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Review Article

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Chemistry, classification, pharmacokinetics, clinical uses and analysis of beta lactam antibiotics: A review

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ABSTRACT

This review attempts to pinpoint the importance of betalactam antibiotics, which encompass penicillins, cephalosporins, cephamycins, carbapenems and monobactams from its chemistry, classification, pharmacokinetics, clinical uses and analysis. β- lactam antibiotics have been used for treatment of bacterial infections. Most antibacterials are chemically semisynthetic modifications of various natural compounds and classified on the basis of chemical /biosynthetic origin into natural, semisynthetic, and synthetic. Also, this classification system is based on biological activity; that antibacterials are divided into two broad groups according to their biological effect on microorganisms, bactericidal agents kill bacteria, and bacteriostatic agents slow down bacterial growth.

Keywords: Beta lactam Antibiotics, Classification, Pharmacokinetics, Clinical uses, Analysis.

INTRODUCTION

1. Classification of beta lactam antibiotics:
1.1. Cephalosporins:
1.1.1 Chemistry:
Cephalosporins are β-lactam antibiotics differ from the penicillins in that the B ring is a 6-membered dihydrothiazine ring. Variations among the cephalosporins are made on either the acyl side chain at the 7-position to change antibacterial activity or at the 3-position to alter the pharmacokinetic profile [1-3]. The cephalosporins inhibit bacterial cell wall synthesis by blocking the transpeptidases [4].

1.1.2. Classification:
Cephalosporins are classified into five generations. The list of chemical structures of oral, parenteral cephalosporins and parenteral cephamycins are shown in Tables 1, 2 and 3, respectively [5].

1.1.2.1. First-generation:
These are most active against *aerobic* gram-positive cocci and include cefazolin, cephalexin, and cefadroxil and they are often used for skin infections caused by *S. aureus* and *Streptococcus*. They have activity against *E. coli* and some activity against *H. influenzae* and *Klebsiella* species, but because of the limited gram-negative coverage, they are not first-line agents for infections that are likely to be caused by gram-negative bacteria [6].

1.1.2.2. Second-generation:
These are more active against gram-negative organisms, such as *Moraxella*, *Neisseria*, *Salmonella*, and *Shigella*. Cefoxitin and cefotetan, also have more coverage against *anaerobic* bacteria. The true cephalosporins that are also part of this class are cefprozil, cefuroxime, cefaclor, cefoxitin, and cefotetan. These drugs are used primarily for respiratory tract infections because they are better against some strains of beta-lactamase producing *H. influenza* [6].

1.1.2.3. Third-generation:
These have the most activity against gram-negative organisms, including *Neisseria* species, *M. catarrhalis*, and *Klebsiella*, while ceftazidime is active against *P. aeruginosa*. These agents have less coverage of the gram-positive cocci, notably methicillin-sensitive *S. aureus*. In addition to the agent with antipseudomonas coverage, this class includes cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftibuten, and ceftriaxone. These drugs are useful for more severe community-acquired respiratory tract infections, resistant infections, and nosocomial infections (because of the high incidence of resistant organisms) [6].

1.1.2.4. Fourth-generation:
Cefepime is involved in this class because it has good activity against both gram-positive and negative bacteria, including *P. aeruginosa* and many *Enterobacteriaceae*. The gram-negative and anaerobic coverage makes cefepime useful for intra-abdominal infections, respiratory tract infections, and skin infections [6].

1.1.2.5. Fifth-generation:
Ceftaroline fosamil is the only advanced generation cephalosporin; it has enhanced activity against many both gram-negative and positive bacteria. It is active against community-acquired pneumonia infections caused by *E. coli*, *H.influenzae*, *Klebsiella*, *S. aureus* (methicillin-susceptible isolates only), and *S. pneumoniae* and safe for treating skin infections caused by multidrug-resistant *S. aureus*. [7-8].

1.1.3. Activity:
In general, the first generation oral cephalosporins have more gram-positive coverage, while the second which includes, cefamandole, cefonicid, ceforanide, and cefuroxime. Cefaclor and cefuroxime axetil are the only orally available second-generation cephalosporins .These antibiotics are usually active against the same organisms, but they have more activity against certain *aerobic* gram-negative bacteria and *H. influenzae*. Cefaclor is generally less active against gram-negative bacteria than the other agents. In vitro, cefmetazole and cefotetan have been shown to be slightly less active than cefoxitin against *Bacteroides* species, Third generation oral cephalosporins have broad spectrum gram-negative coverage. The only orally available third-generation cephalosporin is cefixime. Ceftizoxime and cefotaxime exhibit some activity against *B. fragilis* and other *anaerobes* [9-11].

Table 1. Chemical structures of the oral cephalosporin antibiotics

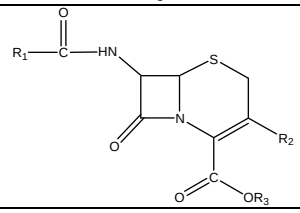
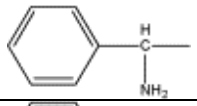
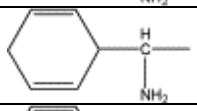
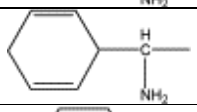
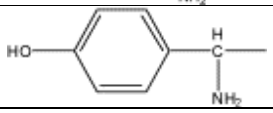
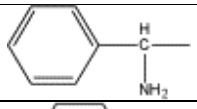
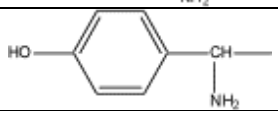
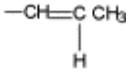
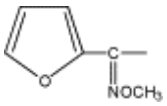
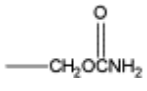
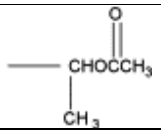
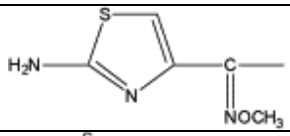
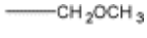
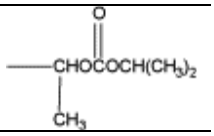
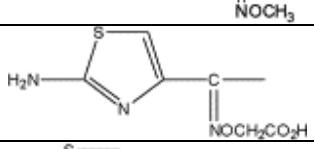
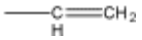
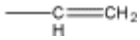
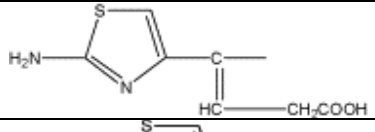
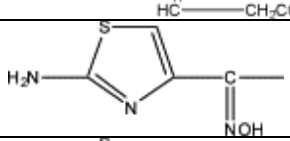
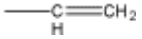
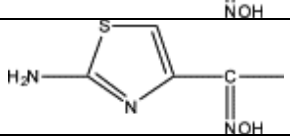
Official/Trade Name	R_1	R_2	R_3
A- Oral cephalosporin			
	First Generation		
Cefalexin(Keflex®)		$-CH_3$	–H
Cephradine (Velosef®)		$-CH_3$	–H
Cefroxadine		$-OCH_3$	–H
Cefadroxil (Duricef®)		$-CH_3$	–H
	Second Generation		
Cefaclor(Ceclor®)		–Cl	–H
Cefprozil(Cefzil®)			–H
Cefuroxime axetil(Ceftin®)			
	Third Generation		
Cefpodoxime proxetil(Vantin®)			
Cefixime(Suprax®)			
Ceftibuten(Cedax®)		–H	–H
Cefdinir(Omnicef®)			–H
Cefetamet		$-CH_3$	–H

Table 2. Chemical structures of the parenteral cephalosporin antibiotics

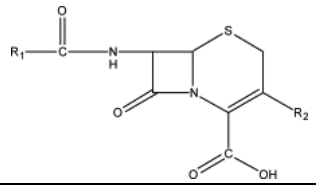
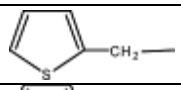
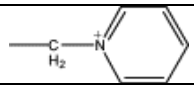
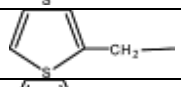
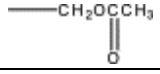
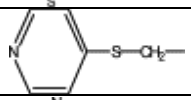
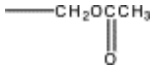
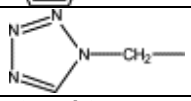
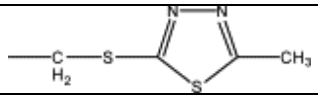
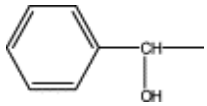
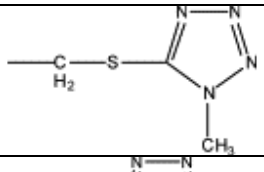
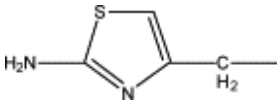
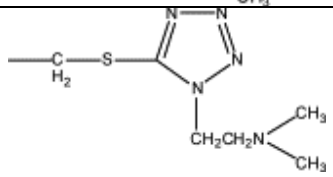
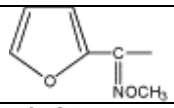
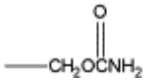
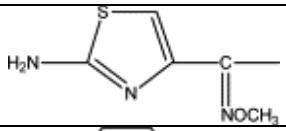
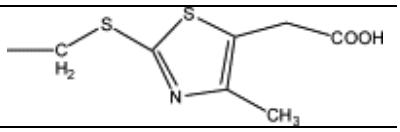
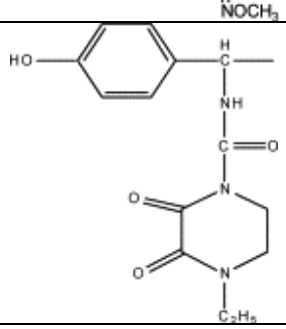
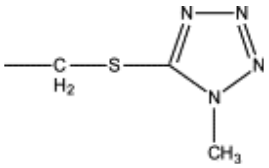
Official/Trade Name	R_1	R_2
B- Parenteral cephalosporin		
First Generation		
Cefaloridine		
Cephalotin(Keflin)		
Cefapirin(Cefadyl®)		
Cefazolin (Ancef®, Kefzol®)		
Second Generation		
Cefamandole(Mandol®)		
Cefotiam		
Cefuroxime (Zinacef®)		
Third Generation		
Cefodizime		
Cefoperazone(Cefobid®)		

Table 2. Continued

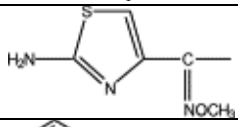
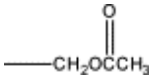
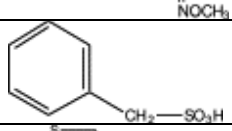
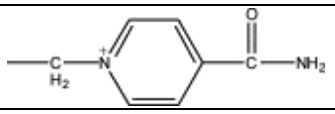
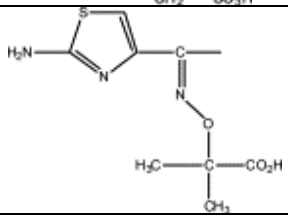
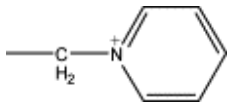
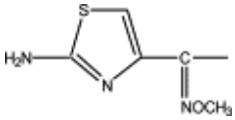
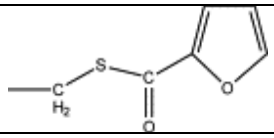
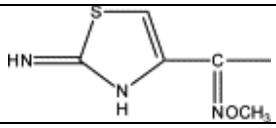
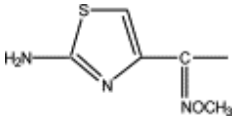
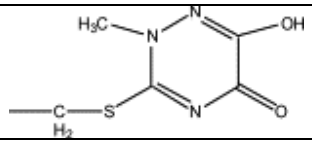
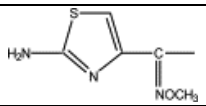
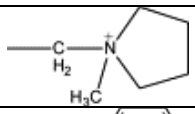
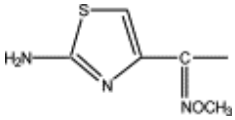
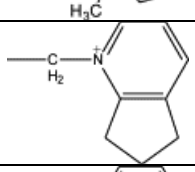
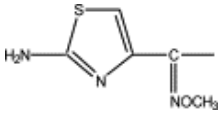
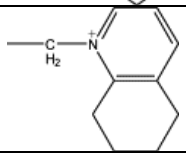
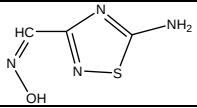
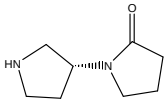
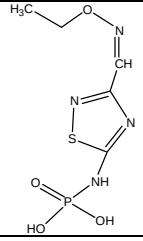
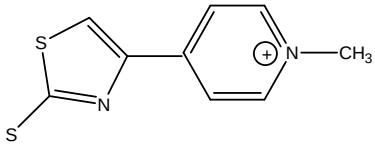
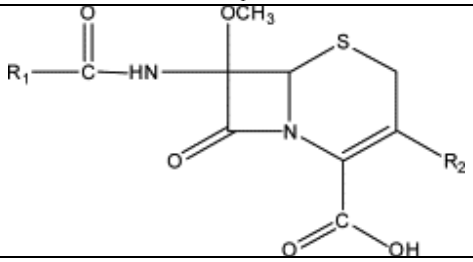
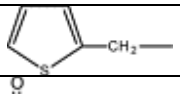
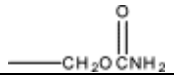
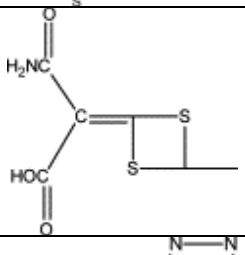
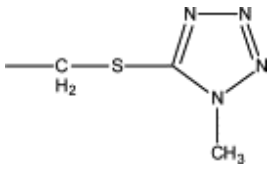
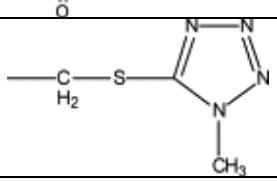
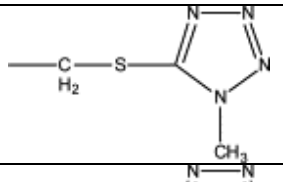
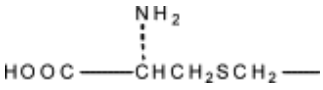
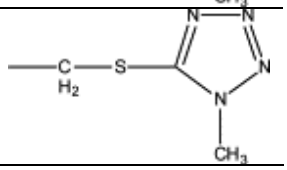
Official/Trade Name	R_1	R_2
Cefotaxime(Clforan®)		
Cefsulodin		
Ceftazidime(Fortaz)		
Ceftiofur		
Ceftizoxime(Cefizox)		–H
Ceftriaxone(Rocephin)		
Fourth Generation		
Cefepime(Wincef)		
Cefpirome(Ceform)		
Cefquinome		
Fifth Generation		
Ceftobiprole(Zevtera)		
Ceftarolin fosamil(Teflaro)		

Table 3. Chemical structures of the parenteral cephamycins antibiotics

Official/Trade Name	R_1	R_2
C- Parenteral cephaamycins		
Second Generation		
Cefoxitin (Mefoxin)		
Cefotetan (Cefotan)		
Cefmetazole(Zefazone)		
Cefminoxl		

1.1.4. Pharmacokinetic parameters: The pharmacokinetic properties of cephalosporin antibiotics are given in Table 4 [12-13].

1.1.5. Clinical uses:

1.1.5.1. Oral cephalosporins:

Cephradine, cefadroxil, cephalexin, and cefaclor are used for the treatment of acute and chronic upper and lower respiratory tract infections related to *S. pneumoniae*, *H.influenzae*, *K. pneumoniae*, *S. aureus*, and *S. pyogenes*. The oral cephalosporins are often used in the treatment of skin and skin-structure infections that may be due to *streptococci* or *staphylococci*. These drugs are also valuable in treating urinary tract infections related to *E. coli* and *Klebsiella* species in patients who cannot tolerate a penicillin or sulfonamide [14].

1.1.5.2. Parenteral cephalosporins:

The 1st-generation cephalosporins are commonly used in patients undergoing operations such as cardiovascular or arthroplasty procedures, in which infection would result in substantially increased morbidity or mortality and are not helpful in patients with meningitis, since these agents do not achieve therapeutic concentrations in the cerebrospinal fluid [15], while the second class which includes, cefoxitin is used in the treatment of intraabdominal and pelvic infections and also used as a prophylactic agent in patients undergoing pelvic surgery [16]. However, cefmetazole is as efficacious as cefoxitin for the treatment of intraabdominal and gynecologic infections. It appears to be an acceptable alternative to cefoxitin and cefotetan [17]. Also, cefuroxime is widely prescribed for community-acquired infections such as pneumonia, and for bone and joint infections [18] and cefonicid has been used to treat meningitis in the pediatric population, urinary tract infections and skin and soft-tissue infections [19].

Table 4. Physicochemical properties and pharmacokinetic properties of cephalosporins

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

However, the third class which includes, cefotaxime is a preferred agent in the treatment of meningitis caused by susceptible gram-negative *E. coli*, and *Klebsiella* [20], while cefotaxime and ceftizoxime are effective against serious gram-negative bacillary infections such as lower respiratory tract, complicated urinary tract, intraabdominal, and gynecologic infections; skin, bone, and joint infections; and bacteremias [21]. Also, ceftazidime is used for empiric therapy in neutropenic patients.

Morever, the fourth class has a greater resistance to beta-lactamases than the third. Many can cross the blood–brain barrier and are effective inmeningitis. They are also used against *P. aeruginosa* [22] and the fifth class is used for the treatment of skin infections [23]. Dosage and common side effects are listed in Table 5.

Table 5. Dosage and common side effect of selected cephalosporins. [24]

Agent	Adult Dosing Range	Pediatric Dosing Range	Common Side Effects
First generation			
Cefadroxil	1–2 g/day in 2 divided doses	30 mg/kg/day in 2 divided doses Max: 2 g/day	Rash, diarrhea
Cefazolin	1–2 g every 8 hrs, or 0.5–1 g every 6 to 8 hrs Max: 12 g/day	>1 mo: 25–100 mg/ kg/day in 3 to 4 divided doses Max: 6 g/day	Phlebitis at infusion site, rash, diarrhea
Cephalexin	250–1000 mg every 6 hrs Max: 4 g/day	>1 yr: 25–100 mg/kg/ day in 3 to 4 divided doses	GI upset, rash
Second generation			
Cefaclor	250–500 mg every 8 hrs	>1 mo: 20–40 mg/kg/ day in 2 to 3 divided doses Max: 1 g/day	Rash, GI upset
Cefotetan	1–2 g every 12 hrs Max: 12 g/day	Not studied for pediatric use	Phlebitis at infusion site, rash, GI upset
Cefoxitin	1–2 g every 6 to 8 hrs Max: 12 g/day	>3 mos: 80–160 mg/kg/day in 4 to 6 divided doses	Phlebitis at infusion site, rash
Cefprozil	250–500 mg every 12 to 24 hrs	>6 mos: 7.5–15 mg/ kg every 12 hrs >2 yrs: 7.5–15 mg/ kg/day in 2 divided doses, or 20 mg/kg every 24 hrs Max: 1 g/day	Rash, GI upset, elevated liver enzymes
Ceftriaxone	IV, IM: 1–2 g every 12 to	50–100 mg/kg/day in 1 to 2 divided doses	Phlebitis at infusion site,

	24 hrs	Max: 4 g/day	rash
Third Generation			
Cefdinir	300 mg every 12 hrs, or 600 mg every 24 hrs	14 mg/kg/day in 1 or 2 doses	Rash, diarrhea
Cefditoren pivoxil	200–400 mg every 12 hrs	Not studied for patients <12 yrs	GI upset, headache
Cefixime	400 mg/day in 1 or 2 doses	>6 mos: 8–20 mg/kg/ day every 12 to 24 hrs Max: 400 mg/day >50 kg or >12 yrs: Use adult dosing	Diarrhea, rash

Table 5. Continued.

Cephalosporins Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Common Side Effects**
Third generation			
Cefotaxime	1–2 g every 4 to 12 hrs	1 mo to 12 yrs (<50 kg): 50–200 mg/kg/ day in 3 to 4 divided doses	Phlebitis at infusion site, rash, GI upset
Cefpodoxime	100–400 mg every 12 hrs	10 mg/kg/day in 2 divided doses Max: 400 mg/day	Diarrhea, nausea, vomiting
Ceftazidime	0.5–2 g every 8 to 12 hrs	IV: 30–50 mg/kg every 8 hrs Max: 6 g/day	Phlebitis at infusion site, rash, GI upset
Ceftibuten	400 mg every 24 hrs	9 mg/kg/day Max: 400 mg/day	Rash, GI upset, headache
Ceftriaxone	IV, IM: 1–2 g every 12 to 24 hrs	50–100 mg/kg/day in 1 to 2 divided doses Max: 4 g/day	Phlebitis at infusion site, rash
Fourth generation			
Cefepime	IV: 1–2 g every 8 to 12 hrs IM: 0.5–1 g every 12 hrs	IV, IM: 50 mg/kg every 8 to 12 hrs Not to exceed adult dosing	Phlebitis at infusion site, GI upset
Five generation			
Ceftaroline fosamil	600 mg every 12 hours	Not studied for pediatric use	Phlebitis at infusion site, GI upset, headache

1.1.6 .Analysis:

There are various methods used for the analysis of cephalosporin in the various forms like chromatographic, UV, electrophoresis and HPLC [25].

1.1.6.1. Chromatographic methods:

There are various methods available for the analysis of antibiotics in different formulations as well as in biological fluids, where illustrated in Tables 6 and 7.

1.1.6.1.1. High-Performance Liquid Chromatographic Methods (HPLC):

HPLC has been used frequently in all fields of β-lactam research. Most methods are reversed-phase or ion-pair reversed-phase LC. [26-29].

1.1.6.1.2. Thin-layer chromatographic methods:

Cefradine and cefalotin were determined by spectrodensitometric method after contact with iodine vapours [30]. 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 [31-32].However, cefalexin was analysed by HPTLC on silica gel F254 plates, the plates were scanned in reflectance mode at 263 nm [33], while 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 [34]. Simultaneous determination of cefalexin and probencid in pharmaceutical preparation was performed by HPTLC using silica Gel 60 F254 HPTLC plate and they were detected at 254 nm [35]. 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. Cefuroxime axetil and ornidazole are determined in combined tablet dosage form by HPTLC using silica gel aluminium plate 60 F254 , toluene–n-butanol–triethylamine (8.5:2:0.5, v/v/v) as mobile phase and scanning at 285nm[36].

Moreover, cefixime and ofloxacin are determined in a bulk drug and pharmaceutical formulations. Chromatographic separation was achieved on aluminum foil plates precoated with silica gel 60GF-254, with n-butanol: ammonia: water: DMSO (8:3:1:2, v/v/v/v) as mobile phase at 297 nm [37].

Table 6. Different chromatographic methods for analysis of cephalosporin with analytical parameters

Method	Type of cephalosporin	Linearity	Precision % RSD	Accuracy & its range	LOD	LOQ	Retention Time
HPLC [38]	cefepime, cefixime and cefoperazone with seven cephalosporins	0.5, 1, 5, 10, 20, 30, and 50 ugmL−1	3.6–7.8 ,4.2–5.9 ,1.6–4.8 (inter day) 5.2–8.0, 6.8–9.8 ,0.8–7.8(intra day)	0.50, 5.00 and 3 0.00ugmL−1.	25, 10 and 15 ngmL−1	80, 35 and 50 ngmL−1	-
HPLC [39]	cefetamet pivoxil in drug substance and powder forms	30.0–80.0 ug ml−1	1.71 – 1.51 % RSD	100.09%	1.03 ug ml−1 degradation	3.15 ug ml−1 Degradation	6.2 min
HPLC [40]	Oral cephalosphorins Plasma(S-1090)	0.09–9 ug/ml	< 6 % RSD	0.09–0.9 ug/ml Recovery, 102.3%	-	0.09 ug/ ml	22 min
HPLC [40]	Oral cephalosphorins Urine(S-1090)	0.5–100 ug/ml	< 6 % RSD	0.9–9 ug/ml 95.8–100.3%	-	0.5 ug/ ml	23 min
HPLC [41]	cephradine in human plasma	0.2- 30 ug/ml	0.2 mg/ml was 4.9% (intra-assay)	0.2 - 30 ug/ml	-	0.2 and 30 ug/ ml	10 min
HPLC [42]	Cefazolin	1 to 50 µg/ml	% RSD 0.8033 and 0.5856 %	95 – 100 %.	0.1 ug/ml,	0.3 ug/ml	UV 254 nm
HPLC [43]	Ceftazidime and Sulbactam in Spiked Plasma	125-750 ppm for ceftazidime and 62.5-375 ppm for sulbactam sodium.	0.11 0.74	98.69±0.12 98.75±0.31	0.11 ppm	0.34 ppm	-
HPLC [44]	Cephalosporin	5-50 – 500 ug/ml	0.993 – 100	93 to 101%.	0.2 to 1.0 ug/ml	-	4 to 6 min
HPLC [45]	cefotaxime, ceftazidime and ceftriaxone Along with alkali induced degradation product and commercial injection.	5-20 ug/ ml.	RSD % of 0.91,2.66 and 1.83 for cefotaxime, ceftazidime and ceftriaxone.	98.6 , 100.1 , 97.6 % in degradation product and 104.9, 102.2, 100.3 In injection. Cefotaxime Ceftazidime Ceftriaxone respectively	0.25 u,g/ ml	-	270 nm
HPLC [46]	CEFPROZIL IN ORAL SUSPENSION CEFZIL	6.51 ⌈u/mL to	97.66 □u/mL	0.40n1.60%	5.96 mg/mL	18.07 mg/mL	UV 280 nm
HPLC [47]	ceftriaxone sodium and sulbactam sodium in injection dosage form	140-250µg/mL	97.65%	100.21± .50	3µg/mL	12 µg/mL	UV 230 nm

Table 6. Continued.

Method	Type of cephalosporin	Linearity	Precision % RSD	Accuracy & its range	LOD	LOQ	Retention Time
HPLC [48]	Cefixime and Cloxacillin in Tablets	160 -240 ug/mL for cefixime and 400 – 600 ug/mL cloxacillin	0.69 for cefixime and 0.77 for cloxacillin	99.99% and 102.24%.	-	-	UV 225 nm
HPLC [49]	Cefuroxime axetil	5-50 µg/ml	0.328 interday 0.545 intraday	100.976 ± 0.439	2.409 ug/ml	7.951 ug/ml	UV 225 nm
HPLC [50]	Five cephalo Cefixime, cefaclore, cefadroxile, cephalexine, cephradine	Cefixime 10 -100 mg/l Rest – 0.1 -	5.8 – 6.9 intraday 8.3 – 7.7 interday	Recovery 80 – 90 %	-	-	UV 240 nm
HPLC [51]	Cefixine and Dicloxacillin	Correlation coefficient 0.9959	% RSD 0.379	99 – 100 %	-	-	UV 220 nm
HPLC [52]	Cefadroxil	Correlation coefficient 0.9941	% RSD 0.02	high	0.06 ppm	0.2 ppm	UV 210 nm
HPTLC [53]	Cefprozil in Tablet Dosage Form	400, -2000 ng/spot	RSD 1.48	101.04±1.78	133, ng/spot	400, ng/spot	Rf – 0.37-0.40
HPTLC [54]	ceftriaxone, cefixime and cefotaxime in dosage forms	125–500 ng	RSD: 1.12–2.91%	99.8 to 101.4%	Satisfactory	satisfactory	-
HPTLC [55]	Cephalexin in Bulk and Pharmaceutical	500–1500 ng	0.7267 % intra day and 1.3623 % Inter day	98.71%.	51.03 ng	154.64 ng	Rf, retardation factor, value–0.56
Electrophoresis [56]	EIGHT CEPHALOSPORIN	3–1000 µg/ ml	0.6–1.6% intra day 0.5 - 1.8%, interday	100%	0.5–5 µg mL–1		

HPTLC [36]	Cefuroxime and Ornidazole	100-500ng	0.491(intra), 0.822(inter) 0.750(intra), 1.033(inter)	98.88-100.59%	0.398ng 0.369ng	1.208 ng 1.118 ng	UV 285 nm

Table 7. Different chromatographic conditions for determination of some cephalosporins

Cephalosporins	Biological fluid/ Formulation	Method	Column	Mobile phase	Detector
cefepime, cefixime and cefoperazone etc 7cephalosphorins [40]	Plasma & Amniatic food	HPLC	XTerra C18 (250mm×4.6mm, 5_m i.d.) column	40mM phosphate buffer, pH 3.2, 18% MeOH, 0.85mLmin−1	photodiode array detector
cefetamet pivoxil [40]	Oral Formulation	HPLC	C18 absorbosphere column (150×4.6 mm i.d., 5 _m particle size),	water–acetonitrile–methanol–phosphate buffer, pH 3.5 (50:35:10:5, v/v), flow rate of 1.5 ml min−1	UV detection at 254 nm.
Cephradine [41]	Suspension formulated in Bangladesh	HPLC	C8 bonded silica	Acetonitrile:monobasic sodium phosphate buffer 15:85(v/v)	UV detection at 255 nm.
Ceftazidime and Sulbactam [44]	Spiked Plasma and Combined Dosage form-Zydotam	HPLC	Hypersil ODS C- 18 column	Acetonitrile and tetrabutyl ammonium hydroxide adjusted to pH 5.0 with orthophosphoric acid in ratio 25:75.	UV detection at 230 nm
Ten Cephalosporins [45]	Plasma	HPLC	C-18 reverse-phase column,	0.01 M sodium acetate and Acetonitrile-methanol.	254-nm UV wavelength
Cephradine [43]	Human Plasma	HPLC	polymeric reversed-phase PLRP-S column	10.5% (v/v) acetonitrile in 20 m*M* ammonium dihydrogen orthophosphate (pH 2.75)	ultraviolet detection at 260 nm
oral cephalosporin, cefmatilen hydrochloride hydrate, and its seven metabolites [57]	Human and animal plasma and urine	HPLC combination of ion-exch pre-column and (ODS) columns	Ion exchange precolumn and ODS column	Phosphate buffer, Methanol, acetonitrile and water.	UV detector 260 nm
cefotaxime, ceftazidime and ceftriaxone [47]	In presence of their alkali induced degradation products and in commercial injections	HPLC method	(150 mm X 6 mm ID) Schimpack GLC-ODS. 5 pm column	Mobile phase composed of acetonitrile-ammonium acetate buffer solution (0.1 M) in a ratio lo:90 (pH 7.5) with peak.	detection at 270 nm using a diode array detector
Cefprozil [55]	Tablet Dosage Form	HPTLC method	silica gel G 60F254(20 cm x10 cm)	chloroform: methanol: toluene: diethyl amine: water in the ratio 4: 4.4: 3.2: 3: 0.8 v/v as mobile	Densitomete r in absorbance mode at 286 nm.

1.1.6.2. Spectroscopic methods:

1.1.6.2.1. 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 [58].

Mixtures of ceftazidime, cefuroxime sodium, cefotaxime sodium and their degradation products were analysed by first-derivative spectrophotometry at 268.6, 306.0, 228.6 nm, respectively [59].

Also, cefotaxime and cefuroxime were determined through the reaction with 1-chlorobenzotriazole at 298 nm [89]. UV, first and second derivatives, were applied for the determination of cefalexin in pharmaceutical preparations [60]. Derivative spectrophotometry was also applied for the determination of some cephalosporins in binary mixtures [61].

A spectrophotometric method was reported for the determination of cefalexin bulk drug and its acid-induced degradation products [62]. UV spectrophotometry [63] and difference UV spectrophotometry [64] were applied to determine cefalexin in tablets. Dissociation constants of cefepime and cefpirome were determined by UV

spectrometry [65-66]. Cefuroxime axetil and probenecid were simultaneously determined in solid dosage forms by UV spectrophotometric method [67]. However, derivative spectrophotometry was reported for the determination of cefprozil in pharmaceutical dosage forms in the presence of its alkali induced degradation products [68]. Binary mixtures of cefalotin and cefoxitin were determined by first-derivative spectrophotometry [69].

Moreover,the analysis of some cephalosporins (ceftriaxone, ceftazidime, cefixime, cefotaxime and cefuroxime) in bulk samples and pharmaceutical dosage forms, which involves diazotization of the cephalosporins with acidified $NaNO_2$ at 0–5 °C and coupling with acidified p-dimethylaminobenzaldehyde. All the cephalosporins gave azo adducts that absorbed light optimally at 400–430 nm at a stoichiometric ratio of 1:1[70].

1.1.6.2.2. Visible spectrophotometric methods:
Determination of cephalosporins could be classified according to the following reactions:

(a) Metal complexation:
Cefpodoxime, ceftizoxime, ceftazidime, ceftriaxone and cefixime were determined by the formation of yellow to yellowish-brown complex with palladium (II) chloride in the presence of sodium lauryl sulfate as surfactant [70]. However, Ferric hydroxamate method was used for the determination of some cephalosporins at 460 nm [71].

Also, 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 [72] and cefaclor was determined through the formation of nickel (II) complex [73-74].

(b) Charge-transfer complexation:
Charge-transfer complexation between cephalosporins as electron donors and certain π-acceptors formed the basis of several spectrophotometric methods such as p-chloranilic acid act as π -acceptor to determine 15 cephalosporin antibiotics. [75].

However, 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 and 7,7,8,8- tetracyano quinodimethane [76].

Also, p-chloranilic, 2,3-dichloro-5,6-dicyano-p-benzoquinone and 7, 7, 8, 8- tetra cyano quinodimethane were used for the determination of cefepime and cefprozil; the absorbance was measured at 460, 841 and 527 nm, respectively [77].

Moreover, cefradine and cefalotin sodium were determined with either iodine in 1,2-dichloroethane at 295 and 365 nm, respectively, or 2,3-dichloro-5,6-dicyano-p-benzoquinone in methanol at 460 nm [78-79].

(c) Redox reactions:
Cefadroxil and amoxicillin were determined by N-bromo succinimide and N-chloro succinimide as oxidizing agents in alkaline medium [80] and potassium iodate was also used for the determination of some cephalosporins [81].

Also, cefotaxime and cefuroxime were determined through their reaction with Ce (IV), the remaining Ce (IV) was determined by its reaction with p- dimethylamino benzaldehyde [60].

(d) Degradation followed by reaction with colouring reagents:
Cefalexin, cefadroxil and cefaclor were determined in their pharmaceutical preparations based on measuring the colour obtained when the alkaline degradation products of these drugs were allowed to react with ascorbic acid [82], while, cefadroxil was determined kinetically by measuring the absorbance at 470 nm [83].

Also, cefaclor was determined 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 [84].

(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 [85]. Cefaclor was also determined through the formation of ion-association complex with methylene blue [86].

1.1.6.2.3. Spectrofluorometric methods*:*
(a) 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 [87-88], while, cefadroxil, cefradine and cefotaxime sodium were determined through mixing with sodium hydroxide and heating at 100°C [89].

Cefalexin, cefaclor and cefradine were determined in formulations by measuring the fluoresence at 416, 417 and 418 nm, respectively [90].

However, cefradine was determined by measuring the fluorescence at 442 nm [91].

(b) Based on redox reactions:
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) [92]. The same technique was used for the determination of 10 cephalosporins [93].

(c) Reaction with fluorogenic agents:
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 [129], while, cefalor was determined spectrofluorometrically based on the derivatization of the drug with 4-(2_cyanoisoindolyl) phenylisothiocyanate [94].

(d) Quenching methods:
Cefadroxil and cefradine were determined in pharmaceutical formulations by fluorescence quenching after mixing each drug with fluorescein-Hg and 1M sodium hydroxide [95].

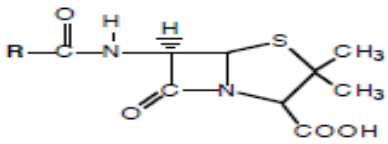
1.1.6.2.4. Chemiluminescence methods:
Cefalotin was determined by the reaction of this drug with luminol in the presence of potassium hexacyanoferrate (III) as a catalyst/co-oxidant and potassium hexacyanoferrate (II) as an emission depressor in an alkaline solution [96-98] and cefalotin was determined based on the ability of this antibiotic to prolong and intensify the chemiluminescence derived from the cobalt(II)-luminol\-hydrogen peroxide system [99].

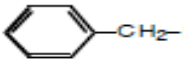
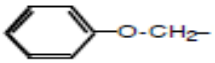
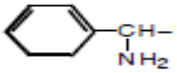
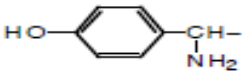
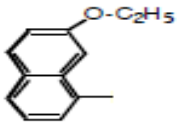
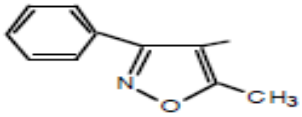
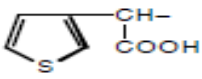
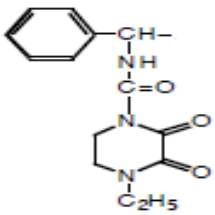
1.1.6.2.5. Atomic absorption spectrometric methods:
Cefotaxime sodium and cefuroxime sodium were analysed by atomic absorption spectrometry after its reaction with silver nitrate or lead acetate in neutral aqueous medium [59].

1.2 Penicillin:
1.2.1 Chemistry:
These are are natural or synthetic antibacterial agents derived from fungi. All penicillins share three basic chemical components: a thiazoldine ring, an attached beta-lactam ring and a side chain. Penicillin colonies inhibited the growth of *staphylococci* on agar plates [100].

1.2.2 Classification:
a- Natural penicillins:
Penicillin G (benzylpenicillin) for parenteral use and penicillin V (phenoxymethylpenicillin) for oral use have the narrowest spectrum of activity. These were the first drugs introduced into clinical use. It is highly effective against susceptible organisms and achieves excellent tissue penetration, which is available in both oral and parenteral form, while penicillin V, the other natural penicillin is stable in gastric secretions, making it the drug of choice when oral administration of natural penicillin is desirable and should be used only in mild, localized infections caused by susceptible organisms [100]. Penicillin V is still considered the drug of choice for *streptococcal pharyngitis* [101].

Table 8. Chemical structures of penicillins



Penicillin	Side Chain
Penicillin G	
Penicillin V	
Ampicillin	
Amoxicillin	
Nafcillin	
Oxacillin	
Ticarcillin	
Piperacillin	

b- Penicillinase-resistant penicillins:

This group of drugs achieves their effectiveness by the addition of a large side chain to the penicillin molecule, which prevents penicillinase produced by *staphylococcus* from entering the penicillin molecule and cleaving the beta-lactam ring [100]. Methicillin is the prototype for these drugs and nafcillin is available only for intravenous use. Also, cloxacillin and dicloxacillin are only available as oral agents, these drugs makes them useful in the treatment of mild infections of the skin and soft tissue, especially when penicillinase-producing staphylococci are the presumed or known causative agents. They may also be useful for hemolytic streptococcal pharyngitis and in pneumonia when penicillinsensitive staphylococcal infections are proven or suspected [102]. However, dicloxacillin is particularly effective against penicillinase-producing staphylococci and is the treatment of choice for mastitis because oral administration achieves relatively high bioavailability in comparison to other drugs [103].

c- Aminopenicillins:

Thees penicillins have activity against gram-negative bacteria, amoxicillin is better absorbed when administered orally than is ampicillin. However, amoxicillin achieves higher serum levels and has a longer half-life [104]. So, amoxicillin has replaced by ampicillin for oral administration. Moreover, ampicillin is the only aminopenicillin available in both parenteral and oral formulations [104].Also; bacampicillin has no therapeutic advantage over either ampicillin or amoxicillin and is more expensive than both. Its only advantage is seen in dosing intervals [102].

Ampicillin is optimally dosed at least every 6 hours. Both ampicillin and amoxicillin are used for prophylaxis against bacterial endocarditis and for prophylaxis prior to gastrointestinal and genitourinary procedures.

d- Extended spectrum penicillins:
The carboxypenicillin group includes carbenicillin and ticarcillin is used for the treatment of *P. aeruginosa* infections [105]. However, piperacillin and the ureidopenicillins have the widest spectrums of antibacterial activity and have enhanced anti-pseudomonas activity and also useful in the treatment of nosocomial.

e- Aminopenicillin /beta lactamase inhibitor combinations:
They are ineffective against betalactamase producing organisms. The addition of betalactamase inhibitors to the aminopenicillins was a critical step in improving their spectrums of activity. The beta lactamase inhibitors have no intrinsic antimicrobial activity [104]. Table 8 summarizes some of the chemical structures of penicillin.

1.2.3. Activity:
The natural penicillins are primarily effective against aerobic, gram-positive organisms such as *streptococi*, *enterococci* and some *staphylococci* that do not produce beta lactamase. Synthetic penicillins such as the aminopenicillins and extended spectrum penicillins have increased this spectrum to include activity against some gram-negative organisms such as *H influenza*, *N. gonorrhoeae*, and *E coli* that have not developed resistance. The addition of beta lactamase inhibitors to some aminopenicillins further increases the activity making the penicillin family one of the broadest spectrum class of antibiotics. [100-101].

1.2.4. Pharmacokinetics:
Table 9 illustrated the pharmacokinetics properties of penicillins . All penicillins have short half-lives (0.5-2 h) and must be given 3-4 times per day [106].

Table 9. Pharmacokinetics properties of penicillins

Penicilin dose	% Oral absorption	Food absorption	% Protein bound	% Metabolite	Total concentratiom (µg/ml)	Free concentratiom (µg/ml)	$t_{0.5}$(hrs) normal	$T_{0.5}$(hrs) renal imp
Pen G	30	Yes	55	20	2	0.9	0.5	10
Pen V	60	No	80	55	4	0.8	1	4
Methicillin	Nil	Yes	35	10			0.5	4
Oxacillin 0.5g	30	Yes	93	45	6	0.4	0.5	1
Cloxacillin 0.5g	50	Yes	94	20	10	0.6	0.5	1
Dicloxacillin 0.5g	50	Yes	97	10	15	0.45	0.5	1.5
Nafcillin 1g	Erratic	Yes	89		1.2	0.16	0.5	1.5
Ampicillin 0.5g	40	No	17	10	3.5	2.9	0.5	1.5
Amoxicillin 0.5g	75	No	17	10	7.5	6.2	1	8
Bacampicillin 0.8g	95	No	17	10	12.9	10.7	0.5	1
Carbenicillin indanyl	30	No	50	2	15	7.5	1.1	15
Ticarcillin 3g	Nil		50	15	190	85	1.2	15
Piperacillin 2g IV	Nil		30		300	150	1.3	4
Clavulanic acid 0.125g	90	No	25	55-75	3.3			
Sulbactam 0.5g IV	Some		38	10	13	7.8	1	4
Tazobactam	Nil							
Temocillin	Nil		85	10			4	17

1.2.5. Clinical uses:

Table .10 Dosage and common side effect of selected penicillins [107]

Penicillins			
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Common Side Effects**
Natural Penicillins			
G benzathine	1.2–2.4 MU	25,000–50,000 U/kg in one dose Max: 2.4 MU divided between 2 injection sites	Rash, GI upset
Penicillin G benzathine or penicillin G procaine	2.4 MU in one dose	<14 kg: O.6 MU 14 to 27 kg: 1.2 MU in one dose	Rash, GI upset
Penicillin G (parenteral/ aqueous)	Up to 24 MU per day	100,000–400,000 U/kg/day in divided doses every 4 to 6 hours Max: 24 MU/day	Rash, GI upset
Penicillin V potassium	250–500 mg 2 to 4 times daily	Pneumonia: 50–75 mg/kg/day in 3 to 4 divided doses Pharyngitis: 250 mg 2 to 3 times per day	Rash, GI upset
Aminopenicillins			
Amoxicillin	250–500 mg every 8 hrs, or 500–875 mg twice daily	>3 months and <40 kg: 20–100 mg/kg/day in divided doses every 8 to 12 hrs ≤3 months: 20–30 mg/kg/day divided every 12 hrs	Rash, diarrhea
Ampicillin	250–500 mg every 6 hrs	PO: 50–100 mg/kg/ day in 4 divided doses Max: 2–4 g/day IV, IM: 100–400 mg/ kg/day in 4 divided doses Max: 12 g/day	Rash, GI symptoms (very common)
Ampicillin and sulbactam	1.5–3 g every 6 hrs IV	≥1 year: IV: 100–400 mg/kg/day in 4 divided doses Max: 8 g/day	Rash, diarrhea, local pain at injection or infusion site (very common with IM use)
Dicloxacillin	125–500 mg every 6 hrs	<40 kg: 12.5–25 mg/ kg/day in 4 divided doses >40 kg: 125–250 mg every 6 hrs	Rash, diarrhea
Nafcillin	IV: 0.5–2 g every 4 to 6 hrs IM: 0.5 g every 4 to 6 hrs	Neonates: 50 mg/kg/ day in 4 divided doses Children: IV: 50–200 mg/kg/day in 4 divided doses IM: 25 mg/kg every 12 hrs	Phlebitis at IV site, neutropenia, rash
Oxacillin	0.25–2 g every 4 to 6 hrs	150–200 mg/kg/day in 4 divided doses Max: 4 g/day	Phlebitis at IV site, hepatitis, rash
Antipseudomonal Penicillins			
Piperacillin or piperacillin/ tazobactam	IV, IM: 3–4 g every 4 to 6 hrs Max: 24 g/day	Neonates: IV, IM: 100 mg/kg every 12 hrs Infants/children: IV, IM: 200–300 mg/kg/day divided every 4 to 6 hrs	Rash, GI upset, phlebitis at infusion site
Ticarcillin or ticarcillin/ clavulanate	3.1 g every 4 to 6 hrs Max: 24 g/day	<60 kg: 200–300 mg/kg/day divided every 4 to 6 hrs >60 kg: Use adult dosing	Rash, GI upset

1.2.6. Analysis:

A-Chromatographic methods:

Table 11 collected some of quantitative methods for the determination of penicillins in different matrix.

Table11. Analysis of some penicillin

Penicillins	Biological fluid/ Formulation	Method	Column	Mobile phase	Detector
Ampicillin, Amoxicillin and Cloxacillin[108]	Dosage form	HPLC	2-5 µm C_{18} column with 30 cm length,	H_2O : CH_3CN : KH_2PO_4 : CH_3CO_2H (9:80:10:1 V/V/V/V)	UV detection at 230 nm.
Amoxicillin and Clavulanic acid [109]	Dosage Form	HPLC	C_{18} column (250 × 4.0 mm, 4 µm)	95:5 (v/v) of pH 5.0 buffer and methanol	UV detection at 220 nm.
Amoxicillin [110]	Plasma	HPLC	LichrosorbR 10µm, C_{18} column	95% phosphate buffer (0.01mol/L), pH=4.8 and 5% acetonitrile mixture.	UV detection at 229nm.
Amoxicillin[111]	Bulk drug and Pharmaceutical dosage	HPLC	a hypersil C18 column (250x4.6mm I.D., particle size 5 µm)	potassium dihydrogen phosphate and methanol in the ratio 95:05 v/v	UV detection at 283 nm.
Ampicillin and Dicloxacillin [112]	Pharmaceutical Formulation	HPLC	ACE 150 mm x 4.6 mm, 5 µ	Buffer: methanol (40: 60, v/v)	UV detection at 220 nm.
penicillin-V [113]	Plasma	HPLC	125 x 4 mm C18 column	66% 0.02 M phosphoric acid buffer and 34%acetonitrile	UV detection at 269 nm.
Ticarcillin and clavulanic acid [114]	Pharmaceutical Formulation	HPLC	Beta-cyclodextrin column (Cyclobond I, 250 x 4.6 mm, 5 microm)	Methanol-16 mM pH 6.0 ammonium acetate buffer (50 + 50, v/v)	UV detection at 220 nm.
Clavulanic acid, Amoxicillin, Ticarcillin [115]	Vials, Tablets and suspensions	HPLC	Reversed phase ODS -2 column	Methanol: Acetonitrile:0.05M sodium dihydrogen phosphate (2:2:96) at pH=5.2	UV detection at 220 nm.
piperacillin and tazobactam [116]	Plasma	HPLC	Piperacillin separation was performed on a microBondapack C(18) column (300 x 3.9, 10 microm) and tazobactam on a Novapack C(18) column (150 x 3.9, 4 microm)	Mobile phase consisted of phosphate buffer-acetonitrile, delivered at 1.5 mL[sol]min	UV detection set at 229 and 225 nm, respectively
Amoxicillin and Sulbactam [117]	Pharmaceutical Formulation	HPLC	Merck ODS inertsil silica C18 (5 µ m, 25 mm x 4.6mm ID)	Buffer:Acetonitrile (10:1) at the pH of 5	UV detection set at 230 nm
Ampicillin and Amoxicillin [118]	human blood plasma and urine.	HPTLC	TLC silica plates	K2HPO4 (0.1 M) + KH2PO4 (0.1 M), 1:1(υ/υ)	UV detection set at 546 nm
Amoxicillin trihydrate and bromhexine hydrochloride [119]	Oral solid dosage forms	HPTLC	TLC silica plates	Butyl acetate:Glachial acetic acid :Methanol:water(5:2:5:2:5:1)(v/v/v/v)	UV detection set at 260 nm

B-Spectrophotometric methods:

Nafcillin sodium in pure form was determined based on the reduction of ferric ions into ferrous ions in presence of o-phenanthroline by nafcillin sodium to form a highly stable orange-red ferroin chelate measured at 510 nm. Maximum color formation was obtained through heating and also by the reaction of nafcillin sodium as n donor with p-chloranilic acid as a π-acceptor to form an orange-red complex measured at 530 nm [120-121].

1.3. Carbapenems

1.3.1 Chemistry:

Carbapenem is considered to be the most potent and to have the widest spectrum of antimicrobial activity. Carbapenems are rapidly bactericidal. Their spectrum of antimicrobial activity includes gram-positive and gram-negative aerobic and anaerobic pathogens. General structure of carbapenem is illustrated in Fig 1 [122].

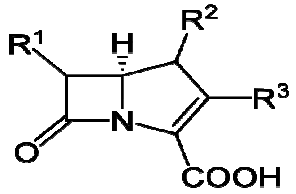
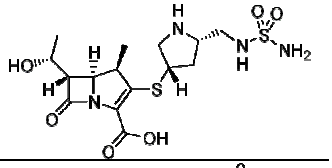
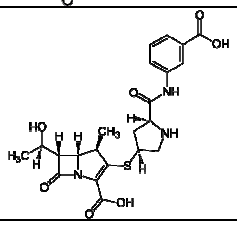
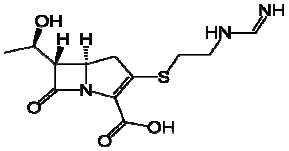
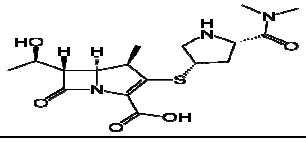


Fig. 1 Structure of carbapenem

1.3.2 Classification:

Chemical structures of carbapenems is proposed in Tables 12 [123]

Table 12. List of chemical structures of carbapenems [124-125]

Generic/Trade Name	Chemical structure
Doripenem(Doribax)	
Ertapenem(Invanz)	
Imipenem (Primaxin)	
Meropenem(Merrem)	

1.3.3. Activity:

Carbapenems are active against many clinically important pathogens and are particularly stable to a wide variety of β-lactamases, they retain activity against a wide variety of multiply resistant pathogens, especially cephalosporin-resistant gram-negative bacteria. However, imipenem, meropenem and ertapenem are considered to be equally active against most gram-negative and gram-positive pathogens. Imipenem and ertapenem have a wide antimicrobial spectrum with excellent activity against *anaerobic* bacteria, including *bacteroides* species. They also cover many gram-positive *cocci*, such as Enterococcus and Streptococcus, as well as many gram-negative bacteria [126]. Moreover, meropenem has somewhat greater activity against gram-negative bacteria, which are not affected by most beta-lactamases, while doripenem has good activity against pseudomonas *aeruginosa*. Also, imipenem and ertapenem are indicated by the U.S. Meropenem is approved by the FDA for treatment of intra-abdominal infections, skin and skin structure infections, and meningitis in patients older than 3 months of age .

1.3.4. Pharmacokinetics:

Table 13 gave the pharmacokinetic parameters. The urinary excretion rates vary from 30% for panipenem to 70% for imipenem and meropenem [126-130]. The elimination half-life is 1 h for all except ertapenem, which has a half-life of 4 h, permitting once-daily dosing. All carbapenems are widely distributed in the body and penetrate a broad range of body tissues and fluids. The usual daily dose for imipenem, meropenem and panipenem ranges from 1.5 to 3.0 g, depending on the pathogen and the site of infection. [131].

Table 13. Pharmacokinetic parameters of the carbapenems

Antibiotic	Dose (mg)	C_{max} (mg/L)	Half-life (h)	Protein binding (%)	Urinary recoveryc (%)
Imipenem[a]	500	12-20	0.95	13-20	70
Meropenem	500	23	0.95	10	70
Panipenem[b]	500	28	1.2	4	30
Biapenem	600	32	1.0	4	60
Ertapenem	1000	155(IV) 67(IM)	4.0	95	38

IV : Intravenous infusion. IM : Intramuscular injection.
[a]In combination with cilastatin. *[b]In combination with betampiron.*

1.3.5. Clinical uses:

Table.14 Dosage and common side effect of selected carbapenems [132]

Agent	Adult Dosing Range	Pediatric Dosing Range	Common Side Effects
Carbapenems			
Doripenem	500 mg every 8 hours	Not studied for pediatric use	Headache, rash, nausea, vomiting, diarrhea, phlebitis
Ertapenem	1 g/day	15 mg/kg every 12 hrs Max: 1 g/day	Diarrhea, nausea, phlebitis at infusion site
Imipenem and cilastatin	≥70 kg: 250–1000 mg every 6 to 8 hrs Max: 4 g/day	<1 wk: 25 mg/kg every 12 hrs 1 to 4 wks: 25 mg/kg every 8 hrs 4 wks to 3 mos: 25 mg/kg every 6 hrs >3 mos: 15–25 mg/kg every 6 hrs Max: 2 g/day (for susceptible infections) or 4 g/ day (for moderately susceptible infections)	Phlebitis at infusion site, rash
Meropenem	1.5–6 g/day in 3 divided doses	30–120 mg/kg/day in 3 divided doses Max: 6 g/day	Diarrhea, nausea, inflammation at the injection site, headache

1.3.6. Analysis:

Chromatographic and spectroscopic methods are illustrated in Tables 15, 16 and 17, respectively.

Table 15. HPLC analysis of some carbapenems

Compound	Sample Matrix	Internal standard	Chromatography			
			Column	Mobile Phase (v/v)	Flow Rate (ml/ min)	Detection
Imipenem	Plasma [133]	Ceftriaxon	Novapak C18 (150 mm x 4.6 mm)	0.2 M boric acid + MeOH adjusted to pH 7.2 (3:97)	-	(UV) 298 nm
	Blood [134]	-	Micro Pak MCH (300 mm x 4.0 mm)	Water + MeOH (93:7)	1.0	(UV) 300 nm
	Serum [135]	-	Hypersil-ODS (150 mm x 4.6 mm; 5 µm)	0.01 M borate buffer (pH 7.2) + MeOH (98:2)	2.0	(UV) 299 nm
	Serum [136]	-	µ-Bondapack C18 (300 mm, 10 µm)	Borate buffer (pH 7.2) /12.4 g of boric acid, 10 mL of 0.1 M NaOH diluted to 1000 water	1.5	(UV) 313 nm
	Blood [137]	-	Nova Pak C18 (150 mm x 3.9 mm, 4 µm)	0.2 M borate buffer (pH 7.2)	1.0	(UV) 300 nm
	Normal saline and human serum[138]	-	µ-Bondapack C18	0.1 M phosphate buffer adjusted to pH 6.21	1.0	(UV) 300 nm
	Plasma rat [139]	Methoxyindole Acetic acid	µ-Bondapack C18	0.2 M borate buffer (pH7.2)	1.0	(UV) 313 nm
	Plasma [140]	-	Resolve C18 Radial-PAK (100 mm x 8.0 mm)	350 mg tetrabutyl ammonium sulphuric acid + 4 ml phosphoric acid (85%) in 1800 of water adjusted to pH 6.85 with KOH	1.4	(UV) 320 nm
	Rat plasma, and mouse blood[141]	Nonstructurally related Compounds	HILIC silica (50 mm x 2.1 mm; 10 µm)	15 mM ammonium formate (pH 3) in 80% ACN Ambient temp.	0.4	MS/MS
Panipenem	Neonatal plasma [142-143]	-	ODS-2 (150 mm x 4.6 mm; 5 µm)	5mM NaH2PO4 containing 5 mM n-dodecylsulfate sodium salt + methanol (65:35)	0.8	(UV) 300

	Hollow-fiber model [144]	-	Novapak C18 (150 mm x 3.9 mm, 5 µm)	0.1% formic acid + 0.1% formic acid in ACN (90:10) (gradient elution)	1.0	MS/MS
	Plasma [145]	-	STR ODS-II (150 mm x 4.6 mm; 5 µm)	2 mM borate buffer +MeOH (93:7)	1.1	(UV) 298
	Plasma [146]	-	PartiSphere SCX	acetate buffer (pH 4.8) + ACN (96:4)	-	(UV) 300
	Plasma and urine [147]	Paracetamol	C18 (250 mm x 4.6 mm; 5 µm)	0.4 mM/L ammonium acetate (pH 4.0) + MeOH (90:10)	1.6	(UV) 299
	Plasma of rats [148]	Mefenamic acid	Cosmosil 5C18 (250 mm x 4.6 mm; 5 µm) Temp.: 40°C	1/15 M acetic acid solution + ACN (50:50)	1.5	(UV) 279
Meropenem	Human serum and urine [149]	Cefepim	C18 RP (150 mm x4.6 mm, 5 µm)	15 mM monobasic potasiumphoshate + ACN + MeOH (84:12:4) pH 2.8 adjusted with orthophosphoric acid	1.0	(UV) 307.6 nm
	Plasma [150]	-	µ-Bondasphere C18 (150 mm x 3.9 mm, 5 µm) Temp: 40°C	10 mM monobasic phosphate buffer (pH 7.4) +ACN (90:10)	1.0	(UV) 300 nm
	Plasma after solid-phase extraction[151]	-	Nucleosil 100 C18(125 mm x 4.0 mm,5 µm)	0.005 M tetrabutylammonium chloride pH 7.4 and MeOH (gradient elution)	1.0	(PAD) 208 nm
	Human plasma [152]	Tinidazole	Hypersil BDS C8(100 mm x 4.6 mm,3 µm)	12.5 mM monobasic potasiumphoshate (pH 6.0) + ACN (96.2:3.8)	1.5	(UV) 296 nm
	Celebrospinal Fluids[169]	-	Symmetry C18 (150 mm x 4.6 mm, 5µm)	10.0 mMphoshate buffer (pH 7.4) + ACN (100:10)	1.0	(UV) 300 nm
	Rate bile [153]	-	LiChrosorb C18 (250 mm x 4.6 mm, 5 µm) Ambient temp.	50 mM monosodium phosphoric acid (pH 3.0) + MeOH (80:20)	1.0	(UV) 298 nm
	Serum [154]	-	C18 (150 mm x 4.6 mm, 3 µm) Ambient temp.	0.01 M phosphate buffer (pH 7.0) with 5Mm tetrabutylammonium-hydrogensulfate + MeOH (70:30)	1.0	(UV) 298 nm
	Human aqueous humor and vitreous[155]	-	C18	Buffer solution + CAN	1.0	(UV) 296 nm
	Human plasma and urine [156]	-	Inertsil ODS-3 C18 (150 mm x 4.6 mm; 5 µm)	0.05 M phosphate buffer (pH 3.0 with 85% orthophosphoric acid) + ACN + MeOH (82:12:12)	0.7	302nm (plasma) 320 nm (urine)
	Plasma [157]	-	Nucleosil C18 (200 mm x 4.0 mm; 5µm)	0.01 M potassium phosphate (pH 7.4) + MeOH (80:20)	1.0	(UV) 296 nm
	Plasma [158]	Ertapenem	Gemini C18 (5 µm)	10 mMdihydrogen phosphate (pH 6.5) + MeOH (88:12)	1.0	(UV) 218 nm
	Plasma[159]	Cefalexin	Gemini C18 (100 mm x 2.0 mm 5 µm)	10 mM ammonium acetate + MeOH (75:25)	0.5	MS/MS
	Blood [160]	Cefepim	Nova-Pak C18	15 mM potassium dihydrogen phosphate (pH 2.8) + ACN + MeOH (84:12:4)	1.0	(UV) 308 nm
	Plasma and bronchoalveolar Lavage[161]	-	Zorbax SB-CN (250 mm x 4.6 mm 5 µm)	50 mM ammonium acetate buffer (pH 5.0) + ACN (90:10)	1.0	(UV) 296 nm
	Human peritoneal fluid, bile[162]	-	Symmetry C18 (150 mm x 4.6 mm, 5 µm) Temp: 40°C	100 mM sodium acetate buffer (pH 4.6) + ACN (197:3)	1.0	(UV) 300 nm
Ertapenem	Plasma, Urine [163-165]	-	Hypersil C18 BDS (100 mm x4.6 mm 5 µm)	25 mM sodium phosphate (pH 6.5) + MeOH (89.5:10.5)	1.0	(UV) 300 nm
	Plasma [166]	-	Hypersil C18 BDS (100 mm x4.6 mm, 5 µm)	25 mM sodium phosphate (pH 6.5) + MeOH (90:10)	2.0	(UV) 300 nm
	Human plasma and bronchoalveolar	-	Protosil 120 AQ C18 (150 mm x4.6 mm, 5 µm)	10 mM phosphate buffer pH 6.5 adjusted with orthophosphoric acid +	1.0	(PAD) 305 nm

	[167]			ACN (gradient elution)		
	Urine [168]	-	Aquasil C18 (100 mm x4.6 mm, 5µm)	Pump 1: 25 mM sodium phosphate buffer, pH 6.5 Pump 2: 25 mM phosphate buffer, pH 6.5 +MeOH (90:10)	2.0 1.8	(UV) 300 nm
	Human cerebrospinal fluid [169]	-	Hypersil C18 BDS (100 mm x4.6 mm 5 µm)	Pump 1: 0.1% formic acid Pump 2: 0.1% formic acid + ACN (85:15) (gradient elution)	1.5 2.0	-
	Murine serum [170]	Meropenem	C18 (100 mm x4.6 mm, 5 µm)	25 mM phosphate buffer (pH 6.5) + MeOH (100:9.5)	1.0	(UV) 300 nm
	Human serum [171]	-	Sybergi Hydro-RP C18 (250 mm x4.6 mm, 0.4 µm)	0.025 M citrate buffer (pH 4.5) + tetrahydrofuran + ACN (89:1:10)	-	(UV) 315 nm
	Human plasma [172]	Ceftazidime	Synergi Polar-RP (100 mm x2.0 mm,4 µm)	Water + 2 mM ammonium acetate + 0.1% acetic acid, pH 3.8) and MeOH (gradient elution)	0.5	MS
	Human plasma, lung tissue, broncho-alveolar lavage fluid[173]	-	Hypersil® ODS (125 mm x3.0 mm, 3µm) Temp: 15°C	25 mM ammonium acetate + MeOH (95:5) and MeOH (gradient elution)	0.08	(UV) 300 nm
	Microdialysates samples from blood and muscle of rats[174]	-	Xterra®MS C18 (150 mm x3.9 mm, 5 µm)	Solvent A (water + formic acid /99.9:0.1/) + solvent B (ACN + formic acid /99.9:0.1/) (82:18)	0.8	MS/MS
Biapenem	Plasma, peritoneal fluids[175-176]	-	µ-Bondaspere C18 (150 mm x 3.9 mm, 5 µm)Temp: 40°C	0.1 M acetate buffer (pH 4.6) + CAN (197:3)	1.0	(UV) 300 nm
	Plasma Urine [177-178]	-	TSK gel ODS 80TM (150 mm x 4.6 mm, 5 µ□m)	0.1 M acetate buffer + ACN (98.5:1.5)Sodium 1-octanesulfate solution + acetic acid +ACN +MeOH(480:3:110:12)	1.2 1.1	(UV) 300 nm 310nm
	Human peritoneal fluid, bile[179]	-	Symmetry C18 (150 mm x 4.6 mm, 5µm) Temp: 40°C	100 mM sodium acetate buffer (pH 4.6) + ACN (197:3)	1.0	(UV) 300nm
Doripenem	Human plasma, peritoneal fluids [180]	Meropenem	XBridge C18 (150 mm x 4.6 mm, 5µm) Temp: 40°C	50 mM sodium Phosphate buffer (pH 3.2) + ACN (935:65)	1.0	(UV) 300 nm
	Serum, peritoneal exudates,prostatic tissue[181-182]	-	XBridge C18 (150 mm x 4.6 mm, 5µm) Temp: 40°C	0.1 M sodium acetate buffer (pH 4.6) + ACN (95:5)	1.0	(UV) 300 nm
	Human and mouse serum[183]	Meropenem	Phenyl hypersil (100 mm x 4.6 mm, 5µm) Ambient temp.	0.026 mM phosphate buffer + MeOH (96.65:4.35)	1.5	(PAD) 295 nm
	Hollow-fiber Model[184]	-	Novapak C18 (150 mm x 3.9 mm, 5µm)	0.1% formic acid + 0.1% formic acid in ACN (90:10) (gradient elution)	1.0	MS/MS
	Human plasma[184]	-	Octadecyl silica C18	50 mM phosphate buffer (pH 6.2) containing 5mM	0.7	(UV) 300 nm

		(250 mm x 4.6 mm, 5 µm)	tetrabutylammonium phosphate + MeOH (80:20)		
Human plasma[184]	-	Octadecyl silica C18 (50 mm X 4.6 mm, 5µm)	20 mM ammonium formate /95:5/ and 20 mM ammonium formate + formic acid + ACN /0.1:15:80/ (gradient elution)	0.6	MS/MS

Table 16. HPLC Methods used for the Analysis of Imipenem, Panipenem, Meropenem, Ertapenem, Doripenem and Biapenem in Pharmaceutical Matrices

Antibiotic	Sample Matrix	Internal standard	Chromatography			
			Column	Mobile Phase (v/v)	Flow Rate (ml/ min)	Detection
Imipenem	Substance [185]	-	Octadecylsilyl Silica gel	8.7 g/L solution of dipotassium hydrogen phosphate adjust with dilute phosphoric acid to a pH 7.3 + ACN (99.3:0.70)	1.0	(UV) 254 nm
	Substance [186]	-	L1 (300 mm x 4.6mm, 5 µm) Temp. 30°C	0.54 g monobasic potassium phosphate adjust with 0.5 M phosphoric acid or 0.5 M NaOH to a pH 6.8	1.5	(UV) 300 nm
	Substance for injection [187]	-	L1 (300 mm x 4.6 mm, 5 µm) Temp. 50°C	0.5 g sodium 1-hexanesulfonate in buffer (pH 6.8) adjust with 0.5 M phosphoric acid or 0.5 M NaOHto a pH = 6.8	2.0	(UV) 254 nm
	Stability studies in aqueous solutions for kinetic studies at pH 4.0 for kinetic studies pH > 4.0 and for degradate isolation [188]	-	Partisil PXS 5/25 (300 mm x 4.6mm) Temp.: 23°C PLRP-S styrene-divinylbenzene copolymer (150mm x 4.6 mm)Temp.:40°C	Water and ACN (gradient elution) 0.02 M potassium hydrophosphate buffer +ACN (pH 7.2) (gradient elution)	2.0 1.2	(PAD) 320 nm 295 nm
	Influence of buffer on substance degradation[189]	-	Spherisorb ODS-2 C18 (250 mm x0.4 cm; 10 µm) ambient temp.	0.01 M phosphate buffer (pH 7.0) + MeOH (93:7)	1.5	(UV) 313 nm
	Determination of substance in infusion[190]	-	Spherisorb CN	10 mM potassium hydroposphate	0.8	(PAD) 300 nm
	Crystallization of substance[190]	-	Microsorb C8 (150 mm x 4.6cm)	1 mM potassium hydrophosphate adjusted to pH 6.8 with 500 mMNaOH	1.5	(UV) 300 nm
	Determination of substance in injection[191]	-	Zorbax C18 (250 mm x4.6 cm; 5µm)Temp.:30°C	ater + propano-2-ol +MeOH(5:10:25)	1.5	(PAD) 225 nm
	Determination of substance in presence of its degradation product[192]	Cefepime hydrochloride	LiChrosorb® C18 (250 mm x 4.6mm; 10 µm)	3-(N-morpholino)-propanesulphonic acid (MOPS) + ACN +MeOH (80:10:10)	1.0	(UV) 299 nm
	Characterization of products[193]	-	ODS C18 (150 mm x 4.6 mm; 3.5µm) Temp.: 25°C	25 mM potassium dihydrogen phosphate buffer,adjusted to pH 3.0 with phosphoric acid + ACN (90:10)	0.8	(UV) 245 nm
Panipenem	Substance [194]	Solution of sodium pstyrenesulfonate in 3-(*N*morpholino) propanesulfonic acid buffer solution (pH =7.0)	Octadecylsilanized silicone polymer coated silica gel (250 mm x4.6 mm; 5µm)Temp. 40°C	0.02 M/L 3-(*N*morpholino) Propanesulfonicacid buffer, pH 8.0 + ACN (50:1)	Adjust the flow rate that the retention time =12min	(UV) 280 nm
	Determination	-	µ-Bondasphere	0.05 M acetate buffer,	1.0	(UV)

	of isomerization kinetics of substance in aqueous solution[195]		C18 (150 mm x 3.9 mm)Temp. 0°C	(pH 5.0) + ACN (94:6)		280 nm
	Determination of substance during stability studies in aqueous solutions[196]	p-styrenesulfonic acid sodium salt	CAPCELL PAK C18 Temp. 40OC	0.02 M 3-(Nmorpholino) ethanesulfonic acid (pH 8.0) +ACN (50:1)	-	(UV) 280 nm
Meropenem	Substance [197]	-	Base-deactivated end-capped octadecylsilyl silica gel Temp.: 40°C	Triethylamine solution, adjusted to pH 5.0 with dilute phosphoric acid + ACN (100:7)	1.6	(UV) 220 nm
	Substance [198]	Solution of benzyl alcohol in triethylamine phosphate buffer, pH = 5.0	Octadecylsilanized silica gel (150 mm x 6.0 mm; µm)Temp: 25°C	Triethylamin - phosphate buffer solution, pH 5.0 + MeOH (83:17)	Adjust the flow rate that the retention time = 7 min	(UV) 220 nm
	Substance [199]	-	Octadecylsilanized silica gel(250 mm x 4.6 mm; 5 µm)	Triethylamin - phosphate buffer solution, pH 5.0 + MeOH (83:17)	Adjust the flow rate that the retention time is about 6-8 min	(UV) 300 nm
	Substance for injection [200]	-	Octadecylsilanized silica gel (250 mm x 4.6 mm; 5 µm)	Solution of tetrabutylammonium adjust with dilute phosphoric acid to pH 7.5 + ACN + MeOH (75:15:10)	1.5	(UV) 300 nm
	Determination of substance in pharmaceutical dosage form, in powder for injection and, reconstituted sample[201-202]	-	LiChrospherR 100 (250 mm x 4.0mm; 5 µm)Temp.: 25°C	30 mM monobasic phosphate buffer + ACN (90:10)	1.0	(UV) 298 nm
	Stability studies in aqueous solutions and in solid state[203-204]	-	Sumpax ODS (150 mm x 6.0 mm; 5 µm)Temp.: 40°C	0.1% Triethylamin □ phosphate buffer solution, pH 5.0 + MeOH (83:17)	1.0	(UV) 220 nm
	Determination of degradation product[205]	-	Sumpax ODS (150 mm x 6.0mm; 5 µm)Temp.: 40°C	Triethylamin + phosphate buffer solution, pH 5.0 + MeOH (100:7)	1.5	(UV) 220 nm
	Determination of substance during thermal and alkaline degradation[206]	-	MetaChem® C18 RP(250 mm x 4.6mm; 5 µm) Temp.: 25°C	30 mM monobasic phosphate buffer + ACN adjusted to pH 3.0 with orthophosphoric acid (90:10)	1.0	(PAD) 298nm 220 nm
	Determination of stability of substance in intravenous solutions, in a portable infusions[207-208]	-	C18	12 mM ammonium acetate + ACN (92:8)	1.2	(UV) 298 nm
	Determination of stability of substance in[209]	Cefepim	µ-Bondapak C18	Solutions 0.01 M 1-heptanesulphonic acid + ACN (92:8)	1.0	(UV) 280 nm
Meropenem	Determination of substance in presence of its degradation	Cefotaxime	LiChrosorbTM C18 (250 mm x4.6 mm; 10 µm)Temp.: 25°C	0.05 M ammonium acetate + ACN + MeOH +triethylamine (75:15:10:0.1), pH was	1.0	(UV) 298

	product[210]			adjusted to 3.0 with orthophosphoric acid		
	Determination of polymerized impurities in substance[211]	-	Kromosil C8 (200mm x4.6 mm; 5µm)	0.1% triethylamine (adjusted to pH 5.0 with acetic acid) and ACN (gradient elution)	1.5	(PAD) 220 nm
	Determination of substance in infusion [212]	-	Nova-Pak C18 (150 mm x3.9mm; 4 µm)	0.02 M tetrabutylammonium hydroxide + MeOH + ACN (75:10:15) pH was adjusted to 7.5 with orthophosphoric acid (85%)	0.8	(PAD) 300 nm
	Determination of stability of substance in polyvinyl chloride bags and an elastometric infusion device [213]	Cefuroksym	C18	0.03 M sodium phosphate (pH 6.5) + ACN + MeOH (88.4:1.9:9.7)	1.2	(UV) 298
	Determination of stability of substance in infusions [214-215]	-	LiChrosorb® C18 (100 mm x4.6mm; 5 µm) Temp.: 25°C	70 mM ammonium acetate buffer (pH 5.0) +ACN (28:72)	1.0	(PAD)
	Determination of stability of substance in solid state[216]	Diprophylline	LiChrosorb® C18 (250 mm x4.0 mm; 5 µm)	12 mM ammonium acetate + ACN (92:8)	1.2	(UV) 298
	Characterization of products [194]	-	ODS C18 (150 mm x4.6 mm; 3.5 µm) Temp.: 25°C	25 mM potassium dihydrogen phosphate buffer, adjusted to pH 3.0 with phosphoric acid + ACN (90:10)	1.2	(UV) 245
Ertapenem	Determination of substance in presence of its degradation Product[217]	-	YMC basic (10 x4.6 cm)	0.05% phosphoric acid in water and ACN (gradient elution)	1.5	(UV) 230
	Determination of substance and impurities[218]	-	YMC C8 (250 mm x 0.46 cm; 5µm)Temp.: 25°C	Dilute phosphoric acid (pH 2.2) and ACN (gradient elution)	1.5	(UV) 220
	Determination of substance in presence of degradation products[219]	-	Inertsil Phenyl (100 mm x2.5cm) Ambient temp.	0.1% sodium phosphate buffer (pH 8.0) and ACN (gradient elution)	1.5	(UV) 220nm
	Determination of stability of substance in aqueous solutions[220]	Diprophylline	LiChrosorb® C18 (250 mm x4.0mm; 5 µm)	25 mM phosphate buffer + MeOH (15:85)	1.2	(UV) 298nm
	Determination of stability of substance in solid state[221]	Diprophylline	LiChrosorb® C18(250 mm x4.0mm; 5 µm)	25 mM phosphate buffer + MeOH (15:85)	1.2	(UV) 298nm
	Identification of degradates of substrate in aqueous matrix[222]	-	Inertsil phenyl (250 mm x4.5cm; 5 µm) Ambient temp.	5–10 mM ammonium acetate pH 5.8 and ACN (gradient elution)	1.5	MS
	Determination of substance in presence of its degradation product[223]	Cefotaxime sodium	LiChrosorbTM C18 (250 mm x4.6 mm; 10 µm) Ambient temp.	0.05 M ammonium acetate + ACN + MeOH +triethylamine(75:15:10:0.1) with ortophosphoric acid adjusted to pH 3.0	1.0	(UV) 298nm
Ertapenem	Determination of substance in presence of its degradation product [194]	Cefepime Hydrochloride	LiChrosorb® C18 (250 mm x4.6mm; 10 µm)	0.05 M ammonium acetale + ACN + MeOH + triethylamine pH was adjusted to 6.5 with orthophosphoric acid	1.0	(UV) 297nm

				(80:10:10:0.1)		
Biapenem	Determination of stability of substance in aqueous solutions[224]	-	Sunfire C18(150mmx4.6mm;5 µm)	0.01 mM ammonium acetate and ACN(gradient elution)	1.0	(UV) 220nm
	Determination of substance in pharmaceutical Preparations[225]	Theophylline	LiChrosorb® C18 (250 mm x4.0mm; 5 µm)	12 mM ammonium acetate + ACN (4:96)	1.0	(UV) 298nm
Doripenem	Determination of substance in pharmaceutical preparations[225]	Theophylline	LiChrosorb® C18 (250 mm x4.0mm; 5 µm)	12 mM ammonium acetate + ACN (4:96)	1.0	(UV) 298nm
	Determination of stability of substance in infusions[226]	-	LiChrosorb® C18 (100 mm x4.6mm; 5 µm)Temp.: 25°C	70 mM ammonium acetate buffer (pH 5.0) +ACN (28:72)	1.0	(PAD)
	Determination of stability of substance in different package[226, 183]	-	Phenyl hypersil (100 mm x 4.6mm, 5 µm) Ambient temp.	0.026 mM phosphate buffer + MeOH (96.65:4.35)	1.5	(UV) 295nm
	Determination of stability of substance in infusions [227]	-	Octadecylsilylated silica gel (150mm x 4.6 cm; 5µm) Temp.: 25°C	2 mM phosphate buffer (pH 5.6) + ACN (97:3)	1.0	(UV) 300nm

Table 17. Derivative spectrophotometry used for the analysis of imipenem, meropenem, ertapenem, doripenem and biapenem in pharmaceutical matrices

Compound	Conditions of Studies	Procedures
Imipenem [228]	Solution of substance in 3-(Nmorpholino)-propanesulphonic acid (MOPS)	First derivative at λ = 318 nm in MOPS, using peak-zero method .
Meropenem [211]	Stability-indicating determination of substance in water	First derivative at λ = 281–315 nm using zero-crossing effect.Zero order of derivative ratio spectra and first-order of derivative ratio spectra λ = 281 nm and λ = 315 nm.Choose of wavelength λ = 220 nm and λ = 298 nm after usage of bivariate method with algorithm of Kaiser.
Ertapenem [229-230]	Selective determination of substance in water	First derivative at λ = 316 nm using zero-crossing effect.Zero order of derivative ratio spectra and first- order of derivative ratio spectra λ = 298 nm and λ = 316 nm Choose of wavelength λ = 215 nm and λ = 297 nm after usage of bivariate method with algorithm of Kaiser. The UV spectrum at λ = 298 nm after subtraction technique.
Biapenem [231]	Stability-indicating determination of substance in aqueous solutions in range of pH 0.82–3.35 Stability-indicating determination of substance in aqueous solutions in range of pH 3.88–10.11	First derivative at λ = 278 nm and λ = 312 nm (zero-crossing effect), using peak-zero method First derivative at λ = 278 nm and λ = 312 nm (zero-crossing effect), using peak-zero method after subtraction technique.
Doripenem [231]	Selective determination of doripenem in aqueous solutions in range of pH 0.82–3.39 Selective determination of doripenem in aqueous solutions in range of pH 3.88–9.41	First derivative at λ = 295 nm and λ = 324 nm using zerocrossing effect First derivative at λ = 295 nm and λ = 324 nm (zero-crossing effect) after subtraction technique.

1.4. Monobactams:

1.4.1. Chemistry:

These have a single beta-lactam core, distinguishing them from the other beta-lactam drugs [232]. Aztreonam is the only available example of this class of drugs. It was originally extracted from *Chromobacterium violaceum*. It is now manufactured as a synthetic antibiotic as shown in Fig 2.

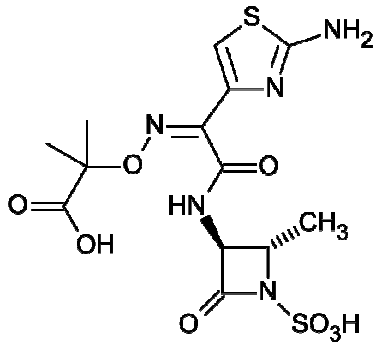


Fig 2. General structure of aztreonam

1.4.2. Activity:

Aztreonam exhibits potent and specific activity *in vitro* against a wide spectrum of gram-negative *aerobic* pathogens including *P. aeruginosa*. The bactericidal action of aztreonam results from the inhibition of bacterial cell wall synthesis due to a high affinity of aztreonam for penicillin binding protein. Aztreonam, unlike the majority of beta-lactam antibiotics, does not induce beta-lactamase activity and its molecular structure confers a high degree of resistance to hydrolysis by beta-lactamases (ie, penicillinases and cephalosporinases) produced by most gram-negative and gram-positive pathogens. It is active against many strains that are multiply-resistant to other antibiotics, such as certain cephalosporins, penicillin, and aminoglycosides. Aztreonam maintains its antimicrobial activity over a pH range of 6 to 8 *in vitro*, as well as in the presence of human serum and under anaerobic conditions [233].

1.4.3. Pharmacokinetics:

Aztreonam does not have significant activity against gram-positive or *anaerobic* bacteria and is primarily used against gram-negative *aerobic* bacteria, including *P. aeruginosa* and *Klebsiella*. It is indicated for use in pneumonia, soft-tissue infections, urinary tract infections, and intra-abdominal and pelvic infections that are caused by gram-negative aerobic bacteria. Aztreonam is absorbed rapidly after intramuscular (IM) dosing, but it cannot be given orally due to instability in stomach acid. It is distributed widely in body tissues and fluids, including inflamed meningeal tissue [234]. Aztreonam is mainly excreted in the urine as an unchanged drug, although there is also minimal hepatic metabolism [35]. Doses must be adjusted for renal insufficiency based on glomerular filtration rate [36].

1.4.4. Clinical uses [233]:

Table 18. Dosage and common side effect of selected monobactam

Agent	Adult Dosing Range	Pediatric Dosing Range	Common Side Effects
Monobactams			
Aztreonam	IV: 1–2 g every 8 to 12 hrs IM: 0.5–1 g every 8 to 12 hrs	30 mg/kg every 6 to 8 hrs Max: 120 mg/kg/day	Rash, nausea, vomiting, phlebitis at infusion site

1.4.5. Methods of analysis of monobactams:

A-Chroamatographic methods:

HPLC systems were developed for the quantitative analysis of aztreonam in human, monkey, rat, mouse, and rabbit sera and urine. The HPLC conditions employed for these analyses were a C_{18} column, a mobile phase made up of 0.005 M tetrabutylammonium hydrogen sulfate at pH 3.0 and acetonitrile or methanol, UV detection at 293 nm, and a flow rate of 2.0 ml/min. HPLC analysis was shown to have excellent detector linearity of aztreonam over a concentration range of 1.0 mg/ml to 0.5 microgram/ml [237].

B-Spectrophotometric methods:

Spectrophotometric and fluorimetric determination of aztreonam were achieved through its reaction with cerium (IV) in acidic medium. The spectrophotometric method involves the quantitation of the amount of ceric equivalent to aztreonam at 317 nm and the corresponding first-derivative value at 284 nm for the blank solution against the reaction solution [237]. In our labouratory we published a series of papers on antibiotics and their metal complexes [238-243].

CONCLUSION

Beta-lactam antibiotics are a broad class of antibiotics, consisting of cephalosporins, penicillin derivatives, monobactams and carbapenems. Most β-lactam antibiotics have been used for treatment of bacterial infections by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics. This review is aimed to discuss the importance the beta lactam antibiotics from five main points, chemistry, classification, pharmacokinetics, clinical uses and analysis.

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