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AUTOMATIC POTENTIOMETERIC DETERMINATION OF SOME THIRD GENERATION CEPHALOSPORIN'S ANTIBIOTICS

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ABSTRACT

A rapid potentiometeric method was suggested for determination of micro amounts of a number of third generation cephalosporin in pure as well as in commercial samples. The method based on oxidation of (cefoperazone, ceftazidime, cefotaxime, ceftriaxone) with iodate in acidic medium. An excess of iodate solution was added to different concentration samples of each drug in sulfuric acid medium of (pH= 2-3) with heating for few minutes, followed by boiling for another 5 minutes to expel iodine. The un reacted amount of iodated was determined potentiomery by back titration with Hg(II) using Ag electrode coupled with calomel electrode(SCE). A concentrations ranging of 0.2 to 12 m mol/liter of each drug were determined by this method were found to be sensitive and precise. The method was applied for the micro determination of the suggested drugs alone or in drug mixtures as in pure and in formulated samples.

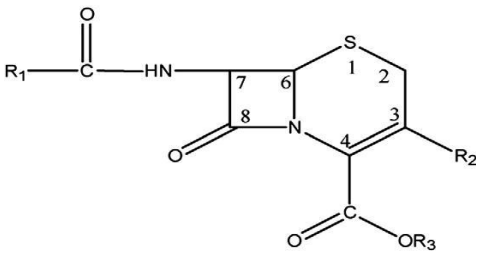
KEYWORDS: Potentiometric titration, cephlosporines, potassium iodate, back titration, pharmaceutical samples.

1.1) 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.

Cephalosporin Structure



Different methods were suggested for cephalosporins determination as

Pasha C. and Narayana B. (2008) suggested a simple method for the spectrophotometric determination of cephalosporins in pharmaceuticals using variamine blue. Solangi A., et al (2007) proposed simple and rapid capillary zone electrophoretic (CZE) method has for separation and quantification of a mixture of eight cephalosporins. Nab S., et al (2004) 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 Y., et al (2011) 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 H., et al (2013) 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 S., et al (2014) showed a spectrofluorimetric analysis of cefotaxime sodium by using 4-fluoro-7-nitrobenzofurazan as derivatization agent. Fogg A., et al (1985) proposed visible spectrophotometric determination of cephalosporins and penicillins by indophenols derivatization with and without alkaline degradation to ammonia. Teixeira M. and Regina H. (2017) 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 M., et al (2017) 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.

2) EXPERIMENTAL SECTION

2.1) Instrumentation

1) Metrohm potentiometer apparatus was used using silver amalgam electrode coupled with calomel electrode.

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

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

4) 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 0.45µm membrane filter (thermo fisher Germany).

2.2) Chemicals and solutions

Chemicals	Company	Molecular formula	Chemicals	Company	Molecular formula
Cefotaxime sodium	fresenius, Italy	$C_{16}H_{17}N_5O_7S_2$	Potassium Iodate	Merck., Germany	KIO_3
Cefoperazone	fresenius i, Italy	$C_{25}H_{27}N_9O_8S_2$	Sulfuric acid	Merck, Germany	H_2SO_4
Ceftriaxone	fresenius, Italy	$C_{18}H_{18}N_8O_7S_3$	Mercury(II)nitrate	Merck, Germany	$Hg(NO_3)_2$
Ceftazidime	fresenius, Italy	$C_{22}H_{22}N_6O_7S_2$	Disodium Hydrogen Phosphate	Merck, Germany	Na_2HPO_4
Acetonitrile	Merck, Germany	C_2H_3N			

2.3) Stock solutions

A sample of ($1x10^{-2}$ M) cefotaxime sodium was accurately weighted (4.77 gm) and quantitatively transferred into a 1000 mL volumetric flask.

A sample of ($1x10^{-2}$ M) cefoperazone sodium was accurately weighted (6.68 gm) and quantitatively transferred into a 1000 mL volumetric flask.

A sample of ($1x10^{-2}$ M) ceftriaxone sodium was accurately weighted (6.62 gm) and quantitatively transferred into a 1000 mL volumetric flask.

A sample of ($1x10^{-2}$ M) ceftazidime penta hydrate was accurately weighted (6.37 gm) and quantitatively transferred into a 1000 mL volumetric flask.

A sample of ($1x10^{-2}$ M) potassium iodate was accurately weighted (1.66 gm) and quantitatively transferred into a 1000 mL volumetric flask.

A sample of ($1x10^{-2}$ M) mercury nitrate was accurately weighted (3.247 gm) and quantitatively transferred into a 1000 mL volumetric flask.

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

All solutions were kept in the refrigerator until right before the analysis.

2.4) Procedure

2.4.1) A procedure for drug only

Take(1-10) ml of certain drug ($1x10^{-2}$ M) M in flask, put(5-15) ml potassium iodate ($1x10^{-2}$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 iodate was potentiometrically determined by back titration with mercury nitrate (II) ($1x10^{-2}$ M) using automatic potentiometer containing Ag electrode coupled with calomel electrode. Record the results and repeat the same steps with other volume and other drug.

2.4.2) Binary mixture

A) To 1ml cefoperazone (10^{-2}M) with 1 ml other drug, to a mixture add 5 ml Iodate and proceed following (2.4.1).

Find out IO_3^- equivalent to cefoperazone +ceftazidime.

B) To a second identical mixture to 1ml cefoperazone (10^{-2}M) add 5 ml iodate and proceed following (2.4.1).

Find out IO_3^- equivalent to cefoperazone.

C) By difference find out iodate equivalent to other drug.

2.4.3) A procedure for quaternary mixture of drugs

A fast, selective, and reproducible high performance liquid chromatography (HPLC) method was developed for the analyses of third-generation cephalosporin antibiotics, namely, (Cefotaxime, Cefoperazone, Ceftriaxone and Ceftazidime). The analysis was carried out on a 15c m 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 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.

2.4.4) Applications

Take 4 (0.5 gm vials) from certain finished product of drugs then mix, take 0.25 gm of the mixed vials then in 100 ml distilled water then take it and Put (10)ml of certain drug in flask, put(15) ml potassium iodate ($1x10^{-2}$M), then put 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 iodate was potentiometer determined by back titration that titrated in potentiometer apparatus with Mercury nitrate (II) ($1x10^{-2}$M) using Ag electrode coupled with calomel electrode.

3) RESULT AND DISCUTION

3.1) Determination of drug only

The results in Tables 1, 2, 3 and 4 showed that the determination of drugs (cefoperazone, ceftizdime, 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 150-300 for cefotaxime, from 350- 420 for ceftriaxone, from 200 -330 for cefoperazone and from 100-340 for ceftazidime respectively.

Table 1: Determination of cefotaxime.

Conc. µg/ml	Volume ml	End point ml	Jump ΔE/ΔV	Recovery %
0.477	1	1.8	150	99
0.954	2	2.2	180	101
1.43	3	3.7	220	102
1.9	4	6.8	220	99
2.38	5	7.1	250	101
2.86	6	7.4	300	10
3.34	7	8.6	300	98
3.82	8	11.2	250	102
4.024	9	11.4	400	99
4.774	10	13.8	800	101

Table 2: Determination of cefoperazone.

Conc. µg/ml	Volume ml	End point ml	Jump ΔE/ΔV	Recovery %
0.66	1	1.9	200	99
1.3	2	2.4	230	101
2	3	3.4	300	101
2.67	4	3.9	270	99
3.34	5	4.7	280	101
4	6	5.1	300	100
4.67	7	6.1	280	102
5.34	8	6.5	330	102
6.01	9	8.3	300	98
6.68	10	9.12	330	101

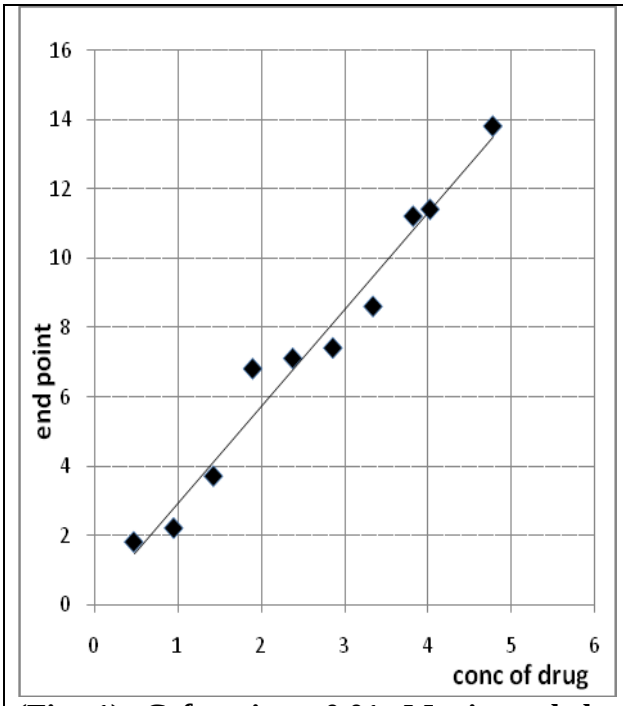
Table 3: Determination of ceftriaxone.

Conc. µg/ml	Volume ml	End point ml	Jump ΔE/ΔV	Recovery %
0.66	1	1.29	350	98
1.32	2	3.44	400	99
1.99	3	4.27	400	102
2.64	4	4.58	400	98
3.31	5	5.66	400	102
3..97	6	6.86	350	103
4.63	7	8.03	350	103
5.29	8	10.38	380	101
5.95	9	11.12	420	99
6.62	10	11.74	400	99

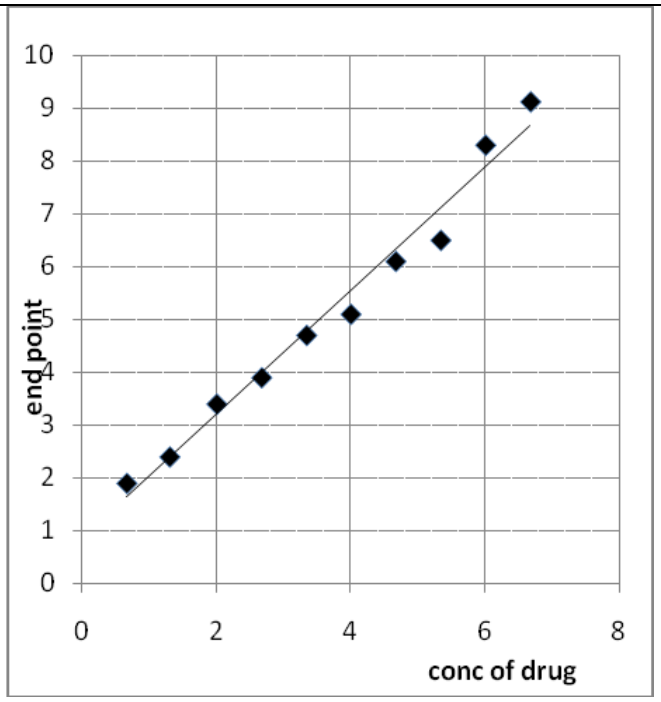
Table 4: Determination of ceftazidime.

Conc. µg/ml	Volume ml	End point ml	Jump ΔE/ΔV	Recovery %
0.637	1	1	160	98
1.27	2	1.2	100	103
1.91	3	2.5	280	102
2.55	4	2.8	330	99
3.2	5	3.1	340	102
3.82	6	3.2	250	101
4.46	7	3.4	140	99
5.1	8	4.4	300	101
5.73	9	4.6	310	102
6.37	10	4.8	220	101

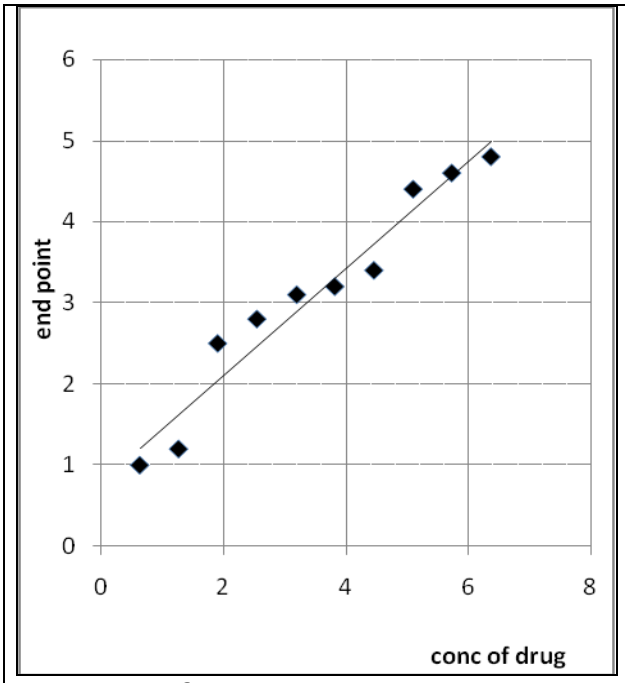
Figures 1, 2, 3, and 4 showed the linearity curves of determination of drugs (cefoperazone, ceftazidime, cefotaxime and ceftriaxone) by oxidation of with iodate in acidic medium. The results showed that there was a linear ship between end point and drug concentration with an exact end point corresponding 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.



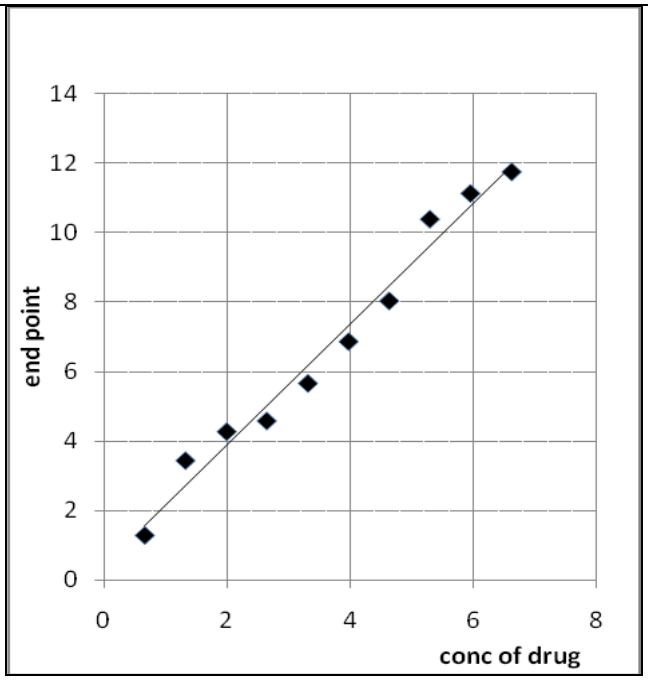
(Fig 1) Cefotaxime 0.01 M titrated by mercury (II) 0.01 M



(Fig 2) Cefoperazone 0.01 M titrated by mercury (II) 0.01 M



(Fig 3) Ceftazidime 0.01 M titrated by mercury (II) 0.01 M



(Fig 4) Ceftriaxone 0.01 M titrated by mercury (II) 0.01 M

3. 2) Determination of binary mixture of drug

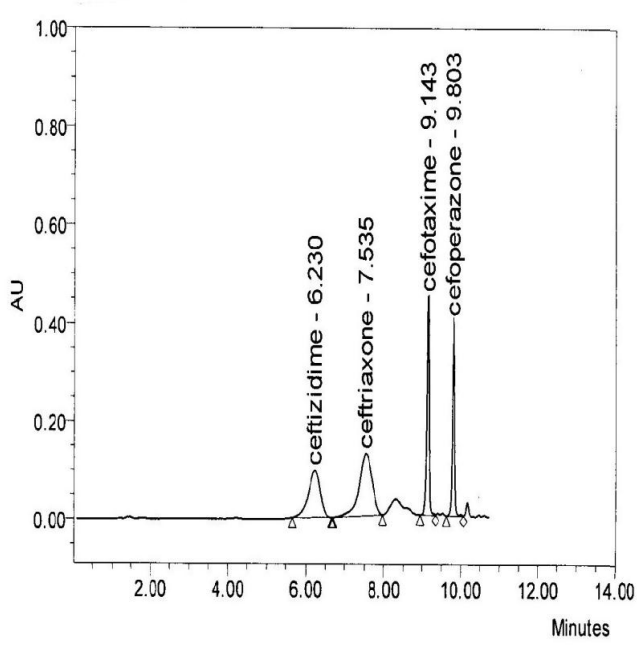
Study the work of binary combination for each of them and estimated one of them by knowing the value of the other. And by adding the amount of quantity information on another type of unknown concentration and measuring it on the results we can determine the concentration of the other antibiotic.

Table 5: Determination of binary mixture of drug.

	Ceftazidime	Ceftriaxone	Cefotaxime	Cefoperazone
Ceftazidime	-	µg/ml3.97	2.86 µg/ml	4 µg/ml
Ceftriaxone	µg/ml3.82	-	2.86 µg/ml	4 µg/ml
Cefotaxime	µg/ml 3.82	µg/ml3.97	-	4 µg/ml
Cefoperazone	µg/ml3.82	µg/ml3.97	2.86 µg/ml	-

3. 3) Determination of quaternary mixture of Drug (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 7.0 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

Fig. 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.

4) 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 6: 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	100.8	0.563
Cefotaxime	Claforan 500 mg (sanofi aventis)	250	245	253	98	1.42
Ceftriaxone	Xoraxon 500mg (MUP)	250	247	252	98.8	1.5
Ceftazdime	Xtrazidime 500 mg (sanofi aventis)	250	255	251	102	1.40

* Recommended method following to British pharmacopeia

5) STATISTICAL TREATMENT OF RESULTS

PARTMETR	Equation	Cefoperazone	Cefotaxime	Ceftriaxone	Ceftazdime
Mean	$\bar{x} = \sum_1 \frac{x1}{n1}$	5.142	7.4	6.737	3.1
Standard Deviation	$SD = \sqrt{\frac{\Sigma_1 (X1 - \bar{X})^2}{n - 1}}$	0.22663354	0.38128729	0.334122447	0.124096736
Relative Standard Deviation	RSD% =(SD/ $\bar{x}$) 100	0.044074978	0.05152530	0.049595138	0.040031205
Standard Error	SEM = (SD/√N)	0.07166782	0. 12057362	0.105658795	0.039242833

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, where they permitted the determination of the examined drugs in the low concentration ranges.

6) CONCLUSION

The method based on oxidation of (cefoperazone, ceftazidime, cefotaxime, ceftriaxone) with excess iodate 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 and senstive are used to separate a mixture of the four antibiotics at the same time with moderate retention time (6 -10 min.)with a good detection limit.

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