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Review

Analysis of cephalosporin antibiotics

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Abstract

A comprehensive review with 276 references for the analysis of members of an important class of drugs, cephalosporin antibiotics, is presented. The review covers most of the methods described for the analysis of these drugs in pure forms, in different pharmaceutical dosage forms and in biological fluids.

Keywords: Cephalosporins; Analytical methods; Pharmaceutical analysis; Biological analysis

Contents

1. Introduction

The discovery of cephalosporins was not a matter of luck. The requirements during World War II stimulated the search for antibiotics produced by micro-organisms. Despite the relatively extended knowledge on these drugs, their qualitative and quantitative analysis still gives rise to many problems. These difficulties are due to the chemical instability of the common β-lactam nucleus and the minor differences in chemical structures between the analogues. Monographs in the '*Analytical Profiles of Drug Substances*', series, were published for cefalotin sodium [1], cefazolin [2], cefalexin [3], cefradine [4], cefaclor [5], cefamandole naftate [6], cefotaxime [7], cefoxitin sodium [8], ceftazidime [9], cefuroxime sodium [10], cefiixime [11] and ceftriaxone sodium [12]. In the last few years, there was no review published covering all different analytical methods used for the determination of cephalosporin antibiotics. The high importance of this class of drugs prompted us to review the most important recent methods for their analysis in pure forms, in different pharmaceutical dosage forms and in biological fluids. Because of the large number of references that appeared as individual methods or as part of clinical and pharmacological studies, it is possible

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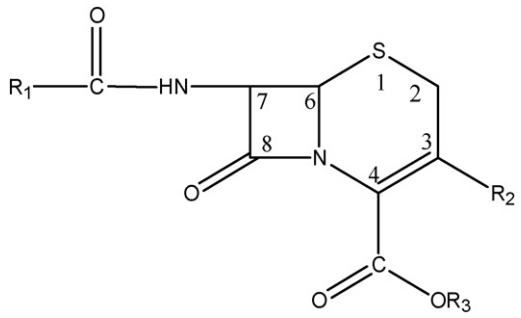


Fig. 1. General chemical structure of cephalosporin antibiotics.

to make reference only to the most important papers. The present review comprises references covering the period from 1990 till 2007.

2. Chemistry

The cephalosporins consist of a fused β-lactam-Δ^3-dihydrothiazine two-ring system, known as 7-aminocephalosporanic acid (7-ACA), and vary in their side chain substituents at C_3 (R_2), and C_7 (acylamido, R_1) (Fig. 1). The molecule has a butterfly shape, resulting in a deviation of 0.02–0.03 nm of the β-lactam N-atom from the plane defined by the substituents. The inherent strain of the four-membered β-lactam ring and distortion of the planar geometry in the bicyclic system (resulting in the loss of acylamide resonance) are commonly thought to be essential factors for the high chemical reactivity of these compounds, but Page [13] demonstrated in a critical analysis that the mentioned factors are less important for the reactivity and biological activity than supposed. In the opinion of this author more important factors are essential for biological activity as transport in biological system, binding of the antibiotic to the receptor site and inhibition of the relevant enzyme systems. Besides the β-lactam ring, the substituents at C_3, C_4 and C_7 are also important factors for their biological activity. The carboxyl group at C_4 must be unsubstituted, while the acylamido side chain at C_7 is a key group governing largely the hydrophilic/hydrophobic character of these compounds [13].

3. Classification

Cephalosporins can be divided into first, second, third and fourth generation agents, based roughly on the time of their discovery and their antimicrobial properties (Tables 1–3). In general, progression from first to fourth generation is associated with a broadening of the Gram-negative antibacterial spectrum, some reduction in activity against Gram-positive organisms, and enhanced resistance to β-lactamases. Individual cephalosporins differ in their pharmacokinetic properties especially plasma protein binding and half-life, but the structural basis for these differences are not obvious.

4. Physico-chemical and pharmacokinetic properties

The pharmacokinetic properties of cephalosporin antibiotics were reported [14,15] and they are almost identical. Table 4 summarises the properties of some of them. They have large volume of distribution and are eliminated mainly by renal excretion and to a greater or lesser extent depending on the compound and metabolic conversion. Within this generalisation, there are quite large differences between the individual compounds.

5. Official methods of analysis

The *United States Pharmacopeia XXX* [16] prescribes a polarographic method for the assay of cefamandole naftate and HPLC methods for the assay of the other cited cephalosporins while the *European Pharmacopeia 2002* [17] prescribes HPLC methods for their assay.

6. Reported methods of analysis

6.1. Analysis in bulk drug and dosage forms

6.1.1. Spectroscopic methods

6.1.1.1. Ultraviolet spectrophotometric methods. Cefotaxime, ceftriaxone and ceftazidime were determined in the presence of their alkali-induced degradation products through spectrophotometric full spectrum quantitation over the range of 265–230 nm [18]. Mixtures of ceftazidime, cefuroxime sodium, cefotaxime sodium and their degradation products were analysed by first-derivative spectrophotometry at 268.6, 306, 228.6 nm, respectively [19]. Cefotaxime and cefuroxime were determined through the reaction with 1-chlorobenzotriazole and the absorbance was measured at 298 nm [20].

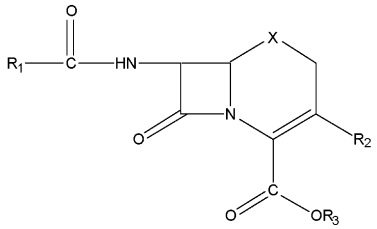
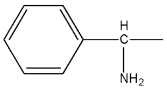
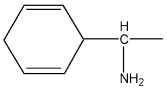
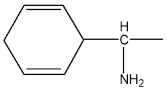
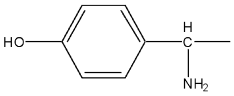
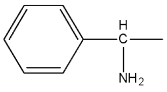
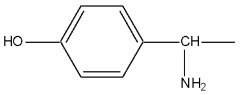
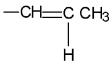
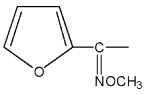
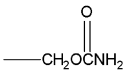
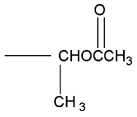
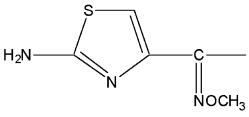
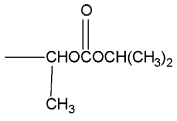
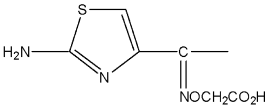
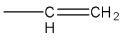
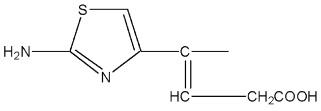
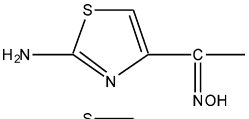
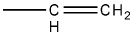
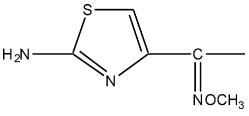
UV, first-derivative, second-derivative and H-point standard addition methods were applied for the determination of cefalexin in pharmaceutical preparations [21]. Derivative spectrophotometry was also applied for the determination of some cephalosporins in binary mixtures [22].

A spectrophotometric method was reported for the determination of cefalexin bulk drug and its acid-induced degradation products [23]. UV spectrophotometry [24] and difference UV spectrophotometry [25] were applied to determine cefalexin in tablets.

In addition, derivative spectrophotometry was used to determine the triethylammonium salt of cefotaxime in the presence of related compounds resulting from the synthesis [26].

Dissociation constants of cefepime and cefpirome were determined by UV spectrometry [27]. Cefuroxime axetil and probenecid were simultaneously determined in solid dosage forms by UV spectrophotometric method [28]. Derivative spectrophotometry was reported for the determination of cefprozil in pharmaceutical dosage forms in the presence of its alkali-induced degradation products [29]. Binary mixtures of cefalotin and cefoxitin were determined by first-derivative spectrophotometry [30].

Table 1
List of chemical structures of the oral cephalosporin antibiotics

Name	R_1	R_2	R_3	X	Generation
A. Oral cephalosporin					
Cefalexin		$-CH_3$	–H	–S–	First
Cefradine[a]		$-CH_3$	–H	–S–	First
Cefroxadine		$-OCH_3$	–H	–S–	First
Cefadroxil		$-CH_3$	–H	–S–	First
Cefaclor		–Cl	–H	–S–	Second
Cefprozil			–H	–S–	Second
Cefuroxime axetil				–S–	Second
Cefpodoxime proxetil				–S–	Third
Cefixime			–H	–S–	Third
Ceftibuten		–H	–H	–S–	Third
Cefdinir			–H	–S–	Third
Cefetamet		$-CH_3$	–H	–S–	Third

[a] Oral and parenteral.

6.1.1.2. Visible spectrophotometric methods. The reported visible spectrophotometric methods for the determination of cephalosporins could be classified according to the following reactions:

(a) Metal complexation;
(b) Charge-transfer complexation;
(c) Redox reactions;
(d) Degradation followed by reaction with colouring reagents;

Table 2
List of chemical structures of the parenteral cephalosporin antibiotics

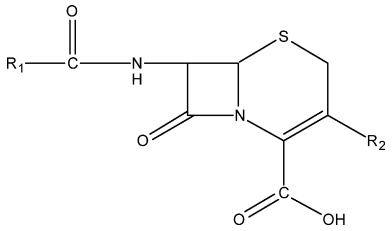
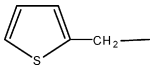
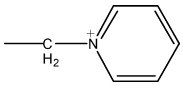
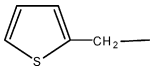
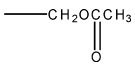
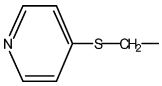
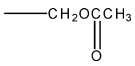
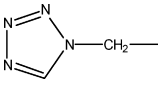
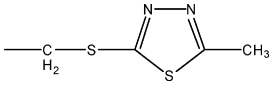
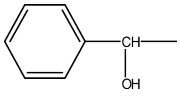
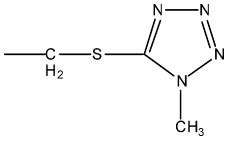
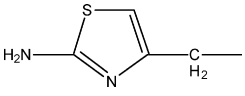
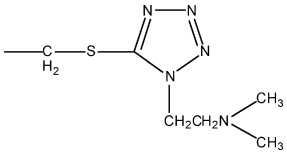
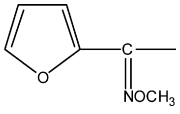
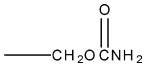
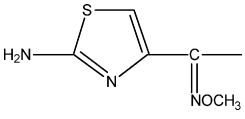
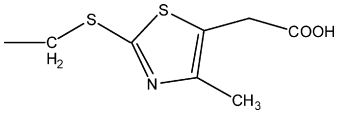
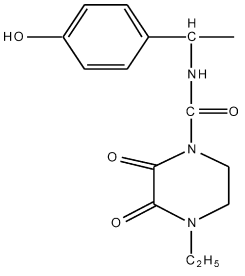
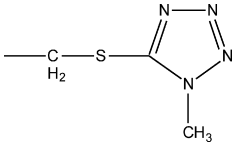
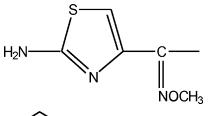
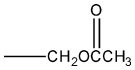
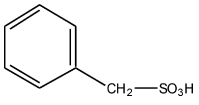
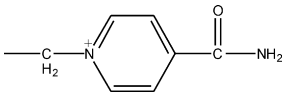
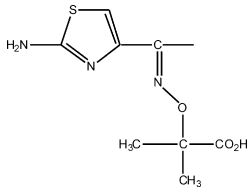
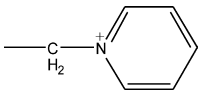
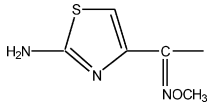
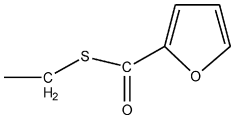
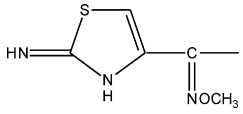
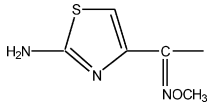
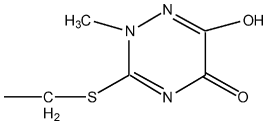
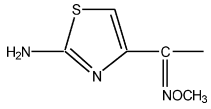
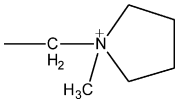
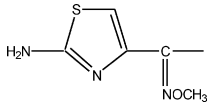
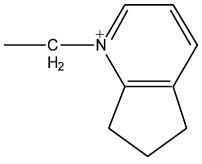
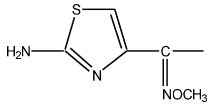
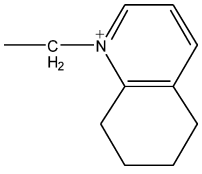
Name	R_1	R_2	Generation
B. Parenteral cephalosporin			
Cefaloridine			First
Cefalotin			First
Cefapirin			First
Cefazolin			First
Cefamandole			Second
Cefotiam			Second
Cefuroxime			Second
Cefodizime			Third
Cefoperazone			Third
Cefotaxime			Third
Cefsulodin			Third

Table 2 (*Continued*)

Name	R_1	R_2	Generation
Ceftazidime			Third
Ceftiofur[a]			Third
Ceftizoxime		–H	Third
Ceftriaxone			Third
Cefepime			Fourth
Cefpirome			Fourth
Cefquinome[a]			Fourth

[a] For veterinary use.

(e) Ion pair formation;
(f) Miscellaneous.

(a) Metal complexation

Cefpodoxime, ceftizoxime, ceftazidime, ceftriaxone and cefixime were determined using a sensitive specrophotometric method based on the formation of yellow to yellowish-brown complex with palladium(II) chloride in the presence of sodium lauryl sulfate as surfactant [31]. Ferric hydroxamate method was used for the determination of some cephalosporins; the absorbance was measured at 460 nm [32]. Cefoperazone sodium, cefadroxil monohydrate and cefprozil anhydrous were determined either through their reaction with copper(II) ion and extraction of the resulting chelate into chloroform or through their nitrosation and subsequent copper(II) chelation [33]. Cefaclor was determined through the formation of nickel(II) complex [34].

(b) Charge-transfer complexation

Charge-transfer complexation between cephalosporins as electron donors and certain π-acceptors formed the basis of several spectrophotometric methods. Saleh et al. [35] used ρ-chloranilic acid (ρ-CA) as π-acceptor to determine 15 cephalosporin antibiotics.

Cefapirin sodium, cefazolin sodium, cefalexin monohydrate, cefadroxil monohydrate, cefotaxime sodium, cefoperazone sodium and ceftazidime pentahydrate were determined through charge-transfer complexation reaction using σ-acceptor such as iodine and some π-acceptors such as 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) and 7,7,8,8-tetracyanoquinodimethane (TCNQ) [36]. DDQ, TCNQ and ρ-CA were used for the determination of cefepime and cefprozil; the absorbance was measured at 460, 841 and 527 nm, respectively [37].

Cefradine and cefalotin sodium were determined with either iodine in 1,2-dichloroethane, measuring the absorbance at 295 and 365 nm, respectively, or DDQ in methanol, measuring the absorbance at 460 nm [38]. Cefotaxime sodium and cefuroxime sodium were determined separately and in their dosage forms using ρ-CA and TCNQ [39].

Table 3
List of chemical structures of the parenteral cephamycins antibiotics

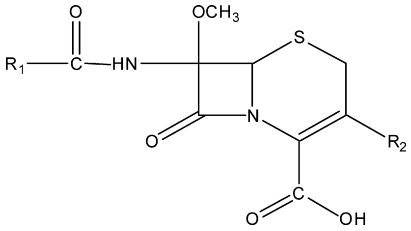
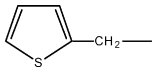
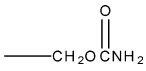
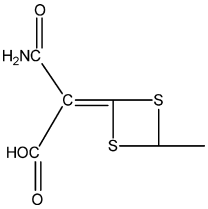
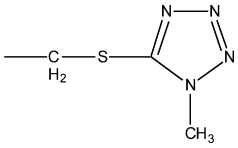
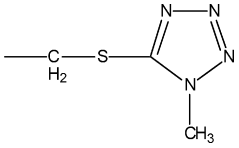
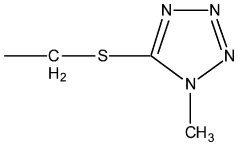
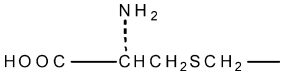
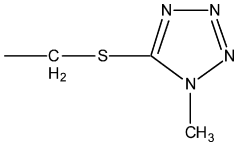
Name	R_1	R_2	Generation
C. Parenteral cephamycins			
Cefoxitin			Second
Cefotetan			Second
Cefmetazole			Second
Cefminox			Second

Table 4
Physico-chemical and pharmacokinetic properties of cephalosporin antibiotics

Drug	pK_a	Salt forms	Elimination half-life (h)	Protein binding (%)	Urinary excretion
Cefaclor	8.03	Monohydrate	0.5–1	24.7	85%, unchanged
Cefadroxil	2.6, 7.3	Anhydrous	1.5	20	90%, unchanged
Cefalexin	5.3, 7.3	Monohydrate, hydrochloride	1	6–15	80%, unchanged
Cefalotin	2.2	Sodium	0.25–0.89	65	70%, unchanged and as metabolite
Cefamandole	2.46	Naftate	0.5–1.5	65–74	80%, unchanged
Cefazolin	2.1	Sodium	1.8	74–86	80%, unchanged
Cefixime	2–2.5	Anhydrous	2.5–3.8	70	
Cefodizime	2.85, 3.4, 4.2	Disodium	2.4–402	73–89	80%, unchanged
Cefotaxime	3.75	Sodium	0.9–1.3	40	40–60%, unchanged, 20%, deacetylated
Cefoxitin	3.5	Sodium	1	65–80	85%, unchanged
Cefpirome	–	Sulphate	1.4–2.3	8.2–11.7	80–90%, unchanged
Cefpodoxime	3.2	Proxetil	1.9–3.2	21–29	40%, unchanged
Cefprozil	2.8, 7.3, 9.7	Monohydrate	1–1.4	36–44	60%, unchanged
Cefradine	2.6, 7.3	Anhydrous	Oral (0.7), intramuscular (2–3)	<10	90% of oral dose and 60–80% of intramuscular dose, unchanged
Ceftazidime	1.8, 2.7, 4.1	Pentahydrate	1.8–2.2	10	80–90%, unchanged
Ceftizoxime	2.95	Sodium	1.3–1.6	30	Nearly all the dose, unchanged
Ceftriaxone	3, 3.2, 4.1	Disodium	6–9	95	40–65%, unchanged
Cefuroxime	2.5	Sodium and axetil	1.25	30	35%, unchanged

(c) Redox reactions

Redox reactions have been used as the basis for many spectrophotometric methods for the determination of cephalosporin antibiotics. Saleh [40] reported a method for the determination of cefadroxil and amoxycillin with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) as the oxidizing agents in alkaline medium. Potassium iodate was also used for the determination of some cephalosporins [41]. Ten cephalosporins were determined through their oxidation using known excess of cerium(IV) in sulphuric acid; the unreacted cerium(IV) was measured at 317 nm [42]. Cefotaxime and cefuroxime were determined through their reaction with Ce(IV), the remaining Ce(IV) was determined by its reaction with ρ-dimethylaminobenzaldehyde (ρ-DMAB) [20].

Another method was proposed for the determination of cefoperazone sodium, cefadroxil monohydrate and cefprozil anhydrous in their pure forms based on selective oxidation of these drugs with either Ce(IV) or Fe(III) in acid medium to give an intense yellow coloured product [43]. Two colorimetric methods were developed for determination of six cephalosporins depending on their reaction with 2,3,5-triphenyltetrazolium chloride or blue tetrazolium to produce highly coloured formazans [44]. Cefotaxime sodium was determined in its dosage forms by heating with iron(III) and *o*-phenanthroline [45].

Al-Momani [46] proposed a spectrophotometric method to determine seven cephalosporins in drug formulation using flow injection analysis based on hydrolysis of these drugs with 0.1 M sodium hydroxide and subsequent oxidation with Fe(III), the produced Fe(II) was then complexed with *o*-phenanthroline and measured spectrophotometrically.

Sastry et al. [47] reported three spectrophotometric methods for the determination of cefadroxil using oxidative coupling reactions. Amin and Ragab [48] proposed a method for the determination of cefotaxime sodium, cefuroxime sodium and ceftriaxone disodium with metol–chromium(VI) reagent. Based on the same principle, a spectrophotometric method was reported for the determination of some cephalosporins with leuco crystal violet [49].

(d) Degradation followed by reaction with colouring reagent(s)

Cefalexin, cefadroxil and cefaclor were determined in their pharmaceutical preparations using sensitive and selective colorimetric method based on measuring the colour obtained when the alkaline degradation products of these drugs were allowed to react with ascorbic acid [50].

Cefalexin and cefadroxil were determined by the reaction of *p*-aminophenol with sulphide ions produced by the alkaline hydrolysis of these drugs in presence of an oxidant to produce a blueish violet colour measured at 550 nm [51].

Cefadroxil and cefotaxime were determined by flow injection spectrophotometry based on the hydrolysis of the two cephalosporins with sodium hydroxide and the produced sulphide ion was allowed to react either with *N*,*N*′-diethyl-*p*-phenylenediamine and Fe(III); the blue colour produced was measured at 670 nm or with *p*-phenylenediamine and Fe(III); the violet colour produced was measured at 597 nm [52]. Cefadroxil and ceftizoxime were determined through the addition of sodium hydroxide followed by iodine and wool fast blue BL; the absorbance was measured at 540 nm [53]. Cefadroxil was determined kinetically by measuring the absorbance at 470 nm [54].

A spectrophotometric method was proposed for the determination of cefaclor based on alkaline hydrolysis of the drug in ammonia buffer solution at pH 10.0 to yield diketopiperazine-2,5-dione derivative and subsequent measurement at 340 nm [55].

A flow-injection spectrophotometric method was reported for the determination of cefalexin and cefradine in pharmaceutical formulations based on hydrolysis of these drugs in basic medium and then reduction of the formed product by the on-line generated iodine in acidic medium, the decrease in the intensity of iodine colour was monitored at 460 nm [56]. Cefalexin, cefapirin sodium, cefazolin sodium, and cefotaxime were determined in pure samples and in pharmaceutical preparations by acid hydrolysis of these drugs and subsequent oxidation with vanadophosphoric acid, the absorbance was measured at 516 nm [57].

(e) Ion pair formation

Cefapirin, cefuroxime, cefotaxime, ceftazidime, cefadroxil, cefaclor, cefazolin and cefoperazone were determined through the formation of ion-pair complexes with ammonium reineckate; the formed precipitate was dissolved in acetone and the absorption was measured at 525 nm [58]. Cefaclor was also determined through the formation of ion-association complex with methylene blue [59].

(f) Miscellaneous

Cefoperazone sodium, cefadroxil monohydrate and cefprozil anhydrous were determined either through their nitration and subsequent complexation with a nuclophilic reagent or through their coupling with diazo reagent [33].

Cefadroxil, cefradine and cefaclor were determined after treatment with glucitol and sodium hydroxide [60]. Cefadroxil and amoxycillin were determined in dosage forms through coupling with diazotized benzocaine and the absorbance of the orange–yellow colour species was measured at 455 nm [61].

A spectrophotometric method for quantitative determination of 7-aminocephalosporanic acid resulting from direct hydrolysis of cephalosporin C with ρ-DMAB was reported; the absorbance was measured at 414 nm [62]. Cefotaxime sodium was determined through its reaction with 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH) in the presence of ferric chloride to form a blue coloured chromogen measured at 690 nm [63].

Abdellatef et al. [64] described a method for colorimetric determination of some cephalosporins in their pure and dosage forms based on the reaction of these drugs with 4-chloro-7-nitobenzofurazan (NBD-Cl). Cefadroxil and Cefalexin were determined in their dosage forms through the reaction with Folin-Ciocalteu reagent to form a blue coloured chromogen [65,27].

Also Folin-Ciocalteu reagent was used for the determination of cefoperazone sodium in pharmaceutical formulations, the absorbance was measured at 668 nm [66]. Cefotaxime sodium was determined in its dosage forms through the reaction of the drug with nitrous acid under alkaline conditions to form a stable violet coloured chromogen with absorption maximum of 560 nm [45].

A spectrophotometric method has been developed for determination of cefadroxil in bulk powder and its pharmaceutical dosage forms based on the reaction of primary amine group with acetylacetone–formaldehyde reagent, which gives a yellow coloured chromogen [67]. Another method was reported for the determination of cefadroxil in pharmaceutical dosage forms through mixing with sulfanilic acid; the absorbance was measured at 440 nm [68].

A comparison of various calibration techniques applied to the ninhydrin-cefoxitin determination was reported, the absorbance of the product obtained from the reaction of cefoxitin with ninhydrin in the presence of sulphuric acid was measured from 300–600 nm [69]. A sequential injection analysis (SIA) for the reaction between cefadroxil and 4-aminoantipyrine in the presence of alkaline potassium hexacyanoferrate(III) to produce a red colour measured at 510 nm has been developed [70].

6.1.1.3. Spectrofluorometric methods. The spectrofluorometric methods for the determination of cephalosporins may be subclassified into the following categories:

(a) Methods based on measurement of the fluorescence of the hydrolytic products;
(b) Methods depending on redox reactions;
(c) Methods depending on reaction with fluorogenic agents;
(d) Fluorescence quenching methods;
(e) Miscellaneous methods.

(a) Methods based on measurement of the fluorescence of the hydrolytic products

Cefalotin gave rise to a fluorescent product when its methanolic solution was incubated for prolonged time periods, the process also occurred in the presence of metal ions [71,72].

Cefadroxil, cefradine and cefotaxime sodium were determined through mixing with sodium hydroxide and heating at 100 °C [73]. Cefalexin, cefaclor and cefradine were determined in formulations by measuring the fluoresence at 416, 417 and 418 nm, respectively [74].

Cefalexin and cefadroxil were determined by using the coupling technique of synchronous fluorometry and H-point standard addition methods [75]. A photochemical fluorometric method was reported for the determination of cefradine; the fluorescence was measured at 442 nm [76].

(b) Methods depending on redox reaction

Cefradine, cefalexin and cefazolin were determined by a luminescence method based on the luminescence of the produced Ce(III) formed after oxidation of the studied drugs by Ce(IV); the luminescence intensity was measured at 355 nm (excitation at 297 nm) [77]. The same technique was used for the determination of 10 cephalosporins [42].

(c) Methods depending on reaction with fluorogenic agents

Hefnawy et al. [78] reported a fluorometric method for the determination of cefaclor, cefadroxil, cefalexin and cefradine on the basis of the reaction of the target compounds with fluorescamine at a specific pH. Cefalor was determined spectrofluorometrically based on the derivatization of the drug with 4-(2′-cyanoisoindolyl) phenylisothiocyanate [79].

(d) Fluorescence quenching methods

Cefadroxil and cefradine were determined in pharmaceutical formulations by fluorescence quenching after mixing each drug with fluorescein-Hg and 1 M sodium hydroxide [80]. Bebawy et al. [81] proposed a method for the determination of four cephalosporins which involved the formation of ternary complex with terbium(III) in the presence of Tris buffer.

(e) Miscellaneous methods

El-Walily et al. [82] proposed a selective fluorometric method for the determination of phenolic β-lactam antibiotics through the formation of their coumarin derivatives based on the reaction between these drugs and ethylacetoacetate, in acidic medium, to give yellow fluorescent products with excitation wavelengths ranging from 401 to 467 nm and emission wavelengths ranging from 465 to 503 nm. Some α-aminocephalosporins, namely cefradine and cefalexin, were determined in pure and pharmaceutical forms through the reaction with acetyl acetone-formaldehyde at pH 4.0, in which the product can emit strong fluorescence [83].

6.1.1.4. Chemiluminescence methods. Cefalotin was determined by the reaction of this drug with luminol in the presence of potassium hexacyanoferrate(III) as a catalyst/co-oxidant and potassium hexacyanoferrate(II) as an emission depressor in an alkaline solution [84,85]. Another chemiluminescence method was reported for the determination of cefalotin based on the ability of this antibiotic to prolong and intensify the chemiluminescence derived from the cobalt(II)-luminol-hydrogen peroxide system [86].

Li and Lu [87] proposed a flow-injection chemiluminescence method for the determination of β-lactam antibiotics based on injection of these drugs into a stream of potassium permanganate with alkaline luminol. Four cephalosporin antibiotics were determined by a flow-injection chemiluminescence method based on enhancement of the chemiluminescence arising from the reaction of luminol with potassium iodate in alkaline solution [88].

Cefadroxil was determined by a flow-injection chemiluminescence method based on the chemiluminescence emitting reaction between cefadroxil and potassium permanganate in sulphuric acid medium, enhanced by formaldehyde [89]. Sun et al. [90] proposed a flow-injection chemiluminescence method for the determination of three cephalosporin antibiotics based on the ability of these antibiotics to enhance chemiluminescence reaction of glyoxal and potassium permanganate in sulphuric acid medium.

A flow-injection method using the tris(2,2′-bipyridyl) ruthenium(II)–potassium permanganate chemiluminescence

was reported for the determination of some cephalosporin antibiotics [91,92]. Aly et al. [93] proposed a method for determination of cefadroxil in pharmaceutical samples and biological fluids based on flow injection chemiluminescence reaction of cefadroxil with potassium permanganate in sulphuric acid, sensitized by quinine. Electrogenerated chemiluminescence coupled to a flow injection analysis system was used for the determination of cefadroxil using tris (2,2′-bipyridine) ruthenium(II) complex, whose luminescence increased with the presence of the cefadroxil [94].

6.1.1.5. Atomic absorption spectrometric methods. Cefotaxime sodium and Cefuroxime sodium were analysed by atomic absorption spectrometry after their alkali-hydrolysis and subsequent reaction with silver nitrate or lead acetate in neutral aqueous medium [39]. Salem and Askal [58] reported a method for the determination of eight cephalosporins through the formation of ion pair complexes between these drugs and ammonium reineckate, the formed precipitates were determined by atomic absorption spectrophotometric procedure through the chromium precipitate formed or the residual unreacted chromium in the filterate.

6.1.2. Chromatographic methods

6.1.2.1. Thin-layer chromatographic methods. Cefradine and cefalotin were determined by spectrodensitometric method after contact with iodine vapours [38]. Cephalosporins were applied to TLC plates coated with a mixture (2:1) of layered double hydroxide of aluminum(III) and magnesium(II) and silica gel G and developed with a range of mobile phases, the spots were detected with iodine vapours and the cephalosporin content was determined [95].

Degradation products of ceftazidime, cefuroxime sodium and cefotaxime sodium were prepared by acid hydrolysis, mixtures of these drugs and their degradation products were analysed by quantitative densitometric TLC [19]. Some cephalosporins in phosphate buffer of pH 3.6 were spotted on TLC plates coated with silica gel with a fluorescent indicator or silica gel RP 18, the spots were visualized at 254 nm or with a colour-forming agent [96].

Ceftriaxone, cefixme, cefotaxime, cefaclor and cefalexin were determined in their pharmaceutical dosage forms using HPTLC and the measurement of each spot was carried out at specified wavelengths using a scanner in absorbance/reflectance mode [97,98]. Shabadi et al. [99] reported a method for simultaneous determination of cefadroxil and cefalexin in pharmaceutical preparations using quantitative TLC. Cefalexin was analysed by HPTLC on silica gel F_{254} plates. The plates were scanned in reflectance mode at 263 nm [100].

Cefuroxime axetil and cefuroxime were determined using TLC densitometry after separation on silica gel using chloroform/ethyl acetate/glacial acetic acid/water (4:4:4:1) as a mobile phase [101].

Dhanesar [102–104] proposed a densitometric method for quantitation of some cephalosporins on a hydrocarbon impregnated silica gel HPTLC plate.

Simultaneous determination of cefalexin and probencid in pharmaceutical preparation was performed by HPTLC using silica Gel 60 F_{254} HPTLC plate and they were detected at 254 nm [105]. Also HPTLC method was used for the determination of ceftriaxone in injection solutions using butanol/acetonitrile/water (3:1:1) as developing solvent and detection at 254 nm [106].

6.1.2.2. High-performance liquid chromatographic methods. The impressive increase in the use of high-performance liquid chromatography in the past thirty years did not pass the β-lactam antibiotics. HPLC has been used frequently in all fields of β-lactam research, not only as an assay method but also as a tool for purification of the antibiotics. Due to the insolubility of these compounds in organic solvents, normal phase LC was sparingly used. Most methods employ reversed-phase or ion-pair reversed-phase LC and chemically bonded packing materials. Table 5 summarises some of the recently reported methods for the analysis of cephalosporins in pure forms and pharmaceutical formulations.

6.1.2.3. Capillary electrophoretic methods. They are classified into:

(a) Capillary zone electrophoresis (CZE);
(b) Micellar electrokinetic capillary chromatography (MEKC);
(c) Isotachophoresis.

(a) Capillary zone electrophoresis (CZE)

Cefotaxime and cefotiam were determined by CZE using applied voltage of +30 kV, with an electrolyte of 0.1 M sodium phosphate buffer of pH 8.0 and detection at 210 nm [144]. CZE was used for the determination of ceftazidime using fused-silica capillary operated at an applied voltage of 20 kV [145]. CZE was used for the determination of the dissociation constants of nine cephalosporins using fused-silica tube operated at an applied voltage of 30 kV [146].

Cefotaxime and its major degradation products were analysed by CZE using fused-silica capillary operated at an applied voltage of 15 kV [147]. CZE was described for the analysis and a stability study of fourteen cephalosporins [148].

(b) Micellar electrokinetic capillary chromatography (MEKC)

A method validation was reported for the determination of the β-lactamic antibiotic cefradine and its main impurity, cefalexin, by MEKC with UV photometric detection [149]. Cefalexin and its related substances were determined by MEKC using fused-silica capillary and detection was performed at 254 nm [150].

Ceftazidime and related compounds were determined by MEKC using uncoated silica capillary operated at an applied voltage of 20 kV and detection at 205 nm [151]. Li et al. [152] reported a MEKC method for the determination of cefadroxil using fused-silica capillary operated at an applied voltage of 18 kV and detection was performed at 254 nm.

Steppe et al. [153] proposed a method for determination of cefalexin in oral suspension using a bare silica capillary

Table 5
HPLC methods for the determination of cephalosporins in pure and pharmaceutical dosage forms

Drug(s)	Column	Mobile phase	Detection	Ref.
Cefaclor	TSK gel ODS-80TM	35% Acetonitile and 10% 0.1 M triethylamine, pH 8.5	Fluorescence (310 and 410 nm) and chemiluminescence	[107]
	YMC ODS	Aqueous 0.69% sodium dihydrogen phosphate pH 4.0/acetonitrile	UV, 220 nm	[108]
Cefadroxil	(a) Alkyl bonded phase C_{18}	(a) Acetonotrile/0.272% potassium hydrogen phosphate	UV, 230 nm	[109]
	(b) poly(styrene-divinylbenzene)	(b) Acetonitrile/0.02 M sodium-1-octanesulfonate/0.2 M phosphoric acid/water		
		Water/acetonitrile/0.02 M sodium octanesulfonate/0.2 M phosphoric acid (129:21:40:10) Poly(styrene-divinylbenzene)	UV, 254 nm	[110]
	Ultrasphere C_8	Sodium phosphate buffer pH 2.6/methanol (17:3)	UV, 230 nm	[111]
Cefalexin	Microbondapak C_{18}	Methanol/1.25% acetic acid (1:3)	UV, 254 nm	[112,113]
	PLRS-S	Acetonitrile/0.02 M sodium-1-octanesulfonate/0.2 M phosphoric acid/water (31:20:10:139)	UV, 254 nm	[114]
Cefdinir	TSKgel ODS-80	33 mM Citrate-phosphate buffer pH 2.0/methanol/dioxane (36:4:1)	UV, 254 nm	[115]
Cefetamet	C_{18} absorposphere	Water/acetonitrile/methanol/phosphate buffer pH 3.5 (50:35:10:5)	UV, 254 nm	[116]
Cefpodoxime	C_{18}	20 mM Ammonium acetate buffer pH 5.0/acetonitrile (62:38)	UV, 235 nm	[117]
Cefradine	(a) Alkyl bonded phase C_{18}	(a) 2 M Acetic acid/sodium acetate/methanol/water (1:17:200:782)	UV, 254 nm	[118]
	(b) Poly(styrene-divinylbenzene)	(b) Acetonitrile/0.02 M sodium-1-octanesulfonate/0.2 M phosphoric acid/water (3:2:1:up to 20)		
Ceftazidime	Ultrasphere ODS	0.01 M Ammonium acetate buffer/methanol (89:11)	UV, 254 nm	[119]
Cefuroxime axetil		0.1 M Potassium dihydrogenphosphate/acetonitrile (7:3), pH 4 Supelco Hypersil C_{18}	UV, 281 nm	[120]
Cefalexin and cefadroxil	Microbondapak C_{18}	Water/aceronitrile/phosphoric acid (9000:1000:146), pH 3.5	UV, 254 nm	[121]
Cefalexin and bromhexine hydrochlorie	3 μm Spherisorb	60% Methanol in water	UV, 214 nm	[122]
Cefalexin and probencid	Novapak C_{18}	Water/methanol/acetonitrile/glacial acetic acid (50:20:30:1)	UV, 254 nm	[123]
	5 μm Hypersil BDS C_{18}	0.1% Orthophosphoric acid/methanol adjusted to pH 7.5 with triethylamine (1:1)	UV, 254 nm	[124]
Cefalexin and carbocisteine	5 μm C_8 Shodex	0.025 M Sodium phosphate/acetonitrile (87:13)	UV, 210 nm	[125]
Cefalexin and 7-aminocephalosporanic acid	Hypersil ODS C_{18}	Acetonitrile/sodium dihydrogen phosphate pH 3.0 (1:9), (1:4) and (1:1)	UV, 254 nm	[23]
Cefotaxime and ceftriaxone	LiChrosirb RP-C_{18}	Acetonitrile/67 mM potassium dihydrogen phosphate pH 2.65 (1:4)	UV, 254 nm	[126]
Cefazolin and cefotaxime	Microbondapak C_{18}	Water/acetonitrile/phosphoric acid (4250:750:73)	UV, 254 nm	[127]
Ceftazidime and pyridine	Spherisorb hexyl reversed phase	Acetonitrile/0.05 M ammonium acetate pH 7.0 (7:93)	UV, 254 nm	[128]
Cefepime and metronidazole	Phenyl	Water/acetonitrile (94.5:5.5) containing 0.015 M pentane sulfonic acid sodium salt	UV, 254 nm	[129]
Cefradine and cefapirin	Vydac reversed-phase C_8	4% Acetonitrile	Pulsed amperometric	[130]
Cefotaxime, ceftazidime and ceftriaxone	Schimpack GLC-ODS	Acetonitrile/0.1 M ammonium acetate buffer (1:9), pH 7.5	UV, 270 nm	[18]

Cefalexin, cefotaxime and salbutamol	Supelcosil ODS	Methanol/phosphate buffer pH 7.0 (3:2)	UV, 215–245 nm	[131]
Cephalosporins, penicillins and lincomycins	Phenomenex luna C_8	Aqueous 90% methanol/0.5 M sodium acetate buffer pH 3.75/water/aqueous acetonitrile 90%	Pulsed electrochemical	[132]
Cefruoxime and aminophylline/theophylline mixture	Ultrasphere ODS	0.1 M Acetate buffer pH 3.4/acetonitrile (10:1)	UV, 254 nm	[133]
Cefalexin, cefadroxil, cefaclor and cefotaxime	Spherisorb ODS-2	Acetate buffer pH 4.0/methanol (78:22)	UV, 265 nm	[134]
Cefalexin, cefadroxil, cefaclor and cefotaxime	SpeedROD RP-18e	Acetate buffer pH 4.0/methanol (9:1)	UV, 265 nm	[135]
Cefazolin, ceftizoxime, cefaloridine and cefaclor	5 μm ODS C_{18}	Aqueous 40% methanol containing 0.5% of acetic acid	UV, 262 nm	[136]
Cefazolin, cefalexin, cefaloridine and cefradine	Spheri 5 ODS-224	Sodium dodecylsulphate	UV, 260 nm	[137]
Cefazolin, Cefalexin, cefadroxil, ampicillin and cefradine	Phenomenex C_{18} and ODS C_{18}	Aqueous 10% acetic acid/propan-2-ol/water (4:9:87)	UV, 240 nm	[138]
Cefadroxil, cefalexin, cefaclor, isoniazid and pyrazinamide	JASCO RP-C_{18}	0.025 M Tetrabutyl ammonium hydrogen sulphate/methanol/acetonitrile (32:1:1), pH 3.0	UV, 248 nm	[139]
Cefalexin, cefaclor, isoniazid, minocycline and pyrazinamide	JASCO Metaphase CrestPAK ODS silica	25 mM Tetrabutyl ammonium hydrogen sulphate/methanol/acetonitrile (48:1:1)	UV, 248 nm	[140]
Cefminoxime, cefprozil, cefotetan, cefotaxime, cefsulodin, ceftazidime and cefixime	Reversed phase	Acetonitrile/water	UV, 254 nm	[141]
Cephalosporins	10 μm Spherisorb ODS	0.1 M Acetate buffer pH 5.0 containing 3.5, 5, 7 or 10% of propan-2-ol	UV, 254 nm	[142]
	OmniPac PAX-500	90 mM Perchloric acid/13.5% acetonitrile to 0.3 M perchloric acid/45% acetonitrile	UV, 254 nm	[143]

operated at an applied voltage of 15 kV and detection was performed at 210 nm.

(c) Isotachophoresis

Capillary isotachophoresis was used for the determination of 12 penicillins and cephalosporins in pharmaceuticals and for the precursors 6-aminopenicillanic acid and 7-aminocephalosoanic acid, detection was performed at 254 nm [154].

6.1.3. Electrochemical methods

Cephalosporins are electrochemically active. On this basis several electrochemical methods were reported for their determination [155]. This section summarises the most recent methods reported for their analysis.

6.1.3.1. Direct potentiometry using ion-selective electrodes. Dumkiewicz et al. [156] described the preparation of ion-selective electrode with a pseudoliquid membrane phase for the determination of cefuroxime. Membrane electrodes and tubular electrodes selective for cefuroxime were constructed with different ion-exchangers and mediator solvents and evaluated for its analysis [157].

6.1.3.2. Voltammetry. Cefadroxil monohydrate was determined by differential pulse voltammetry (DPV) through electrooxidation at a glassy carbon electrode [158].

Cefaclor is not reducible at a mercury electrode, but it can be determined polarographically and by cathodic stripping voltammetry (CSV) [159]. Cefaclor was also determined in pharmaceutical formulations by CSV [160].

Electrochemical reduction of cefepime at the mercury electrode and linear relationship between peak current intensity and cefepime concentration allowed the differential pulse polarographic (DPP) determination of cefepime in pharmaceutical formulations [161]. The electrochemical reduction and electrochemical oxidation of cefoperazone and ceftriaxone were studied by differential pulse polarography and cyclic voltammetry and both antibiotics showed a single electro-oxidation peak at a carbon-paste electrode at +1.05 V (versus SCE) [162].

CSV was utilized for the determination of ceftazidime in a supporting electrolyte containing 0.45 μg ml^{-1} poly-L-lysine in Britton–Robinson (B–R) buffer pH 10.0 [163]. Electrooxidation of cefotaxime was investigated using specially activated glassy carbon (GC), platinum and carbon paste (CP) electrodes in different supporting electrolyte solutions and at different pHs. The activated glassy carbon (GC) working electrode and 0.2 M phosphoric acid as supporting electrolyte gave the best results [164].

A differential pulse polarographic (DPP) method was described for the determination of ceftazidime, ceftizoxime and ceftriaxone in pharmaceutical formulations [165]. A voltammetric method for oxidation and determination of cephalosporin antibiotics at both carbon-paste and modified fatty acid carbon-paste electrodes was described; the electroanalytical technique used was dc stripping voltammetry [166]. The polarographic behaviour of cefuroxime in various buffer solutions of pH

1.0–10.0 was investigated using a dropping Hg working electrode, a Pt wire auxiliary electrode and Ag/AgCl reference electrode [167].

Cefalexin does not give a reduction peak at a dropping mercury electrode, whereas its degradation product does, so on this basis either adsorptive stripping voltammetry (ASV) in 0.1 M NaOH was used for its determination; the peak current was directly proportional to its concentration [168]. The electrochemical behaviour of cefazolin sodium in Britton–Robinson buffers (pH 2.0–11.0) at the mercury electrode was studied by means of dc-polarography, cyclic voltammetry, controlled-potential coulometry and square-wave adsorptive stripping voltammetry techniques [169].

Adsorptive stripping voltammetry (ASV) was developed to determine cefalotin based on the adsorptive accumulation of the drug at a hanging mercury drop electrode and then a negative sweep was initiated, which yield a well defined cathodic peak at −625 mV versus Ag/AgCl reference electrode [170]. The same technique (ASV) was applied for determination of cefoperazone in different media [171]. Electrochemical reduction behaviour of cefixime and cefpodoxime proxetil has been studied by using different voltammetric techniques in Britton–Robinson buffer system [172]. The accumulation of the mercury salt of ceftazidime allowed the indirect cathodic-stripping voltammetric determination of this drug using the reduction peak of the mercury salt at −0.7 V [173].

Cefalexin was determined polarographically in pure form and in pharmaceutical preparations based on the catalytic hydrogen wave noticed in presence of cobalt(II) and the drug at a potential of −1.47 V (versus SCE) [174]. The electrooxidation of cefalexin at boron-doped diamond electrodes and glassy carbon electrodes was investigated by cyclic voltammetry [175]. Cefepime was determined by electrochemical reduction and oxidation at carbon electrode in aqueous buffer solution of pH < 8.0 [176]. Electoanalysis of cefalexin was studied in 0.1 M carbonate buffer of pH 9.2 using boron-doped diamond thin-film electrodes by cyclic voltammetry [177].

6.2. Analysis in biological fluids

6.2.1. Chromatographic methods

6.2.1.1. High-performance liquid chromatographic methods. This technique is the most frequently applied technique for the determination of cephalosporins in biological fluids (blood, plasma, urine, cerebrospinal fluid, etc.), animal tissues, food, etc. Table 6

summarises the recent HPLC reported methods for the analysis of cephalosporins in biological fluids, animal tissues, food, etc.

6.2.1.2. Capillary electophoretic methods. They are classified into:

(a) Capillary zone electrophoresis (CZE);
(b) Micellar electrokinetic capillary chromatography (MEKC).

(a) Capillary zone electrophoresis (CZE)

Nine cephalosporins were determined using capillary zone electrophoresis after hydrodynamic injection on a fused-silica capillary and detection was performed at 210 nm [178].

Mrestani et al. [179] proposed a CZE method for the determination of four cephalosporins after injection on a fused-silica capillary with detection at 270 nm and 30 kV separation potential. Cefixime and five of its metabolites were determined in human digestive tissues by high-performance capillary electrophoresis on a fused-silica capillary tube with detection at 280 nm [180].

CZE was used to determine β-lactam antibiotics, aminoglycosides, quinolones and tetracyclines in biological samples [258]. Cefotaxime and its deacetyl metabolite were determined by CZE using a fused-silica capillary with borate buffer pH 9.2 as electrolyte [259]. CZE was used for the determination of four cephalosporins in clinical samples [260].

(b) Micellar electrokinetic capillary chromatography (MEKC)

Cefuroxime was determined in human serum by MEKC using a fused-silica capillary with 150 mM sodium dodecyl sulfate in 20 mM sodium phosphate and borate (pH 9.0) as electrolyte, with applied potential of 15 kV and detection at 274 nm [261].

Yeh et al. [262] proposed a MEKC method for determination of ceftazidime in plasma and cerebrospinal fluid using Tris buffer with sodium dodecyl sulfate as background electrolyte and detection was performed at 254 nm. MEKC was used for determination of cefotaxime and its deacetyl metabolite using a fused-silica capillary with phosphate buffer pH 8.0 containing 165 mM sodium dedecylsulphate as separation electrolyte [259]. Cefpirome was estimated in human microdialysis and plasma samples by MEKC [263].

6.2.2. Electrochemical methods

Two methods (direct and indirect) based on DPP were developed for determination of ceftazidime in urine samples; the peaks were detected at −0.45 and −0.6 V for direct and indirect methods, respectively [264]. Ceftriaxone was determined by differential-pulse adsorptive stripping voltammetry in aqueous humor and serum samples [265].

Cefradine was determined polarographically by different ASV techniques in a cell fitted with a silver/silver chloride/saturated potassium chloride reference electrode and a platinum wire counter electrode [266].

A differential-pulse adsorptive stripping voltammetric method was described for the determination of ceftriaxone in plasma using mercury drop electrode [267]. The voltammetric behaviour of cefixime was studied using cyclic, linear sweep, differential pulse and square wave voltammetric techniques [268].

The electrochemical behaviour of ceftazidime at four different kinds of electrodes, namely static mercury drop electrode (SMDE), controlled growth mercury electrode (CGME), glassy carbon electrode (GCE) and carbon paste electrode (CPE) was reported [269]. Differential-pulse cathodic stripping voltammetric determination of ceftazidime with a hang-

Table 6
HPLC methods for the determination of cephalosporins in biological fluids, animal tissues, food, etc.

Drug(s)	Column	Mobile phase	Detection	Ref.
Cefaclor	Diamonsil C_{18}	Methanol/water/formic acid (80:20:1)	Tandem mass spectrometry	[181]
	Corning glass tube	0.1 N Hydrochloric acid	UV and differential pulse adsorptive stripping voltammetry	[182]
Cefadroxil	ABZ	Acetonitrile/10 mM phosphate buffer pH 7.0 (13:87)	UV, 260 nm	[183]
Cefalexin	Octadecyl	0.01 M Phosphate buffer pH 7.5/acetonitrile(92:8)	UV, 260 nm	[184]
	Microbore reversed-phase	Methanol/100 mM monosodium phosphoric acid (25:75), pH 5.0	UV, 260 nm	[185]
	C_{18} Bond Elut	Acetonitrile and 0.05 M sodium dihydrogen phosphate	UV, 442 nm	[186]
	5 μm hypersil ODS	Merthanol/0.05 M sodium acetate buffer pH 3.5 (1:4)	Tandem mass spectrometry	[187]
Cefaloridine	Microbore reversed-phase C_{18}	Methanol/20 mM monosodium phosphate (25:75), pH 5.5	UV, 254 nm	[188]
Cefazolin	5 μm LiChroCART Purospher C_{18}e	0.05% Trifluoroacetic acid in water/methanol/acetonitrile	UV, 270 nm	[189]
	Microbore reversed-phase	Methanol/acetonitrile/100 mM monosodium phosphoric acid (20:10:70), pH 4.5	UV, 270 nm	[190]
	5 μm HD ODS	10 mM Aqueous sodium dihydrogen orthophosphate/methanol (9:1), pH 5.0	UV, 273 nm	[191]
Cefazolin	5 μm Econosphere C_{18}	Sodium dihydrogen phosphate/methanol (77:23), pH 5.0	UV, 270 nm	[192]
	Ultrasphere C_8 or C_{18}	0.01 M Sodium dihydrogen phosphate pH 5.3/acetonitrile (17:3 with C_{18} for plasma; 41:9 with C_8 for protineal dialysis fluid)	UV, 254 nm	[193]
Cefcanel	(a) Supelcosil LC8	(a) Acetonitrile/0.02 M sodium dihydrogen phosphate bulfer, pH 4.7 (13:87)	UV	[194]
	(b) Ultrasphere ODS	(b) Acetonitrile/0.1 M phosphate buffer, pH 2.0 (30:70)		
Cefepime	LiChrosorb RP-18	100 mM Monosodium phosphoric acid pH 3.0/methanol (87:13)	UV, 270 nm	[195]
	Nucleosil C_{18}	Acetonitrile/ammonium acetate pH 4.0	UV, 280 nm	[196]
	Hypersil ODS C_{18}	25 mM Sodium dihydrogen phosphate monohydrate pH 3.0 and methanol (87:13)	UV, 270 nm	[197]
	5 μm Shandon Hypersil BDS C_{18}	25 mM Sodium dihydrogen phosphate monohydrate buffer pH 3.0/methanol (87:13)	UV, 270 nm	[197]
	5 μm Hypersil BDS	Acetonitrile/acetate buffer, pH 4 (2.8:97.2)	UV, 254 nm	[198]
	5 μm Ultrasphere C_8	Acetonitrile/phosphate buffer (3:23)	UV, 280 nm	[199]
Cefixime	C_8	Acetonitrile/water/formic acid (80:120:1)	Tandem mass spectrometry	[200]
Cefmatilen	Inertsil ODS-2	0.03 M Phosphoric acid/acetonitrile (87:13) containing 3 mM sodium 1-nonanesulfonate	UV and electrochemical	[201]
Cefodizime	5 μm ODS	5 mM Sodium heptanesulphonate containing 27% acetonitrile and 2% acetic acid	UV, 263 nm	[202]
Cefotaxime	Zorbax SB-C_{18}	0.05 M Aqueous ammonium acetate/acetonitrile/tetrahydrofuran (87:11:2), pH 5.5	UV, 254 nm	[203]
	C_{18} microbore	Methanol/100 mM monosodium phosphoric acid (25:75), pH 5.5	UV, 254 nm	[204]
	Nova-pack C_{18}	50 mM Phosphate buffer pH 6.0/acetonitrile (88:12)	UV, 254 nm	[205]
	C_{18} SPE	Aqueous 50% acetonitrile	UV, 514 nm	[206]
Cefoxitin	10 μm Microbondapak C_{18}	Acetic acid/acetonitrile/5 mM potassium dihydrogen phosphate (1:44:155)	UV, 235 nm	[207]
Cefpirome	Microbondapak C_{18}	Tetrabutylammonium hydroxide in 0.05 M sodium acetate buffer pH 5.1/methanol (41:9)	UV, 240 nm	[208]
Cefpodoxime	ODS	25 mM Acetate buffer pH 4.3/15 mM triethylamine/acetonitrile (92.5:7.5)	UV	[209]
	5 μm Supelcosil LC 18	0.05 M Acetate buffer pH 3.8/methanol/acetonitrile (87:10:3) or (43:6:1)	UV, 235 nm	[210]

Table 6 (*Continued*)

Drug(s)	Column	Mobile phase	Detection	Ref.
	Ultrasphere Xl-ODS	21.5 mM Ammonium acetate/acetonitrile (93:7), pH 5.0	UV, 254 nm	[211]
Cefquinome	Supersher 100 RP 18e	Phosphate buffer pH 6.5/acetonitrile (12:1)	UV, 270 nm	[212]
Cefradine	C_{18} RP	20 mM Sodium dihydrogen phosphate/10% acetonitile, pH 2.7	UV, 260 nm	[213]
	Polymeric reversed-phase PLRP-S	10.5% (v/v) Acetonitrile in 20 mM ammonium dihydrogen orthophosphate pH 2.75	UV, 260 nm	[214]
Cefroxadine	Capcell Pak C_{18}	50 mM Ammonium formate buffer pH 3.5/acetonitrile (9:1)	UV, 254 nm	[215]
Cefsulodin	Microbore RP	Methanol/100 mM monosodium phosphoric acid (1:9), pH 5.0	UV, 265 nm	[216]
Ceftazidime	Microbore reversed phase	Methanol/acetonitrile/0.1 M phosphate buffer pH 3.0 (1:1:8)	UV, 254 nm	[217]
	5 μm C_{18} Kromasil	10% Acetonitrile/25 mM phosphate buffer pH 7.4 (1:9)	Electrochemical	[218]
	10 μm C_{18} silica	20 mM Tetrabutyl ammonium hydrogen sulphate in acetonitrile/phosphate buffer (9:91)	UV, 255 nm	[219]
	5 μm LiChrospher 100 RP-18	70 mM Potassium hydrogen phosphate pH 6.5/methanol (93:7)	UV, 255 nm	[220]
	C_8 silica SPE	10 mM Sodium dihydrogen phosphate pH 5.0/acetonitrile (46:1)	UV, 258 nm	[221]
	3 μm Ultremex	Aqueous 25% acetonitrile containing 5 mM dodecanesulphonate and 0.1% phosphoric acid	UV, 258.5 nm or photo-diode array, 200–340 nm	[222]
Ceftibuten	5 μm Spherisorb ODS	Acetonitrile/ammonium acetate (9:191)	UV, 254 nm	[223]
	(a) Waters Micropondapak C_{18}	(a) Acetonitrile/0.05 M ammonium acetate (2:98)	UV	[224]
	(b) Partisil 10 ODS-3	(b) Acetonitrile/0.05 M sodium phosphate buffer pH 7 (2.5:97.5)		
	Microbondapak phenyl	2% Acetonitrile in 0.1 M ammonium acetate, pH 6.5	UV	[225]
Ceftizoxime	5 μm Ultrasphere Octyl	20% Methanol/10 mM tetrabutylammonium dihydrogen phosphate in 40 mM potassium phosphate buffer pH 7.0	UV, 254 nm	[226]
Ceftriaxone	C_{18}	Acetonitrile/0.1 M phosphate buffer pH 7.4/water (6:1:13)	UV, 270 nm	[227]
	Microbore	Methanol/100 mM monosodium phosphoric acid (3:17), pH 7.0	UV, 280 nm	[228]
	Chromegabond C_{18}	0.6% Hexadecyltrimethylammonium bromide in phosphate buffer pH 7.2/acetonitrile/water (1:40:39)	UV, 280 nm	[229]
Cefuroxime	5 μm Waters Symmetry C18	5% Acetonitrile in 0.05 M ammonium phosphate pH 3.2	UV, 280 nm	[230]
Cephalosporins	Phenomenex Synergi Polar-RP	Mobile phase A: 0.005% formic acid in water Mobile phase B: methanol	Tandem mass spectrometry	[231]
	ODS	Acetonitrile/1% acetic acid (7:13)	Mass spectrometry	[232]
	Supelcosil LC-18	Phosphoric acid/potassium dihydrogen phosphate/acetonitrile/sodium decansulphonate/sodium dodecylsulphate	UV, 260 or 290 nm	[233]
	Nova-pack C_{18}	0.01 M Acetate buffer pH 4.7/methanol/acetonitrile (87:11:2) and 0.01 M acetate buffer pH 4.7/methanol/acetonitrile (87:2:11)	Pulsed amperometry from 1.28 to -0.28 V	[234]
	5 μm β-cyclodextrin bonded phase	Methanol/tetraethyl ammonium acetate (TEAA) buffer	UV, 230 nm	[235]
	Sephadex gel G-10 or G-50	0.22 M Sodium chloride, 0.1 M and 0.01 M phosphate buffers pH 7.0 and 0.5 M sodium chloride in 0.1 M phosphate buffer pH 7.0	UV, 254 nm	[236]
Cefotaxime and desacetylcefotaxime	Aqua C_{18}	50 mM ammonium dihydrogen phosphate buffer pH 3/acetonitrile/trimethylamine (439:60:1), pH 3.0	UV, 285 nm	[237]
	LiChrospher 100 RP-18	0.01 M Acetate buffer pH 4.8/methanol (85:15)	UV, 254 nm	[238]
	5 μm Spherisorb ODS2 C_{18}	0.007 M Phosphoric acid/acetonitrile (17:3)	UV, 262 nm	[239]

Table 6 (*Continued*)

Drug(s)	Column	Mobile phase	Detection	Ref.
Cefalexin and cefaclor	Hibar Lichrospher 100 RP 8	Methanol/0.025 M potassium dihyrogen phosphate (1:3)	UV, 255 nm	[240]
	5 μm YMC-ODS	2.25–25% Acetonitrile in 50 mM sodium phosphate pH 4	UV, 220 nm	[241]
Cefazolin and ceftriaxone	Nova-Pak C_{18}	10 mM Dibasic potassium phosphate buffer containing 10 mM cetyltrimethylammonium bromide pH 6.5/acetonitrile (73:27)	UV, 274 nm	[242]
Cefatazidime and piperacillin	5 μm Spherisorb ODS C_{18}	Acetonitrile/0.05 M phosphate buffer pH 3.8	UV, 254 nm	[243]
Ceftazidime and meropenem	Nucleosil C_{18}	Acetonotrile/50 mM sodium dihydrogen phosphate buffer pH 5 (5:95 and 4:96 for meropenem and ceftazidime, respectively)	UV, 258 and 296 nm for ceftazidime and meropenem, respectively	[244]
Cefepime and cefpirome	Supelcosil ABZ+	Acetonitrile/20 mM potassium dihydrogenphosphate buffer (6:94)	UV, 263 nm	[245]
Ceftazidime and cefepime	Microbondapak C_{18}	Acetatae buffer/acetonitrile (9:1 and 45:1 for ceftazidime and cefepime, respectively)	UV, 257 and 280 nm for ceftazidime and cefepime, respectively	[246]
Cefuroxime and cefadroxil	5 μm LiChrospher 100 RP-18	Water/acetonitrile/acetic acid (850:150:1) for cefuroxime and 0.02 M potassium dihydrogen phosphate/acetonitrile (19:1) containing 0.003% (w/v) hexanesulphonic acid sodium salt, pH 3.0 for cefadoxil	UV, 275 and 260 nm for cefuroxime and cefadroxil, respectively	[247]
Cepodoxime and cefmetazole	Develosil C-30-UG-3	Water/acetonitrile/formic acid (550::450:1)	Tandem mass spectrometry	[248]
Ceftazidime and cefotaxime	Shim-pack C_{18}	Phosphate buffer pH 7.0/methanol (85:15) and (70:30) for ceftazidime and cefotaxime, respectively	UV, 254 nm	[249]
Cefotaxime, desacetylcefotaxime, ofloxacin and ciprofloxacin	5 μm Hypersil ODS	0.01 M Sodium dihydrogen phosphate/15% acetonitrile/6% dimethylformamide, pH 3.0	UV, 285 nm	[250]
Cefoxitin, cefminox and cefmetazole	5 μm Nucleosil-5 C_{18}	0.1 M Potassium phosphate pH 6.0/acetonitrile	UV, 265 nm for cefoxitin and 272 nm for cefminox and cefotaxime	[251]
Cefazolin, cefoperazone, cefquinome and ceftiofur	Waters Nova-Pak phenyl	0.005 M Octansulphonic acid pH 2.52/acetonitrile/methanol	UV, 270 nm	[252]
Cefoxitin, cefuroxime, cefalexin and cefaloridine	Partisil ODS-3	0.02 M Acetate buffer pH 4.3/acetonitrile (17:3)	UV, 254 nm	[253]
Cefalexin, Cefazolin, cefotaxime, cefuroxime and cefoxitin	LiChrospher 100 RP 18	Acetonitrile/0.05 M sodium dihydrogen phosphate pH 3.0	Diode array, 220–600 nm	[254]
Cefaloridine, cefalotin, cefamandole, cefazolin, cefodizime, cefoperazone, cefoxitin, ceftizoxime, ceftriaxone and cefuroxime	C_{18}	Methanol/acetonitrile/0.01 M phosphate buffer pH 7.0 (20:15:65) and 5 mM TBA HSO_4	UV, 267 nm	[255]
Cephalosporins and penicillins	Alltima C_{18}	A gradient of acetonitrile in water, each containing 0.1% formic acid	Electrospray ionization tandem mass spectrometry	[256]
Cephalosporins, cephamycins and penicillin's	10 μm AQ-C_{18}	Methanol or acetonitrile/water containing 0.1% trifluoroacetic acid	Electrospray ionization tandem mass spectrometry	[257]

ing mercury drop electrode using its reduction peak at −0.43 V in Britton–Robinson buffer pH 4.0 has been reported [270].

Both osteryoung square wave voltammetry and cyclic voltammetry have been utilized to elucidate and confirm the possible complexation reaction that occur between the various cephalosporin antibiotics and either the toxic, non-essential metal ion, viz. Cd(II), or the essential but toxic (when their concentration exceeds certain level in serum) metal ions, viz. Cu(II) and Zn(II) [271]. Cefalexin was determined polarographically in pharmaceuticals and human serum [272].

Cathodic stripping voltammetric determination of the cephalosporin antibiotic ceftriaxone was reported at the mercury electrode in aqueous and biological media [273]. Square-wave voltammetry (SWV) for determination of cefoperazone in some buffers, bacterial culture, urine, and milk was described [274].

The voltammetric behaviour of cefotaxime was investigated by cyclic and square-wave voltammetry, the cathodic reduction peak was detected at −0.5 V [275]. The electrochemical behaviour of cefminox in phosphate buffer solutions over pH range 2.0–9.0 using differential-pulse polarography, dc-tast

polarography, cyclic voltammetry and linear sweep voltammetry (staircase) has been studied and used for the determination of the drug in urine [276].

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