% and acetonitrile (10:90 V/V)	1.0	20	UV 254 nm	—	Adamivics (1987)
Serum	Nucleosil CIS (150 × 4.6 mm^2, 5 μm)	1: Dihydrogen phosphate sodium 47 mM + sodium dodecil sulfate 80 mm:phosphoric acid 2-propanol 3 mM at pH 3.3 (92:8 V/V) 2: Dihydrogen phosphate sodium 45 mM + sodium dodecil sulfate 80 mM : phosphoric acid 2-propanol 5 mM at pH 3.1 (92:8 V/V) 3: Dihydrogen phosphate sodium 40 mM + sodium dodecil sulfate 80 mm:phosphoric acid 2-propanol 10 mM at pH 2.9 (92:8 V/V)	1.0	100	UV 260 nm	23	Haginaka et al. (1987)
Serum, urine and bile	Ultrasphere ODS (250 mm or 150 × 4.6 mm^2, 5 μm)	Ammonium acetate 20 mM and acetonitrile at pH 5 (92:8 V/V)	1.0	20	UV 254 nm	8.4	Jehl et al. (1987)
API	MOS-Hypersil (10 × 0.3 mm^2, 5 μm)	Buffer (citric acid 0.0011 M + disodium phosphate 0.031 M with force 0.083) at pH 7.65 + water (1:3 V/V) and methanol (93:7 V/V)	0.8	10	UV 254 nm, 25°C	17.5 and 14	Fabre et al. (1986)
Hemolyzate blood	μ-Bondapak C_{18}	Sodium phosphate buffer 0.1 M at pH 6.1 and acetonitrile 8% (92:8 V/V)	2.0	—	UV 299 nm	—	Welch and Bawdon (1986)
Plasma and urine	SC-02 (125 × 4.6 mm^2, 10 μm)	Ammonium acetate 0.2% and methanol (5:1 V/V)	—	10	UV 254 nm	—	Togashi (1985)
Plasma and urine	$C_{18}\mu$Bondapak (300 × 4.5 mm^2, 10 μm)	Phosphoric acid 0.007 *M* and acetonitrile (85:15 V/V)	1.3	20	UV 254 nm	8.7	
Urine	Radial-Pak C_{18} (100 × 8 mm; μm)	Water and acetonitrile (83:17 V/V)	4.0	5—20	UV 270 nm	6.03	Demotes-Mainard et al. (1984)
Plasma and urine	LiChrosorb RP-18 (120 × 4.7 mm^2, 5 μm)	Buffer dihydrogen phosphate potassium 0.2 mol/L and methanol (20:80 V/V)	1.0	20	UV 254 nm	Method 3: 10, method 4: 40	Lecaillon et al. (1982)
Serum and bile	Hibar RT 250—4 LiChrosorb RP 18 (250 × 4 mm^2, 7 μm)	Dihydrogen phosphate sodium 20 mM in water, methanol and acetonitrile (83:7:10 V/V/V)	1.5	—	UV 254 nm	4.8	Kees et al. (1981)
Plasma and urine	ODS Spherisorb (100 × 3 mm^2, 5 μm)	Water, methanol and glacial acetic acid (87:12:1 V/V)	1.1	20	UV 262 nm	14 and 18	Dell et al. (1981)

organic impurities content and the test for injectable solution and lyophilized powder for solution for injection are performed under the same conditions as the content for the raw material (United States Pharmacopeia Convention, 2014).

The British Pharmacopoeia presents monographs for API (active pharmaceutical ingrediente) and injectable solution. The monograph for API presents tests for assay and related substances by HPLC under the same analysis conditions: C_{18} column with dimensions 150 × 3.9 mm^2, 5 μm, temperature of 30°C, mobile phase buffer phosphate solution with pH adjusted to 6.25 with phosphoric acid and methanol with gradient elution, flow rate 1.0 mL/min and a UV detector at 235 nm. The monograph for the injectable solution includes related substances testing and content by HPLC analysis under the following conditions: C18 column with dimensions 250 × 4.6 mm^2, 5 μm, temperature 25°C, mobile phase phosphate buffer with pH adjusted to 7.0 with phosphoric acid and methanol 100: 37.5 (V/V), flow rate 1.0 mL/min and a UV detector at 235 nm (The Stationary Office, 2014).

HPLC provides good precision and accuracy in the analysis. It is a separation technique and there are many possibilities of mobile phases, stationary phases and detectors, which permit an excellent selectivity and analysis of different compounds simultaneously. Among the methods for the drug in literature, the majority use buffer solution in the mobile phase, with consequent precipitation in the equipment and chromatographic column over time, reducing their life time and improving the analysis cost (Moreno and Salgado, 2008, 2012; Pedroso and Salgado, 2014; Rugani and Salgado, 2014).

The reported methods by spectrophotometry and HPLC for cefotaxime quantification use considerable amounts of toxic reagents and solvents by the operator and the environment, which have a great environmental impact considering the waste generatied. With the growing concern about these matters, exploring the reduction of the use of compounds that require waste treatment and great care for the operator's safety is increasingly demanded by pharmaceutical industries and academic analysis. Thus, the application of green chemistry, sustainability and reduced waste generation in analytical chemistry and quality control procedures is helpful for the preservation of the environment and to provide a better quality of life for analysts and for the population in general (Rodrigues and Salgado, 2016).

The HPLC and spectrophotometry techniques should be used with conscience by the analyst, trying to reduce the use of toxic reagents and solvents applying some of the principles of green chemistry, as using automatic and miniaturized methods, replace of toxic reagents and solvents, reducing the use of samples and the number of samples, avoiding sample treatment, when it is possible, and using sustentable, renewable and biodegradable solvents (Galuszka et al., 2013). Some alternative green solvents were reported in literature by Espino et al. (2016): ionic liquids, deep eutetic solventes and, recently, natural deep eutetic solvents, which have many advantages including biodegradability, low cost, low toxicity and sustainability. Other solvents such as water, ethanol, propanol and butanol should be used as an alternative (Welton, 2016).

One alternative technique of analytical method that can be employed in quantifying cefotaxime is the infrared spectroscopy. Consortti and Salgado (2017) developed and validated an analytical method for the quantification of cefotaxime in lyophilized powder by infrared spectroscopy as a green alternative to HPLC and spectrophotometry.

The method used the absorbance relative to the peak height in the region from 1825 to 1740 cm^{-1} in the sodium cefotaxime spectrum (relative to the stretching of the double bond between carbon and oxygen (carbonyl) of the lactam group. The method has low toxicity, cost, waste generation and toxicity for analyst, and it is able to quantify the drug with confidence, which makes it a green alternative method for use in quality control routine.

Conclusion

The development of an ideal antibiotic with high safety and efficacy and low toxicity and microorganism resistance remains a challenge.

This paper conducted a detailed critical review of the methods for the analysis of cefotaxime sodium in different matrices (such as plasma, serum, urine, milk and medicines) and a large number of methods employing HPLC and spectrophotometry in the UV and visible regions were observed.

Despite the advantages of the techniques and methods used, most of them include the use of toxic solvents introduced in the environment and to which the operator is exposed; in addition, they generate a large amount of waste. In light of the growing awareness of the need to adopt green procedures, developing new methods to reduce the use of these consumables and waste generation for pharmaceuticals analysis is of great value.

Relevant points to consider in the analytical methods for quantifying cefotaxime in biological matrices are the complexity, the amount of analyte and the need for sample treatment, usually with harmful solvents and reagents to operator and environment. It is not always possible to replace and reduce the use of these solvents and reagents and miniaturize the samples.

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