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Spectrophotometric Determination of Cefepime Hydrochloride, Cefoperazone Sodium, Ceftazidime Pentahydrate, Cefuroxime Sodium and Etamsylate Using Ammonium Molybdate

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Abstract:

A simple, rapid and sensitive spectrophotometric method has been developed for the quantitative determination of five drugs of pharmaceutical interest; cefepime HCl , cefoperazone Na , ceftazidime pentahydrate , cefuroxime Na and etamsylate in pure form as well as in pharmaceuticals. The method is based on the reduction of the chromogenic agent , ammonium molybdate (Mo^{6+}) , into molybdenum blue (Mo^{5+}) by the examined drugs in sulphuric acid medium and by aid of heating in boiling water bath. The resulting "blue coloured" product possess a characteristic λ_{max} at 695-716 nm. Beer s law is obeyed over the concentration range of 2-70 µg ml^{-1} with molar absorpitivities ranging from $2.704x10^3$ –$24.14x10^3$ $L.mol^{-1}.cm^{-1}$ and Sandell sensitivities ranging from $1.03x10^{-3}$ –$5.4x10^{-3}$ µg cm^{-2}. The proposed method has been applied successfully for the determination of the examined drugs both in pure form and in pharmaceutical formulations. The accuracy and precision of the proposed method are comparable with those of the reported methods .

Keywords: **spectrophotometry,ammonium molybdate,etamsylate cephalosporins, dosage forms.**

INTRODUCTION:

Cephalosporins are penicillinase-resistant antibiotics derived from moulds of "Cephalosporium" species. They differ in their antimicrobial spectrum, resistance to β-lactamase and method of administration[1]. In this work four cephalosporins have been determined, cefoperazone Na , ceftazidime pentahydrate, cefuroxime Na and the non official cephalosporin, cefepime HCl. Several procedures have been reported for analysis of cephalosporins e.g. spectrophotometry[2-10], fluorometery[11], HPLC[12-18], polarography[19-21], voltammetry[22-24], Infra red reflectance spectroscopy (IR)[25,26] and NMR[27].

Etamsylate is a haemostatic agent which is used for prophylaxis and control of heamorrhage from small blood vessels[1]. It has been determined by several methods e.g. spectrophotometry[28,29], HPLC [30], chemiluminescence[31],voltammetry[32],polarography[33,34]and potentiometry[35].

The aim of this work is to investigate the analytical utility of ammonium molybdate in the assay of the previously mentioned drugs in their pure forms and in some pharmaceutical formulations .

EXPERIMENTAL:

Apparatus :

*Shimadzu 260 UV recording spectrophotometer with matched 10 mm quartz cells was used for all absorbance measurements.

Materials and Reagents :-

All reagents were of analytical grade. Doubly distilled water was used throughout all absorbance measurements.

1- Cefepime hydrochloride;Bristol Myers Squibb, Egypt ,A Bristol Myers Squibb company, New York

2-Cefoperazone sodium; Pharco Pharmaceuticals, Alexandria, Egypt.

3-Ceftazidime pentahydrate; T3A Pharmaceuticals, Assuit, A.R.E.

4-Cefuroxime sodium;Glaxo wellcome Egypt,S.A.E., Cairo, A.R.E., under licence from Glaxo wellcome operations, U.K.

5-Etamsylate;Memphis Co. for Pharm. &Chem. Industries under licence for of OM lab. Ltd. ,Meyrin-Geneva-Switzerland.

6-Ammonium molybdate;3-4% was prepared by dissolving 3-4 gm of ammonium molydbate tetrahydrate (BDH) in 100 ml distilled water.

7-Sulphuric acid 5-6%; was prepared in distilled water.

Standard drug solutions :-

Drug stock solution of 1 mg ml^{-1} was prepared by dissolving the requisite drug amounts in distilled water. Working solutions were prepared by serial dilutions of standard drug solutions.

Formulations :

The following commercial formulations were subjected to the analytical procedures :-

1-Maxipem®vials;Bristol Myers Squibb, Egypt, containing 500 mg cefepime hydrochloride per vial.

2-Cefazone®vials;Pharco Pharmaceuticals, Alexandria, Egypt, containing cefoperazone sodium equivalent to 500 mg cefoperazone.

3-Peracef®vials;T3A Pharmaceuticals,Assuit,Egypt,containing 1.035 gm of cefoperazone sodium equivalent to 1 gm of cefoperazone.

4-Fortum® vials; Made for Glaxo Group Ltd, by Glaxo operations UK Ltd, Greenford, England, containing 2 gm of ceftazidime as pentahydrate.

5-Cetazime®vials;T3A, Assuit, A.R.E., containing 642 mg of ceftazidime pentahydrate-sodium carbonate mixture equivalent to 500 mg ceftatzidime.

6-Zinnat®tablets; Glaxo wellcome Egypt, Cairo, Egypt, containing 250 mg cefuroxime sodium.

7-Zinnat®vials;Glaxo wellcome, S.A.E., Cairo, Egypt containing cefuroxime sodium equivalent to 250 mg cefuroxime.

8-Dicynone®tablets;Memphis Co. for Pharm. and Chem. Ind. containing 250 mg etamsylate/tablet.

9-Haemostop®ampoules,Amoun Pharmaceutical CO., El-Obour city, Cairo, Egypt. Each ampoule contains 250 mg etamsylate.

Tab. 1. Optical characteristics for the reaction of examined drugs with ammonium molybdate ."Calibration data" .

Drug	Detection range (µg ml^{-1})	Molar absorpitivity ($L.mol^{-1}cm^{-1}$)	Sandell sensitivity (µg cm^{-2})	r	b	a
1-Cefepime HCl	5-35	12.75×10^3	2.45×10^{-3}	0.99999	0.0249	- 0.00359
2-Cefoperazone Na	3-28	19.8×10^3	2.97×10^{-3}	0.9999	0.0274	0.0177
3-Ceftazidime.5 H_2O	5-45	12.78×10^3	2×10^{-3}	0.99999	0.0197	0.0048
4-Cefuroxime Na	2-15	24.14×10^3	5.4×10^{-3}	0.9999	0.0541	-4.32×10^{-5}
5-Etamsylate	5-70	2.704×10^3	1.03×10^{-3}	0.9999	0.0072	0.0625

* ***Regression equation*** **:- A=a+bc**

a = intercept b = slope c = concentration (µg ml^{-1}) A = absorbance unit

Procedure:

For pure pharmaceuticals *:*

Aliquots of the standard drug solutions ranging from 20 -700 µg ml^{-1} (Tab.1) were pipetted into test tubes, followed by 2 ml of 3% - 4% ammonium molybdate and 1 - 2.5 ml 5% - 6% sulphuric acid respectively, the mixture was shaken and heated on boiling water bath maintained at ($97 \pm 0.5C^0$) for the specified times. After completion of heat treatment the solution was cooled to room temperature, transferred carefully and quantitatively to 10 ml volumetric flasks,diluted to the mark with distilled water and thoroughly mixed. The absorbance was measured at a specific wavelength (Fig.1) against a reagent blank

similarly treated (drug is omitted). The concentration is then calculated from the calibration graphs or from the regression equations.

For dosage forms:

For vials :

For analysis of injection contents, the contents of two vials are mixed well and the requisite amount equivalent to 100 mg drug was transferred to 100 ml volumetric flask and diluted to the mark with distilled water. The drug content in the diluted solution was determined as described above.

For Tablets:

Ten tablets were accurately weighed and pulverized to fine powder, an amount equivalent to 100 mg drug was extracted with 3 x 25 ml portions of distilled water, the portions were filtered into 100 ml volumetric flasks,the filter washed with distilled water and the solution diluted up to the mark with water.The drug content in the obtained extract is determined as under the general procedure.

For Ampoules:

The requisite volume equivalent to 100 mg of the active ingredient was transferred to 100 ml volumetric flasks & diluted to the mark with distilled water. Drug content is determined following the general procedure.

Results and Discussion:

The absorption spectra of the reaction products were measured against a reagent blank in the range of 500-900 nm. It shows a characteristic λ_{max} at 695 nm for cefepime HCl , cefoperazone Na and cefuroxime Na, at 710 nm for ceftazidime pentahydrate and at 716 nm for etamsylate where the blue colour was fully developed which could be attributed to the reduction of ammonium molybdate (Mo^{6+}) into molybdenum blue (Mo^{5+}) by the tested drugs in sulphuric acid medium. (Fig.1).

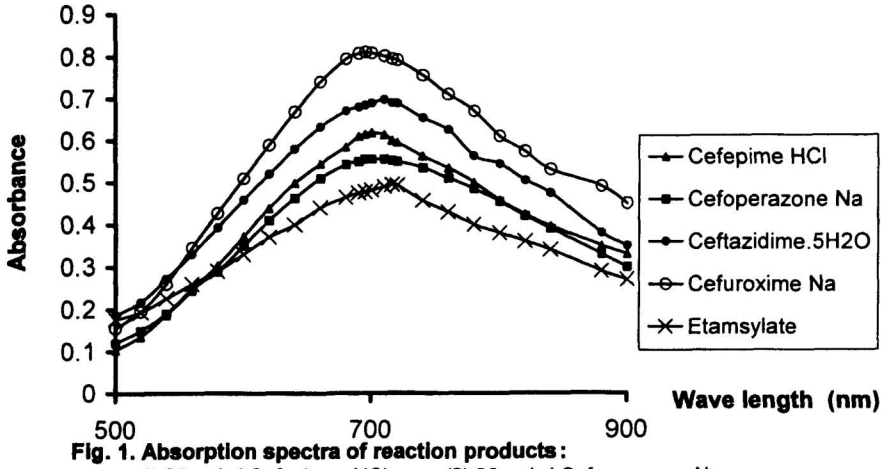

Fig. 1. Absorption spectra of reaction products:
(1) 25 ug/ml Cefepime . HCl (2) 20 ug/ml Cefoperazone Na
(3) 35 ug/ml Ceftazidime .5 H2O (4) 10 ug/ml Cefuroxime Na
(5) 60 ug/ml Etamsylate

A preliminary study was performed to determine the optimum reaction conditions which were established depending on the development of maximum colour intenisty and stability of the reaction products on variation of parameters such as concentration and volume of both ammonium molybdate and sulphuric acid, reaction temperature, time of heating and sequence of addition of the reactants.

Tetracycline HCl was determined using sodium molybdate in hydrochloric acid medium , the amber colour developed which absorps at 430 nm was attributed to formation of molybdenum (III)[36] , however on using hydrochloric acid for determination of the cited drugs with ammonium molybdate; it caused disappearance of the blue colour at acidity higher than 5%, while turbidity occurred at lower acidity (less than 3%). So for these reasons, HCl is omitted and sulphuric acid is used instead.

The sequence of addition of the reactants recommended in the general procedure produced quantitative results, other orders as

described by Sultan [36]or Basavaiah[37] caused a marked decrease in absorbance in case of etamsylate , however no marked difference in absorbance in case of other drugs. So for etamsylate, we should preceed strictly as described under the general procedure.

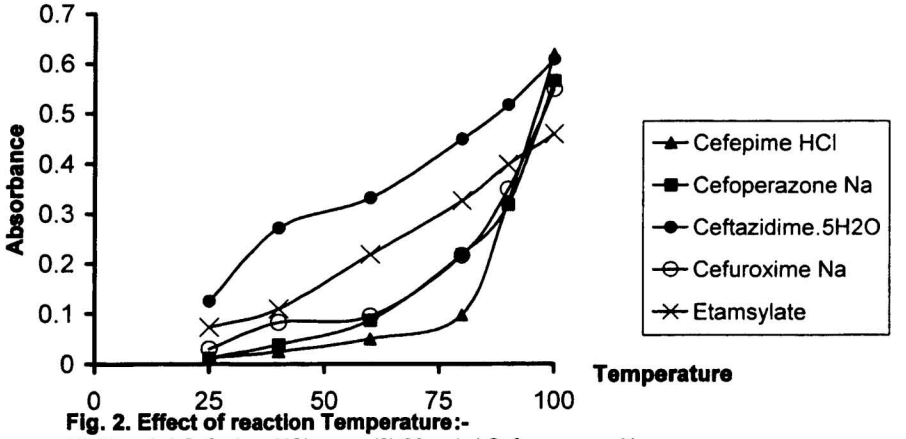

Fig. 2. Effect of reaction Temperature:-
(1) 25 ug/ml Cefepime.HCl (2) 20 ug/ml Cefoperazone Na.
(3) 35 ug/ml Ceftazidime.5H2O (4) 10 ug/ml Cefuroxime Na.
(5) 55 ug/ml Etamsylate.

Samples prepared as described under the general procedure were left at different sets of temperatures ranging from 25 - 100°C for a fixed time (Fig.2&3). Maximum absorbance and sensitivity were obtained by heating the reactants on boiling water bath (97± 0.5°C) ,measurements taken before the recommended times rendered inaccurate results and heating beyound these times decreased the absorbance (Fig.3). At lower temperatures (below 97°C) , the rate of colour development becomes progressively slower where at room temperature there was no visible formation of any coloured product, for these reasons; development times (Fig. 3) on boiling water bath were adopted for all subsequent measurements to insure complete oxidation of the drug.

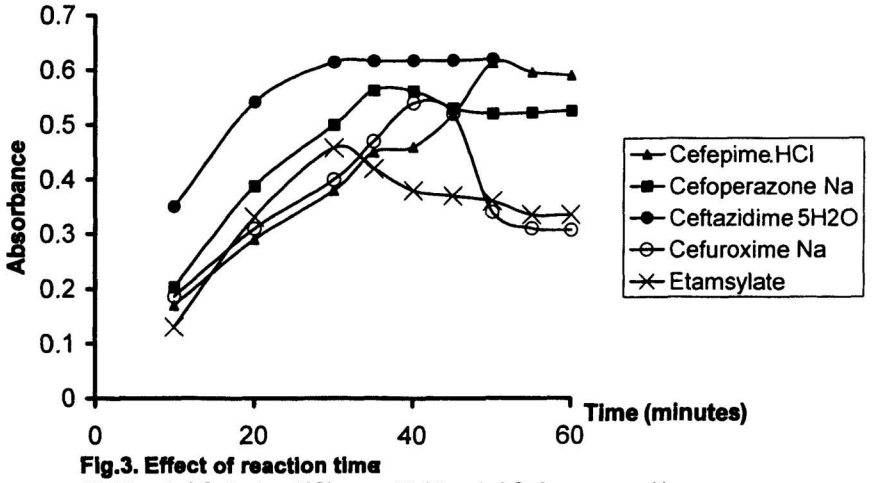

Fig.3. Effect of reaction time
(1) 25 ug/ml Cefepime.HCL (2) 20 ug/ml Cefoperazone Na
(3) 35 ug/ml Ceftazidime.5H2O (4) 10 ug / ml Cefuroxime Na
(5) 55 ug/ml Etamsylate.

Various concentrations of ammonium molybdate from 1-6% were used to investigate maximum colour development in presence of a fixed concentration of sulphuric acid.Alternatively,various concentrations of sulphuric acid ranging from 1 - 10% were used in presence a fixed concentration of ammonium molybdate. It is found that 3% - 4% ammonium molybdate was suitable (Fig.4), lower or higher concentrations gave deviant results. Concerning H_2SO_4 , 5% - 6% was suitable where higher concentrations (specially 10%) caused fading of the blue colour while lower concentrations gave marked lower absorbance (Fig.5).

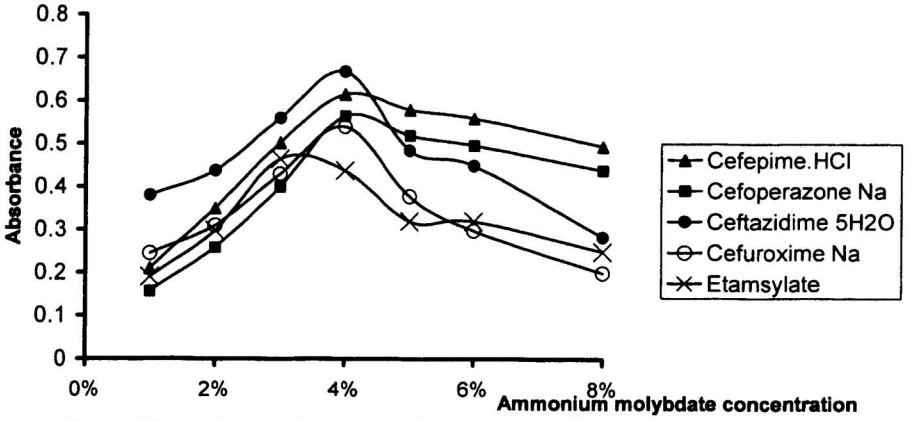

Fig.4. Effect of Ammonium molybdate concentration:
(1) 25 ug/ml Cefepime.HCl (2) 20 ug/ml Cefoperazone Na.
(3) 35 ug/ml Ceftazidime.5H2O (4) 10 ug / ml Cefuroxime Na
(5) 55 ug/ml Etamsylate.

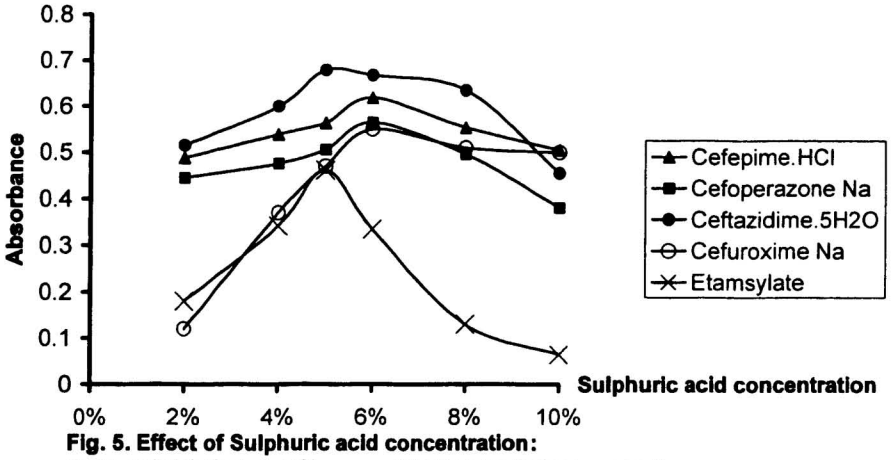

Fig. 5. Effect of Sulphuric acid concentration:
(1) 25 ug/ml Cefepime.HCL (2) 20 ug/ml Cefoperazone Na.
(3) 35 ug/ml Ceftazidime.5H2O (4) 10 ug / ml Cefuroxime Na.
(5) 55 ug/ml Etamsylate.

Another study on the needed volumes of the fixed concentrations of both ammonium molybdate and sulphuric acid showed that 2-2.5 ml of ammonium molybdate (3 - 4%) and 1-2.5 ml of H_2SO_4 (5 - 6%) were adequate for maximum absorbance , higher or lower volumes gave deviant results.(Fig. 6&7).

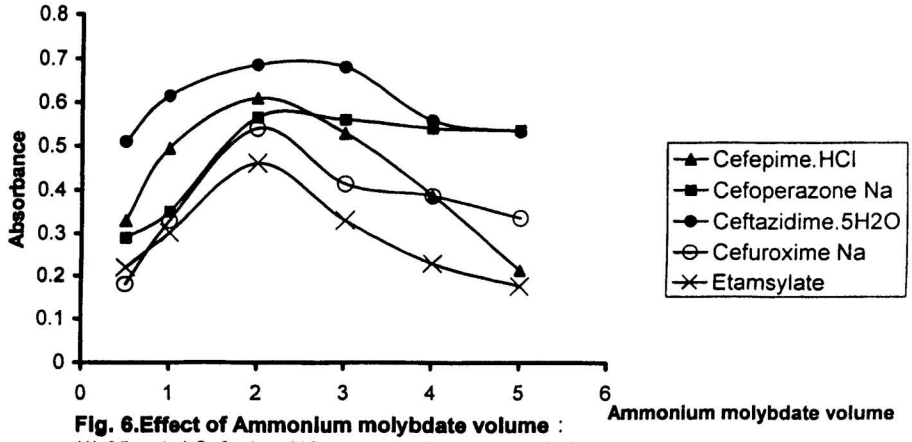

Fig. 6.Effect of Ammonium molybdate volume :
(1) 25 ug/ml Cefepime.HCl (2) 20 ug/ml Cefoperazone Na.
(3) 35 ug/ml Ceftazidime.5H2O (4)10 ug / ml Cefuroxime Na.
(5) 55 ug/ml Etamsylate.

The colour obtained was found to be stable for at least 24 hours at room temperature. The effects of common additives and excepients were studied and it was found that there were no interferences. So the examined drugs can be assayed directly in their dosage forms by the suggested method without prior extraction or separation.

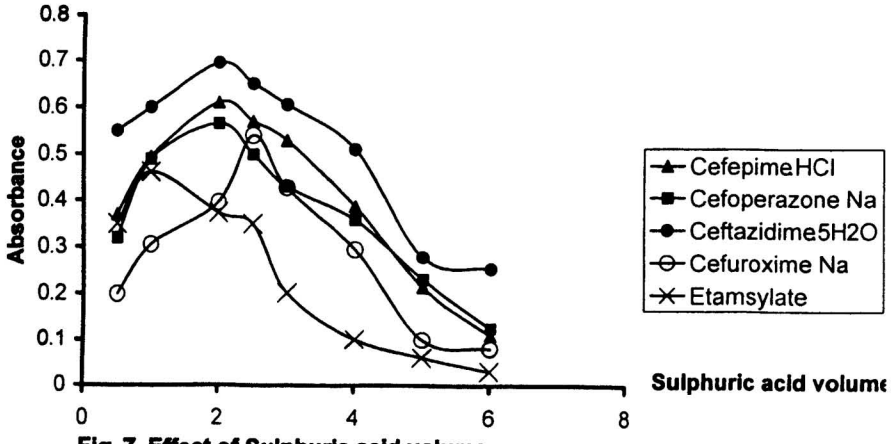

Fig. 7. Effect of Sulphuric acid volume
(1) 25 ug/ml CefepimeHCl (2) 20 ug/ml Cefoperazone Na
(3) 35 ug/ml Ceftazidime5H2O (4) 10 ug / ml Cefuroxime Na
(5) 55 ug/ml Etamsylate

Tab. 2. Comparative analytical results of the proposed and the reported methods for the tested drugs in pure forms:-

Statisical parameters	Cefepime .HCl		Cefoperazone Na		Ceftazidime .5H_2O		Cefuroxime Na		Etamsylate	
	Proposed method	Reference method (8)	Proposed method	Reference method (6)	Proposed method	Reference method (10)	Proposed method	Reference method (10)	Proposed method	official method (38)
Mean %recovery	99.99	99.81	99.9	99.6	99.96	100.4	100	99.98	100.099	100.3
N	11	5	9	7	8	5	8	5	9	4
Variance	0.02	0.059	0.165	0.176	0.084	0.185	0.025	0.102	0.336	0.250
S.D.	0.141	0.243	0.406	0.420	0.290	0.430	0.159	0.320	0.580	0.500
S.E.	0.043	0.109	0.135	0.159	0.103	0.192	0.056	0.143	0.193	0.250
R.S.D.	0.141	0.243	0.406	0.422	0.290	0.428	0.159	0.320	0.579	0.499
"t"	1.536(2.145)		1.44(2.145)		2.019(2.201)		0.130(2.201)		0.636(2.201)	
F	2.95 (3.48)		1.067(3.58)		2.202(4.12)		4.08 (4.12)		1.344(4.07)	

N = Number of experiments
S.E. = Standard error
S.D. = Standard deviation
t = "t" test of unpaired data
F = Variance test

Calibration graphs:

Calibration graphs were constructed by plotting the concentration of the drug against the corresponding absorbance values. The resulting graphs were linear from 5 - 35 μg ml^{-1} for cefepime HCl ,3 – 28 μg ml^{-1} cefoperazone Na ,5 – 45 μg ml^{-1} ceftazidime pentahydrate, 2 - 15 μg ml^{-1}cefuroxime Na and 5 - 70 μg ml^{-1} etamsylate. The linearity of calibration graphs is apparent from the correlation coeffecient, r, and the intercepts which are nearly close to zero. All calibration data are calculated and listed in (Tab.1)

Tab.3. Comparative analytical results of the proposed and reported method for the tested drugs in same pharmaceutical formulations.

Formulation	Statistical Parameters	Proposed method		Reference method
		Calibration method	Standard addition method	
1- Maxipem® vials	Mean %recovery	99.87	100.05	99.8 (8)
	N	11	10	5
	Variance	0.244	0.109	0.152
	S.D.	0.494	0.330	0.390
	S.E.	0.149	0.104	0.174
	R.S.D.	0.495	0.330	0.391
	"t"	0.306 (2.145)	1.233 (2.160)	
	F	1.605 (3.48)	1.394 (3.63)	
2-Cefazone® vials	Mean %recovery	99.79	99.5	99.2 (6)
	N	8	9	5
	Variance	0.336	0.185	0.198
	S.D.	0.580	0.430	0.445
	S.E.	0.205	0.143	0.199
	R.S.D.	0.581	0.432	0.449
	"t"	2.065 (2.201)	1.224 (2.179)	
	F	1.697(4.12)	1.07 (3.84)	
3-Peracef ® vials	Mean %recovery	100.1	99.8	100 (6)
	N	8	8	5
	Variance	0.219	0.112	0.201
	S.D.	0.468	0.335	0.448
	S.E.	0.165	0.118	0.200
	R.S.D.	0.468	0.336	0.448
	"t"	0.386 (2.201)	0.861 (2.201)	
	F	1.09 (4.12)	1.795(4.12)	
4- Fortum® vials	Mean %recovery	99.6	100.18	100 (10)
	N	9	13	5
	Variance	0.812	0.102	0.298
	S.D.	0.901	0.319	0.546
	S.E.	0.300	0.088	0.244
	R.S.D.	0.905	0.318	0.546
	"t"	1.034 (2.179)	0.694 (2.120)	
	F	2.725(3.84)	2.92 (3.26)	

Formulation	Statistical Parameters	Proposed method		Reference method
		Calibration method	Standard addition method	
5- Cetazime ® vials	Mean %recovery	101.1	100.8	100.9 (10)
	N	9	9	5
	Variance	0.397	0.033	0.118
	S.D.	0.630	0.183	0.344
	S.E.	0.210	0.061	0.154
	R.S.D.	0.623	0.182	0.341
	"t"	0.768 (2.179)	0.604 (2.179)	
	F	3.364(3.84)	3.576 (3.84)	
6- Zinnat® tablets	Mean %recovery	99.07	99.38	99.47 (10)
	N	7	10	5
	Variance	0.280	0.114	0.397
	S.D.	0.529	0.337	0.630
	S.E.	0.200	0.107	0.282
	R.S.D.	0.534	0.339	0.633
	"t"	1.157 (2.228)	0.298 (2.160)	
	F	1.418 (4.53)	3.482(3.63)	
7- Zinnat ® vials	Mean %recovery	99.08	99.14	99.3 (10)
	N	8	8	5
	Variance	0.370	0.155	0.260
	S.D.	0.608	0.394	0.510
	S.E.	0.215	0.139	0.228
	R.S.D.	0.614	0.397	0.514
	"t"	0.702 (2.201)	0.599 (2.201)	
	F	1.423(4.12)	1.677 (4.12)	
8-Dicynone® tablets	Mean %recovery	98.6	99	99.38 (38)
	N	9	11	4
	Variance	0.706	0.297	0.608
	S.D.	0.840	0.545	0.780
	S.E.	0.280	0.164	0.390
	R.S.D.	0.852	0.551	0.785
	"t"	1.625 (2.201)	0.898 (2.160)	
	F	1.161 (4.07)	2.047 (3.71)	
9-Haemostop® ampoules	Mean %recovery	99.2	100.4	99.8 (38)
	N	9	7	7
	Variance	0.221	0.335	0.504
	S.D.	0.470	0.579	0.710
	S.E.	0.157	0.219	0.268
	R.S.D.	0.474	0.577	0.711
	"t"	1.932 (2.145)	1.734 (2.179)	
	F	2.281 (3.58)	1.504 (4.28)	

N = Number of experiments S.D. = Standard Deviation S.E. = Standard Error
R.S.D.= Relative Standard Deviation t = "t" test of unpaired data. F = Variance test

Sensetivity, Accuracy and Precision

The mean molar absorpitivity **(Σ)** and Sandell's sensitivity **(S)** for each drug was calculated from Beer's law and their values are given in (Tab.1) . The % S.D. and % range of S.E. at 95% confidence limits are given in (Tab. 2&3).

The utility of this method was verified by means of replicate measurements of pharmaceutical formulations and recovery experiments.

Recoveries were determined either by standard addition method or by calibration method.

The performance of this method was assessed by calculation of "t" and F values compared with the reported methods for determination of these drugs, results showed that no significant difference in accuracy and precision between the reported methods and the proposed method (Tab. 2&3).

Conclusion

The proposed method is advantageous when compared to many of the reported spectrophotometric methods in having higher sensitivity. The data given before reveal that the proposed spectrophotometric method is simple & sensitive with good accuracy and precision. It doesn't require expensive toxic chemicals or sophisticated experimental setup. It can be used directly to determine the examined drugs without prior extraction as common additives don't interfer.

REFERENCES:

[1] Martindale ,The Complete Drug Reference, 32nd edition , (1999).

[2] Morelli B.
First - and second – derivative spectrophotometric assay of mixtures of cefuroxime and cephalexin.
J. Pharm. Biomed. Anal. 1988;6: 199-209.

[3] Morelli B.
"Zero – crossing" derivative spectrophotometric determination of mixtures of cefapirin sodium and cefuroxime sodium in pure form and in injections.
Analyst 1988;113:1077-82.

[4] Morelli B.
Application of "zero – crossing" derivative spectrophotometry to the analysis of mixtures of cefoperazone and cefamandole nafate in pure and pharmaceutical dosage forms.
Anal. Lett. 1988;21(5): 759-72.

[5] Issopoulos P B.
Spectrophotomeric detrmination of certain cephalosporins using molybdophosphoric acid.
Analyst 1989;114(2): 237-9.

[6] Galal S M.
Colourimetric determination of five cephalosporins using mercurochrome.
Acta Pharm. Jugol. 1991;41(1): 25-31.

[7] Parra A,Garcia-Villanova J, Rodenas V, Gomez M D.
First- and second – derivative spectrophotometric determination of cefoperazone and sulbactam in injections.
J. Pharm. Biomed. Anal. 1994;12: 653-7.

[8] Rodenas V, Parra A, Garcia- Villanova J, Gomez M D.
Simaltanious detrmination of cefepime and L– arginine in injections by second – derivative spectrophotometry.
J. Pharm. Biomed. Anal. 1995 ;13(9): 1095-99.

[9] Kelani K, Bebawy L I, Abdel-Fattah L.
Stability – indicating soectrophotometric and densitometric methods for determination of some cephalosporins.
J. AOAC Int. 1998;81: 386-93.

[10] Amin A S, Khalil H M, Saleh H M,
Spectrophotometric estimation of cefuroxime and ceftazidime in bulk and dosage forms.
Sci. Pharm. 2001; 69:143-50.

[11] Murillo J A, Lemus J M, Garcia L F.
Spectrofluorimetric analysis of cefuroxime in pharmaceutical dosage forms.
J. Pharm. Biomed. Anal. 1994 ;12(7):875-81.

[12] Dupont D G, De-Jager R L.
High – performance liquid – chromatographic determination of cefoperazone in serum.
J. Liq. Chromatogr. 1981; 4(1) :123-8.

[13] Hwang P T R, Meyer M C.
High – performance liquid – chromatographic micro – assay for cefoperazone in human plasma , urine and c.s.f. .
J. Liq. Chromatogr. 1983; 6(4): 743-54.

[14] Leeder J S, Spino M, Tesoro A M, Macleod S M.
High – performance liquid – chromatographic analysis of ceftazidime in serum and urine.
Antimicrob. Agents Chemother. 1983 ;24 (5): 720-4.

[15] Nahata M C, Morosco R S.
Measurement of ceftazidime arginine in aqueous solution by HPLC.
J. Liq. Chromatogr. 1992;15 (9):1507-11.

[16] Bompadre S, Ferrante L, Alo F P, Leone L.

Online solid – phase extraction of ceftazidime in serum and determination by HPLC.
J. Chromatogr. B, Biomed. Appl. 1995; 669(2): 265-9.

[17] Barnes A R.
Determination of ceftazidime and pyridine by HPLC , application to a viscous eye drop formulation.
J. Liq. Chromatogr. 1995;18(15): 3117-28.

[18] El-Khaili H, Linger L, Monteil H, Jehl F.
High – performance liquid – chromatographic assay of cefepime in serum.
J. Chromatogr., - B:- Biomed. Appl. 1997, 690 (1-2), 181-8.

[19] Bernacca G, Nucci L, Pergola F.
Polarographic behaviour of beta lactam antibiotic cefuroxime and study of reaction mechanism in acidic media.
Electroanalysis (NY) 1994;6: 327-32.

[20] Reddy G V S, Reddy S J.,
Estimation of cephalosporin antibiotics by differential pulse polarography.
Talanta1997;44:627-31.

[21] Ferreira V S, Zanoni M V B, Furlan M, Foggy A G,
Differantial pulse polarographic determination of ceftazidime in urine samples with or without prior extraction.
Anal. Chem. Acta 1997;351(1-3):105-14.

[22] Ogorevc B, Krasna A, Hudnik V, Gomiscek S.
Adsorptive stripping voltammetry of selected cephalosporin antibiotics and their direct determination in urine.
Mikrochim. Acta 1991; I (3-4): 131-44.

[23] Ali A M M, El-Maali N A, Ghandour M A.
Electrochemical reduction and oxidation of two cephalosporin antibiotics: ceftriaxone (Rociphen) and cefopeazone (Cefobid).
Electroanalysis (Ny) 1993 ;5(7): 85-9.

[24] Ferreira V S, Zanoni M V B, Foggy A G.
Indirect cathodic – stripping voltammetric determination of ceftazidime as mercury salt.
Anal. Chim. Acta 1998;367(1-3):255-9.

[25] Corti P, Dreassi E, Ceramelli G, Lonardi S, Vivani R, Gravina S.
Near infera – red reflectance spectroscopy applied to pharmaceutical quality control . Identification and assay of cephalosporins.
Analusis1991;19:198-204.

[26] Bugay D E, Newman A W, Findlay W P.
Quantation of cefepime dihydrochloride dihydrate in cefepime dihydrochloride monohydrate by diffuse reflectance IR and powder X – ray differaction techniques.
J. Pharm. Biomed. Anal. 1996;15: 49-61.

[27] Ryan D A, Sanders J K , Curtis G C, Hughes H.

NMR study of whole rat bile: The biliary excretion of cefoperazone and benzyl chloride by an isolated perfused rat liver. J. Pharm. Biomed. Anal. 1995;13(6): 723-34.

[28] Huang S, Bi Q, Sun N.
Determination of the content of ethamsylate injection by cerimetry and by UV sprctrophotometry.
Yaowu Fenxi Zazhi 1988,8(5), 319-27.

[29] Xu Z C, Li X Y, Shi J, Yao X J, Liu A Z, He Z S.
Determination of Dicynone (ethamsylate) in gastric mucosa by UV spectrophotometry.
Fenxi Huaxue 1994;22(4):420.

[30] Ma J, Liu Y.
Quantitative analysis of etamsylate by HPLC.
Yaowu Fenxi Zazhi 1984;4(4):209-11.

[31] Zhang C X, Huang J C, Feng M L, Zhang Z J.
Flow injection Chemiluminescence determination of etamsylate with electrogenerated hypochlorite.
Anal. Lett. 1998,31(11), 1917-28.

[32] Yang C J, Jin L T, Leng Z Z.
Determination of microscale ethamsylate on a carbon paste electrode with adsorptive voltammetry.
Yaowu Fenxi Zazhi 1998;18: 311-14.

[33] Noninski V, Sobovale E, Dryanovska-Noninska L.
Anodic polarographic determination of ethamsylate (Dicynone) with the help of the self rotating electrode.
Farmacia 1987;35(3):175-9.

[34] Wang Y, Wang W, Qing G.
Determination of ethamsylate in injection solution by a.c. oscillopolarography.
Yaowu Fenxi Zazhi 1990;10(2):113-4.

[35] Hassan S S M, El-Banhasawy R M, Rizk N M.
Membrane sensors for batch and flow injection potentiometric determination of ethamsylate in pharmaceutical preparations.
Microchim. Acta 1997;126(3-4): 217-222.

[36] Sultan S M.
Spectrophotometric determination of tetracycline with sodium molybdate.
Analyst 1986 ;111: 97-9.

[37] Basavaih K, Krishnamurthy G.
Spectrophotometric assay of some antipsychotropic and anticholinergic phenothiazine drugs using ammonium molybdate.
Anal. Lett. 1998;31(6):1037-1046.

[38] British Pharmacopeia, The Stationary Office, London 1998 :547.

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