Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2019, 11(2): 47-58

Research Article

ISSN: 0975-7384
CODEN(USA): JCPRC5

Applications Involving Oxidation with Bromate Rapid Potentiometric Determination of Some β Lactam Drug

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ABSTRACT

A micro amounts of (cefoperazone, ceftizdime, cefotaxime, cefotriaxone) were determined by two different technique. A) Potentiometrically Technique using a potassium bromate as an oxidant. The method based on oxidation of each drug to the corresponding nitro or carbonyl derivative with $KBrO_3$ in acidic medium, the reaction are complete under acid medium of pH ranging from 2-3 the un reacted bromate are then reduced to bromide which in titrated potentiometrically with $AgNO_3$ using silver electrode coupled with silver silver chloride electrode, the range of drugs concentrations determined were found to be 0.1 to 15 m mol liter of each drug respectively. B) HPLC Technique: The method involved a determination of binary mixture and reanalysis with analysis of ternary mixture using HPLC technique. The method finds a wide application for the drugs determination in both pure and pharmaceutical formulation samples with high accuracy and precise.

Keywords: Potentiometric titration; Cephlosporines; Potassium bromate; Back titration; Ternary mixture; HPLC; Pharmaceutical samples

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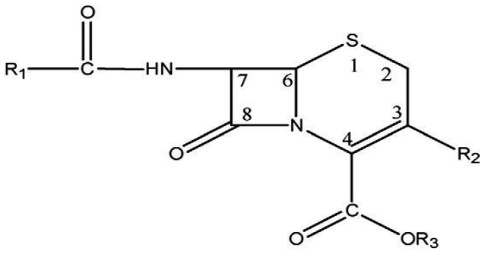
INTRODUCTION

The cephalosporin class is very extensive so a good classification system is necessary to distinguish different cephalosporins from each other. There are few chemical and activity features that could be used for classification, for example chemical structure, side chain properties, pharmacokinetic, spectrum of activity or clinical properties. Despite these variable features the most common classification system for cephalosporins is to divide them into generations. The generation system is based on different antimicrobial activity shown by different cephalosporins. The majority of third generation cephalosporins have the aminothiazole group at position C-7. Different groups are

found at the 7-α-position like 7-α-iminohydroxy and 7-α-iminomethoxy. Ceftibuten however possesses a 7-α-ethylidene group. This group gives ceftibuten higher resistance to enhanced spectrum β-lactamases. Many of the oral third generation cephalosporins are esters of parenteral forms and are hydrolysed by esterases in the digestive tract (Cefteram-pivoxil). Some of the third generation drugs can be absorbed orally without the need of esterification. This is for example done with Cefixime and Cefdinir by putting a vinyl group in the C-3 position Cephalosporins are used to treat pneumonia, strep throat, staph infections, tonsillitis, bronchitis, otitis media, various types of skin infections, gonorrhea. Cephalosporin antibiotics are also commonly used for surgical prophylaxis. Cephalosporins are closely related to the penicillins. Cephalosporins have a bactericidal effect by inhibiting the synthesis of the bacteria cell wall. The cephalosporins are the largest and most diverse family of beta-lactam antibiotics. They are structurally and pharmacologically related to the penicillins. Cephalosporins have a beta-lactam ring structure, infused to a 6-membered dihydrothiazine ring, thus forming the cephem nucleus. Cephalosporin compounds were first isolated from cultures of bacteria Cephalosporium acrimonious found in a sewage outfall off the Sardinian coast in 1948 by Italian scientist Giuseppe Brotzu. The first agent cephalothin (cefalotin) was launched by Eli Lilly in 1964 (Scheme 1).



Scheme 1. Cephalosporin structure

Pasha and Narayana [1] suggested a simple method for the spectrophotometric determination of cephalosporins in pharmaceuticals using variamine blue. Solangi et al. [2] proposed simple and rapid capillary zone electrophoretic (CZE) method has for separation and quantification of a mixture of eight cephalosporins. Nab et al. [3] studied the chromatographic behavior of some cephalosporins has been studied on synthetic inorganic ion-exchanger (stannic oxide) layers using citrate and borate buffers as mobile phases. Hassan et al. [4] discussed a fast, selective, and reproducible high performance liquid chromatography (HPLC) method was developed and validated for the analyses of third-generation cephalosporin antibiotics. Gabriel et al. [5] suggested a rapid and simple capillary electrophoresis method has been developed for the simultaneous determination of six extensively used cephalosporin antibiotics (cefaclor, cefadroxil, cefalexin, cefuroxim, ceftazidim and ceftriaxone). Daniela et al. [6] showed a spectrofluorimetric analysis of cefotaxime sodium by using 4-fluoro-7-nitrobenzofurazan as derivatization agent. Fogg et al. [7] proposed visible spectrophotometric determination of cephalosporins and penicillins by indophenols derivatization with and without alkaline degradation to ammonia. Teixeira M and Regina H. discussed a validation and a useful analytical method for the quantification of ceftriaxone sodium in powder for injection, using Fourier-transform infrared (FT-IR) transmission spectroscopy.

Masoud et al. [8] suggested The metal complexes of cefoperazone with transition metals (Cr(III), Mn (II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)) were synthesized.

EXPERIMENTAL SECTION

Instrumentation

Metrohm potentiometer apparatus was used using silver electrode coupled with silver chloride electrode (Switzerland).

An HPLC system (SHIMADZU, prominence-I LC-2030C) consisting of a solvent delivery pump (binary pump model eco), an automatic injector.

The pH of the solutions was controlled by using a multiparameter CyberScan PCD 6500 with a pH glass electrode. (Thermo fisher Germany),

Purified water was prepared using a Barnstead EASY pure RoDi water system, having a conductivity of 17.6 MΩ-cm, and then filtered through a 0.45 μm membrane filter (thermo fisher Germany).

Chemicals and Solutions

Chemicals with their molecular formula and company names are listed below in Table 1.

Table 1. Chemical names and their molecular formula

Chemicals	Company	Molecular formula
Cefotaxime	Fresenius, Italy	$C_{16}H_{17}N_5O_7S_2$
Cefoperazone	Fresenius, Italy	$C_{25}H_{27}N_9O_8S_2$
Ceftriaxone	Fresenius, Italy	$C_{18}H_{18}N_8O_7S_3$
Ceftazidime	Fresenius, Italy	$C_{22}H_{22}N_6O_7S_2$
Potassium bromate	Merck, Germany	$KBrO_3$
Sulfuric acid	Merck, Germany	H_2SO_4
Silver nitrate	Merck, Germany	$AgNO_3$
Disodium Hydrogen Phosphate	Merck, Germany	Na_2HPO_4

Stock Solutions

1×10^{-2} M cefotaxime sodium was prepared by weighted (4.77 g) and quantitatively transferred into a 1000 mL volumetric flask.

1×10^{-2} M of Cefoperazone sodium was prepared by weighted (6.68 g) and quantitatively transferred into a 1000 mL volumetric flask.

1×10^{-2} M of ceftriaxone sodium was prepared by weighted (6.62 g) and quantitatively transferred into a 1000 mL volumetric flask.

1×10^{-2} M of ceftazidime was prepared by weighted (6.37 g) and quantitatively transferred into a 1000 mL volumetric flask.

1×10^{-2} M of potassium bromate was prepared by weighted (1.66 g) and quantitatively transferred into a 1000 mL volumetric flask. Standardized with (1×10^{-2}) M Na_2SO_3 according to Vogel [9].

1×10^{-2} M of silver nitrate was prepared by weighted (3.247 g) and quantitatively transferred into a 1000 mL volumetric flask and standardized with (1×10^{-2}) M NaCl according to Vogel.

Sulfuric acid by 1:1 was accurately prepared by taken (50 ml) of concentrated acid and quantitatively transferred into a 100 mL volumetric flask, and then complete with 50 ml distilled water.

0.025 M of Disodium hydrogen phosphate was prepared by weighted (3.4 g) and quantitatively transferred into a 1000 mL volumetric flask.

Acetonitrile 80% was prepared by measuring (20 ml) and quantitatively transferred into a 100 mL volumetric flask standard solutions (0.10-1.0 mg/mL) of the drugs were prepared in methanol by weighing (0.10–1.0) mg of powder in a 1.5 ml vials, dissolving the powder in 1 ml of methanol.

All solutions were kept in the refrigerator until right before the analysis [10-15].

Procedure

Potentiometrically method

For drug only by using potassium bromate: Take 1-10 ml of certain drug (1×10^{-2} M) M in flask, put 5-15 ml potassium bromate (1×10^{-2} M), then add drops from sulfuric acid (1:1) to reach pH 2.5, Heat gently for about 5 minutes and then cool to room temperature. The un reacted amount of bromate was potentiometrically determined by back titrated with silver nitrate (1×10^{-2} M) using automatic potentiometer containing Ag electrode coupled with Ag/AgCl electrode. Record the results and repeat the same steps with other volume and other drug.

For Binary mixture by using potassium bromate: A) To 1 ml cefoperazone (1×10^{-2} M) with 1 ml ceftazidime, To a mixture add 5 ml bromate and proceed following (3.3.1) Find out BrO^{3-} equivalent to cefoperazone+ceftazidime. (B) To a second identical mixture. To 1 ml Cefoperazone (1×10^{-2} M) add 5 ml bromate and proceed following (3.3.1). Find out BrO^{3-} equivalent to cefoperazone. (C) By difference find out bromate equivalent to other drug.

HPLC determination of cephalosporins

Ternary mixture drug: A fast, selective, and reproducible high performance liquid chromatography (HPLC) method was developed for the analyses of third-generation cephalosporin antibiotics, namely, (cefotaxime or cefoperazone or ceftriaxone or ceftazidime). The analysis was carried out on a 15 cm C18 column the mobile phase used was

0-6 min 4% ACN “80%”: 96% phosphate 0.05 M Buffer

6-10 min 50% ACN "80%": 50% phosphate 0.05 M Buffer,

at a flow rate of 1.5 mL/min with 254-nm UV detection. The separation factors of all studied compounds were in the range of 1.50-10.05 and the resolution factors ranged from 1.15 to 9.47. The percentage recoveries of these antibiotics in sample were 23.57, 34.81, 21.89 and 19.73% for Ceftazidime, ceftriaxone, cefotaxime and cefoperazone, respectively. The four antibiotics were separated within 7.0 min.

Applications

Formulated drug: Take 4 (0.5 g vials) from certain finished product of drugs then mix, take 0.25 g of the mixed powder and dissolved it in 100 ml distilled water then take (10) ml of certain drug in flask, take (15) ml potassium bromate (1×10^{-2} M), put drops from sulfuric acid to reach pH 2.5, heat gently for about 5 minutes and then cool to room temperature. The unreacted amount of bromate was determined potentiometrically by back titration that titrated in potentiometer apparatus with silver nitrate.

(1×10^{-2} M) using Ag electrode coupled with Ag/AgCl electrode. A concentrations ranging of each drug were determined by this method [16-22].

RESULT AND DISCUSSION

Potentiometrically Technique

Determination of drug only: The results in Tables 1-5 showed that the determination of drugs (cefoperazone, ceftazidime, cefotaxime, ceftriaxone) by oxidation with iodate in acidic medium. The un reacted amount of iodate was determined by back titration with mercury nitrate (II) using Ag electrode coupled with calomel electrode. A concentrations ranging from 0.66 to 6.68 µg/ml for cefoperazone, from 0.47 to 4.77 µg/ml for cefotaxime, from 0.66 to 6.6 µg/ml for ceftriaxone and from 0.63 to 6.3 µg/ml for ceftazidime respectively. The results also showed that good potentiometric titration jump (ΔE\ΔV) ranging from 150-400 for cefotaxime, from 160-400 for ceftriaxone, from 160-360 for cefoperazone and from 250-340 for ceftazidime respectively.

Table 2. Determination of cefotaxime

Conc. µg/ml	Volume ml	End Point ml	Jump ΔE/ΔV	Recovery%
0.477	1	0.95	150	103
0.954	2	1.44	160	99
1.43	3	2.41	200	102
1.9	4	2.75	210	103
2.38	5	4.8	260	101
2.86	6	5.3	300	100
3.34	7	6	300	99
3.82	8	7.17	250	99
4.024	9	8.12	400	100

4.774	10	9.6	200	99

Table 3. Determination of cefoperazone

Conc. µg/ml	Volume (ml)	End Point (ml)	Jump ΔE/ΔV	Recovery %
0.66	1	1	160	96
1.3	2	1.61	150	98
2	3	2.68	250	97
2.67	4	2.76	210	98
3.34	5	3.35	160	101
4	6	3.86	180	102
4.67	7	4.99	250	100
5.34	8	5.23	270	100
6.01	9	5.74	360	98
6.68	10	6.79	310	99

Table 4. Determination of ceftriaxone

Conc. µg/ml	Volume ml	End Point ml	Jump ΔE/ΔV	Recovery%
0.66	1	1.62	160	98
1.32	2	3.52	200	98
1.99	3	5.85	250	103
2.64	4	7.33	260	99
3.31	5	9.7	270	102
3..97	6	10.24	300	100
4.63	7	12.3	310	101
5.29	8	13.56	300	100
5.95	9	14.7	280	98
6.62	10	18.3	400	99

Table 5. Determination of ceftazidime

Conc. µg/ml	Volume ml	End Point ml	Jump ΔE/ΔV	Recovery%
0.637	1	2.14	250	98
1.27	2	3.19	260	102

1.91	3	4.58	320	98
2.55	4	5.75	320	103
3.2	5	6.87	330	101
3.82	6	8.3	340	101
4.46	7	10.2	340	99
5.1	8	11.5	330	98
5.73	9	11.74	330	99
6.37	10	12.8	320	100

Figures 1-5 showed the linearity curves of determination of drugs (cefoperazone, ceftazidime, cefotaxime and ceftriaxone) by oxidation of with iodate in acidic medium. The results showed that there was a linear ship between end point and drug concentration with an exact end point corresponding to each voltage difference. This Potentiometric method has many advantages: high recovery %, they do not need expensive apparatus, they are sensitive and less time consuming.

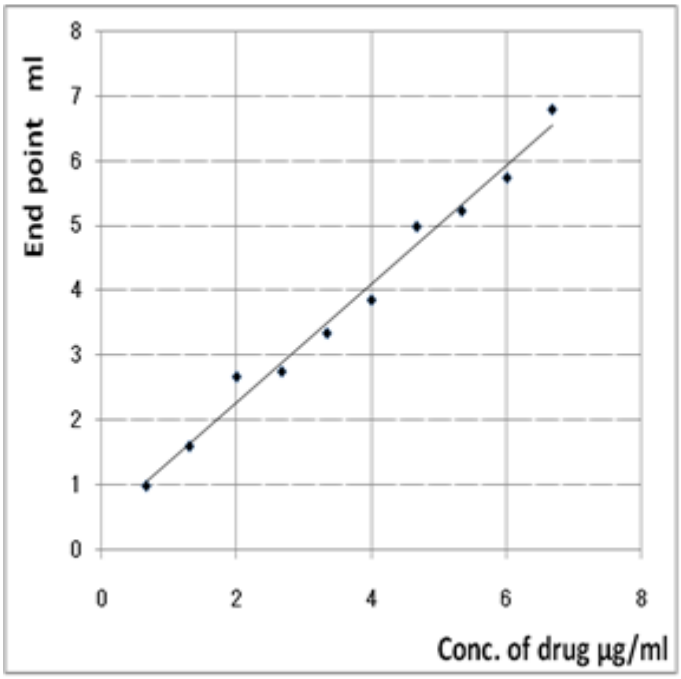


Figure 1. Cefoperazone 0.01 M titrated by silver nitrate 0.01 M

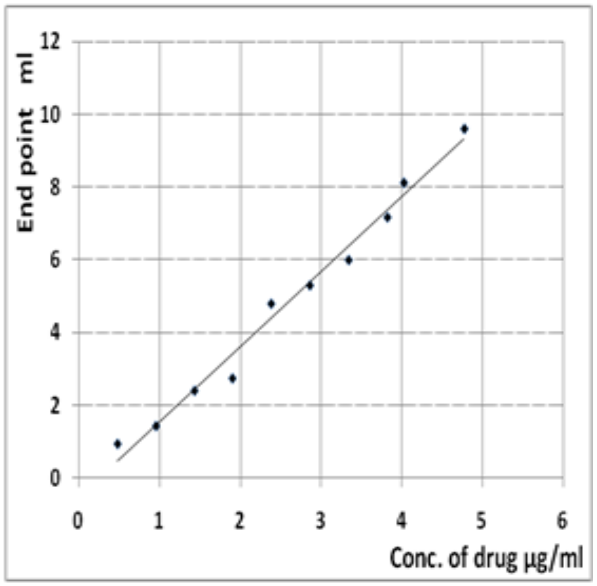


Figure 2. Cefotaxime 0.01 M titrated by silver nitrate 0.01 M

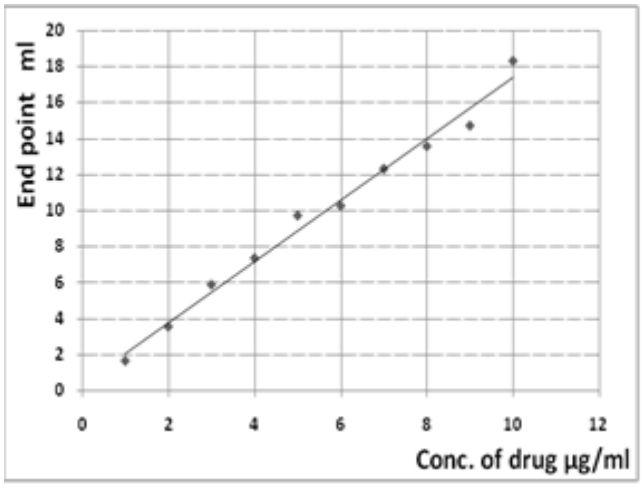


Figure 3. Ceftriaxone 0.01 M titrated by silver nitrate 0.01 M

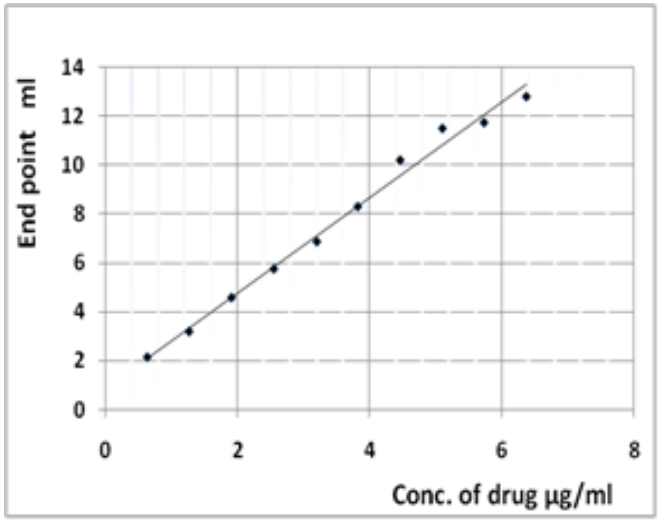


Figure 4. Ceftazidime 0.01 M titrated by silver nitrate 0.01 M

Determination of Binary Mixture of Drug

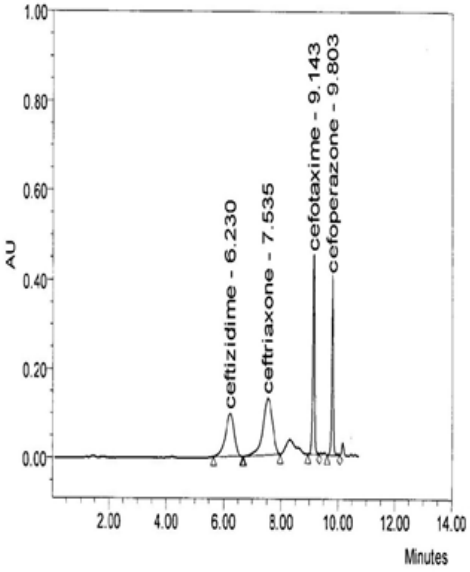
Study the work of binary combination for each of them and estimated one of them by knowing the value of the other. And by adding the amount of quantity information on another type of unknown concentration and measuring it on the results we can determine the concentration of the other antibiotic (Table 6).

Table 6. Determination of binary mixture of drug

Drug	Ceftazidime conc.	Ceftriaxone conc.	Cefotaxime conc.	Cefoperazone conc.
Ceftazidime	-	3.97 µg/liter	2.86 µg/liter	4 µg/liter
Ceftriaxone	3.82 µg/liter	-	2.86 µg/liter	4 µg/liter
Cefotaxime	3.82 µg/liter	3.97 µg/liter	-	4 µg/liter
Cefoperazone	3.82 µg/liter	3.97 µg/liter	2.86 µg/liter	-

HPLC Technique

Determination of quaternary mixture of drugs (HPLC): A mixture of the four antibiotics and their separation into HPLC device after the work of a mixture of four antibiotics and their separation of the four antibiotics were separated within 10 min.



Processed Channel Descr.:

	Peak Name	RT	Area	% Area	Height
1	ceftizidime	6.230	2023178	23.57	96597
2	ceftriaxone	7.535	2988461	34.81	126429
3	cefotaxime	9.143	1879369	21.89	441449
4	cefoperazone	9.803	1693305	19.73	394937

Figure 5. Quaternary mixture of drugs

The reported methods are new, develop fast, effective, reproducible, and inexpensive HPLC methods that can be combination methods accepted widely for the analyses of (cefoperazone, ceftazidime, cefotaxime, ceftriaxone antibiotics, The retention times of these antibiotics are moderate and have a good detection limits. These reported methods are not cost effective because of the use of costly mobile phases.

Applications

Application of innovative methods successfully in the identification of antibiotics under study on some different pharmaceutical samples with a comparison with the approved methods and gave the results of good and accurate (Table 7).

Table 7. Determination of drug in some industrial samples

Drug	Name of preparation	Proposed method		Recommended method* mg	Recovery%	RSD%
		Taken mg	Found mg			
Cefoperazone	cefoped 500 mg (Pfizer)	250	252	251	1.008	0.563
Cefotaxime	Claforan 500 mg (sanofi aventis)	250	245	253	0.980	1.42
Ceftriaxone	Xoraxon 500 mg (MUP)	250	247	252	0.988	1.5
Ceftazdime	Xtrazidime 500 mg (sanofi aventis)	250	255	251	1.02	1.40

*Recommended method following to British pharmacopeia.

STATISTICAL TREATMENT OF RESULTS

Table 8. Statistical analysis of the obtained results was carried out

Statistical Parameters	Equation	Cefoperazone	Cefotaxime	Ceftriaxone	Ceftazdime
Mean	$x^- = \sum_1 \frac{x1}{n1}$	3.801	4.854	9.712	7.707
Standard deviation	SD= $\sqrt{\frac{\sum_1 (X1-X^-)^2}{n-1}}$	0.1770392	0.2931947	0.5215659	0.3783892
Relative standard deviation	RSD% =($\frac{S}{X^-}$) 100	0.04657701	0.0604027	0.0537032	0.0490968
Standard error	SEM = ($\frac{S}{\sqrt{n}}$)	0.0559847	0.0927163	0.1649336	0.119657

Statistical analysis of the obtained results was carried out and they proved that the standard deviation and the error rate in the four methods were low. The Proposed method offer higher sensitivity and selectivity (Table 8) [23-29].

CONCLUSION

The method based on oxidation of (cefoperazone, ceftazidime, cefotaxime, ceftriaxone) with excess bromate in acidic medium was determined by this method in a micro amount of each cephalosporin drug. Among the analytical methods the potentiometric methods are simple and involve less expensive equipment with low running cost.

Sufficient sensitivity is generally obtained for drug analysis by high % recovery and low standard error. The present study describes the successful development of sensitive, selective, accurate and rapid potentiometric method for the accurate determination of (cefoperazone, ceftazidime, cefotaxime, Ceftriaxone) in pure raw materials and in formulated forms. These reported methods of separation by HPLC which are rapid sensitive are not cost effective because of the use of costly mobile phases, a mixture of the four antibiotics and their separation into HPLC device of the four antibiotics were separated within 7.0 min.

REFERENCES

[1] C Pasha; B Narayana. *Eclet Quím*. **2008**, 33 1678-4618.

[2] AR Solangi; SQ Memon; MY Khuhawar; MI Bhanger. *Acta Chromatogr*. **2007**. 19, 81-96.

[3] SA Nab; E Laiq; A Islam. *ACTA Chromatogr.* **2004**, 14, 95-101.

[4] YA Hassan; A Imran; H Iqbal; S Kishwar; AA Zeid. *LCGC Magazine Special Issues*. **2011**, 29(4), 18-23.

[5] H Gabriel; K Hajnal; R Aura; G Arpad. *J Serb Chem Soc*. **2013**, 78(9), 1413-1423.

[6] S Daniela; V Ioana; R Gabriel-Lucian. *UPB Sci Bull*. **2014**, 76(3), 1454-2331.

[7] AG Fogg; MA Abdalla. *J Pharm Biomed Anal.* **1985**, 3(4), 315-321.

[8] M Masoud; A Ali; G Elasala; SH Kolkaila. *J Chem Pharm Res*. **2017**, 9(4), 171-179.

[9] AI Vogel. Text book of quantitive inorganic analysis (6thedn), Pearson London. **2002**.

[10] A Ahmed; A Othman; A Mahmoud; S Hamdy. *Monatshefte fuÈ r Chemie*. **2000**, 131, 1031-1038.

[11] SA Alaa; HR Gamal. *Spectrochimica Acta*. **2003**, 60, 2831-2835.

[12] S Gunnar; B Lars. Drugs of natural origin: a treatise of Pharmacognosy (6revedn), Stockholm: Apotekarsocieteten. **2009**.

[13] British Pharmacopeia, The Stationary Office, London. **1998**.

[14] G David. Antimicrobial Drugs: Chronicle of a Twentieth Century Medical Triumph. OUP Oxford. **2008**.

[15] JA García-Rodríguez; JL Muñoz Bellido; JE García Sánchezx. *Int J Antimicrob Agents*. **1995**, 5(4), 231-243.

[16] Goodman & Gilman's The pharmacological basis of therapeutics. (12thedn), New York: McGraw-Hill Medical.

[17] L Gutmann; R Williamson; E Collatz. *Ann Intern Med*. **1984**, 101(4), 554-557.

[18] JMT Hamilton-Miller. *Int J Antimicrob Agents*. **2008**, 31(3), 189-192.

[19] H Jin; S Jin; H Maeng. *Biomed Chromatogr*. **2014**, 28(11), 1565-87.

[20] D Frank. Medicinal chemistry: principles and practice (2thedn), Cambridge: Royal Soc of Chemistry. **2002**.

[21] ML Klein; PJ Prescott; AD Harley. Microbiology (6thedn), Boston, Mass.: McGraw-Hill Higher Education. **2005**.

[22] T Lemke. Foye's principles of medicinal chemistry. Philadelphia: Lippincott Williams & Wilkins. **2008**.

[23] F Malouin; J Blais; S Chamberland; M Hoang; C Park; C Chan; K Mathias; S Hakem; K Dupree; E Liu; T Nguyen; MN Dudley. *Antimicrob Agents Chemother*. **2003,** 47(2), 658-664.

[24] L Miguet; A Zervosen; T Gerards; AF Pasha; A Luxen; M Distèche-Nguyen; A Thomas. *J Med Chem*.

2009, 52(19), 5926-5936.

[25] AJ Powell; J Tomberg; AM Deacon; RA Nicholas; C Davies. *J Biol Chem*. **2008**, 284 (2), 1202-1212.

[26] H Sader. *Antimicrobic Newsletter*. **1992**, 8(12), 75-82.

[27] J Singh. *Semin Pediatr Infect Dis*. **1999**, 10(1), 14-22.

[28] CC Sanders; WE Sanders. *J Infect Dis*. **1985,** 151(3), 399-406.

[29] M Trindade; H Salgado. *Phys Chem*. **2017**, 7(3), 55-62.