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Indirect Spectrofluorometric Method for the Determination of Cefotaxime Sodium, Ciprofloxacin Hydrochloride and Famotidine in Pharmaceuticals Using Bromate-Bromide and Acriflavine Dye

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Abstract:

An Indirect simple sensitive and applicable spectrofluorometric method has been developed for the determination of Cefotaxime Sodium (CEF), ciprofloxacin Hydrochloride (CIP) and Famotidine (FAM) using reaction system bromate-bromide and acriflavine (AF) as fluorescent dye. The method is based on the oxidation of drugs with known excess bromate-bromide mixture in acidic medium and subsequent determination of unreacted oxidant by quenching fluorescence of AF. Fluorescence intensity of residual AF was measured at 528 nm after excitation at 402 nm. The fluorescence-concentration plots were rectilinear over the ranges 0.1-3.0, 0.05-2.6 and 0.1-3.8 µg ml^{-1} with lower detection limits of 0.013, 0.018 and 0.021 µg ml^{-1} and quantitation limits of 0.044, 0.060 and 0.069 µg ml^{-1} for CEF, CIP and FAM respectively. The common excipients and additives didn't interfere in their determination. The developed method was successfully applied for determination of the studied drugs in their dosage forms resulted in a good agreement with standard British pharmacopeia method and standard addition procedure.

Key words: Acriflavine, Cefotaxime Sodium, Ciprofloxacin Hydrochloride, Famotidine, Spectrofluorometric Determination.

Introduction:

Cefotaxime sodium (CEF) (Fig. 1) has the common name Claforan (1), chemically known as: Sodium-3-[(acetyloxy)methyl]-7-[[(2Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino) acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2- carboxylate (2). It is the first antibiotic of the third generation of cephalosporins (3). It is an antibacterial agent used to treat several types of bacterial infections (1). Literature contains various procedures for the estimation of CEF; HPLC (4, 5, 6), spectrophotometric (7, 8, 9), spectrofluorimetric (10, 11) and atomic absorption spectroscopic methods (12).

Ciprofloxacin hydrochloride (CIP) (Fig. 1) chemically: 1-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (2). It is used as a second- or third-line treatment for bacterial infections of urinary tract (13).

Due to the importance of CIP, many methods and technics have been reported for its determination; HPLC (14, 15, 16), spectrophotometric (17-20), spectrofluorimetric (21) and electrochemical methods (22, 23, 24).

Famotidine (FAM) (Fig. 1) chemically named 3-[[[2-[(Diaminomethylene)amino]thiazol-4-yl]methyl]sulfanyl]-N`-sulfamoylpropanimidamide (2). It is used as a histamine-H_2 blocker for treatment of peptic ulceration and regulation of gastric acid secretion (1). Several methods have been developed for the determination of FAM. For example; HPLC (25, 26, 27), spectrophotometric (28, 29, 30, 31) and Polarographic methods (32).

Acriflavine (AF) (Fig. 1) (10-methyl-3,6-diaminoacridinium chloride) is a basic fluorescent yellow staining dye (33). It binds to DNA for microscopical characterization (34). It is also used as antiseptic (35, 36). It has improved the responding of tumors toward medical therapy (37). Because of AF fluorescence characteristic, it has been used to estimate some drugs fluorometrically by quenching fluorescence of the dye (38, 39, 40). According to this advantage, this paper suggests an indirect fluorometric method for the determination of CIP, CEF and FAM drugs in acidic medium

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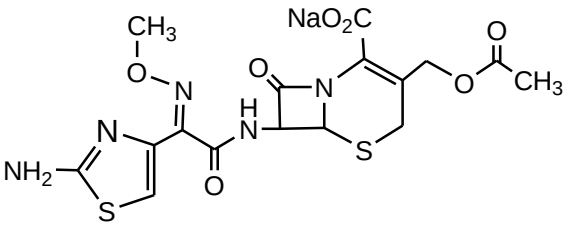
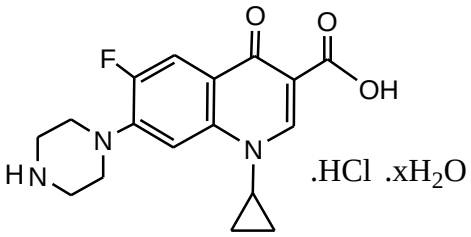
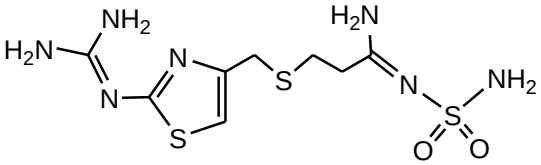
using reaction system bromate-bromide and AF as fluorescent dye. The aim of the present work was to develop a new, simple and sensitive spectrofluorometric method for routine evaluated procedure of studied drugs in their dosage forms.



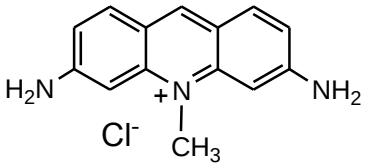
Cefotaxime sodium



Ciprofloxacin hydrochloride



Famotidine



Acriflavine

Figure 1. Chemical structures of studied drugs and AF dye

Experimental:

Apparatus

Fluorescence measurements were accomplished by using Shimadzu RF-5301PC Spectrofluorophotometer-Japan with xenon lamp. A standard 1 cm path-length quartz cell was used for all the measurements. Heating processes were carried out by BS-11 water bath equipped from Lab. Companion-Korea. A KERN ABS-Germany electronic balance was used for weighing. For pH measurements a pH meter OAKTON pH2100 with CE 10-12 electrode was used. For a perfect dissolving POWER SONIC 405 ultrasonic Cleaner equipped from Lab Tech-Korea was used.

Chemicals and Reagents

All chemicals used were of analytical reagent grade. distilled water was used to prepare all the solutions. Stock solutions equivalent to 100 µg ml^{-1} of pure CEF, CIP and FAM (SDI-Iraq) were prepared by dissolving 0.0100 g each of them in distilled water (with heating in case of FAM) then diluted to 100 ml with distilled water. Working standard solutions equivalent to 10 µg ml^{-1} CEF, CIP and FAM were obtained by appropriate dilution of stock solution.

Hydrochloric acid (1 mol l^{-1}) was prepared by diluting 16.6 ml of concentrated acid (Scharlau-Spain, Sp.gr. 1.19 g cm^{-3}) to 200 ml with distilled water. AF solution was prepared by dissolving 0.0100 g of dye powder (BDH) in distilled water and diluting to 200 ml in a calibrated flask to get 50 µg ml^{-1}.

A standard solution equivalent to 2.0×10^{-3} mol l^{-1} $KBrO_3$-2.0×10^{-2} mol l^{-1} KBr was prepared by dissolving 0.0334 g of $KBrO_3$ (BDH) and 0.2380 g of KBr (BDH) in distilled water and diluting to 100 ml in calibrated flask to obtain 334 µg ml^{-1}. The latter solution was diluted appropriately with distilled water to get a working concentration of 25 µg ml^{-1}.

Procedure for calibration graph: A 1 ml of 1 mol l^{-1} HCl was added to a series of 10 ml volumetric flask, followed by adding 1 ml of 25 µg ml^{-1} bromate-bromide mixture. An increasing volume of 10 µg ml^{-1} of drug solution was added to cover the range 0.1-3.0, 0.05-2.6 and 0.1-3.8 µg ml^{-1} of CEF, CIP and FAM respectively. The mixing flasks were allowed to stand at room temperature for 10 min (or 15 min in case of CEF). Then 1.2 ml of 50 µg ml^{-1} AF solution was added, the volume was adjusted to the mark with distilled water and mixed well. After 10 min, the fluorescence intensity was measured at 528 nm with excitation wavelength of 402 nm.

Formulations: Different brands of CIP, CEF and FAM have been obtained (three brands of each). CIP formulations were 500 mg of each: Ciproneer from PIONEER Pharmaceuticals-Iraq, Cipronatin from ATABAY Pharmaceuticals-Turkey and Alcipro from ALKEM Laboratories LTD-India. CEF vial formulations obtained in 1 g dosages were: Cefotaxime Normon from Laboratorios Normon-Spain, Cefagen from BiLim Pharmaceuticals-Turkey and Brucitax from BRAWN Laboratories Limited-India. FAM

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preparations were: Gastrofam 40 mg from ATABAY Pharmaceuticals-Turkey, Ulceran 20 mg from MEDOCHEMIE LTD-Cyprus and Famodar 20 mg from Dar Al Dawa-Jordan.

Procedure for tablets: Ten tablets of each brand (certified value 500 mg CIP, 40 or 20 mg FAM) were weighed and ground into a fine powder. An accurately weighed portion of powder equivalent to one tablet was transferred into a 500 ml calibrated flask. The volume was made up to the mark with distilled water. After being sonicated for 10 min, the solution was filtrated through Whatman No. 42 filter paper, the filtrates were suitably diluted to obtain 10 µg ml^{-1} as a suitable concentration for the analysis.

Procedure for vials: Contents of three vials of each brand were weighed (certified value 1 g for each vial), their average was taken and dissolved in distilled water then diluted to 100 ml in calibrated flask. The solutions were suitably diluted to obtain 10 µg ml^{-1} for each brand.

Results and Discussions:

AF is a basic fluorescent yellow dye (33). It gives a maximum fluorescence intensity at 528 nm with excitation wavelength of 402 nm in the presence of 1 ml of 1 mol l^{-1} HCl (Fig. 2). The fluorescent characteristic of the dye seems interesting to develop a new indirect method for the determination of CEF, CIP and FAM. The method involved oxidizing the drugs with known excess amount of bromate-bromide reagent in acidic medium. The unreacted oxidizing agent could be determined by adding a fixed amount of AF and measuring the fluorescence intensity at 528 nm with excitation at 402 nm. The increasing in drug concentration will decrease bromate-bromide reagent which decreases its quenching effect on AF fluorescence intensity. In other words, increasing the fluorescence intensity (by releasing the quenching effect of oxidizing agent on the dye) is equivalent quantitatively the concentration of studied drugs.

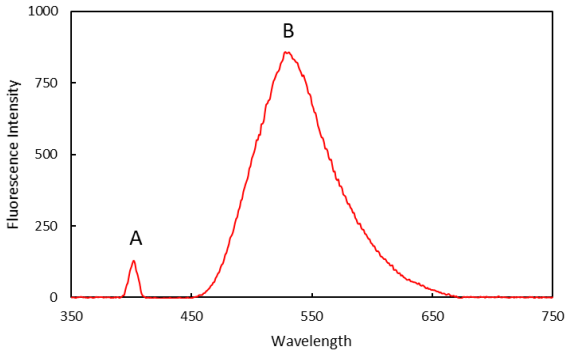

Figure 2. Fluorescence spectra of 6 µg ml^{-1} AF, A and B excitation and emission bands respectively.

Optimization of reaction variables

Preliminary experiments were performed to fix the upper limit of AF dye that could be determined spectrofluorimetrically, and this was found to be 6 µg ml^{-1} (1.2 ml of 50 µg ml^{-1}) as shown in in Fig. 3. A bromate-bromide concentration of 2.5 µg ml^{-1} was required to quench the fluorescence intensity quantitatively in hydrochloric acid medium (Fig. 4). Hence, different amounts of each studied drug were reacted with 1 ml of 25 µg ml^{-1} oxidant before determining the surplus bromate-bromide as described under the respective procedure.

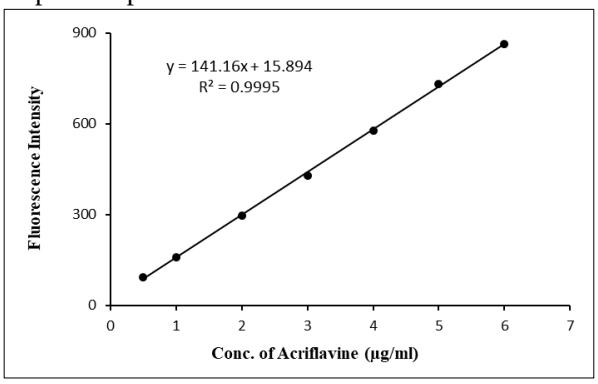

Figure 3. Standard graph of AF dye in the presence of 1 ml HCl (1 mol l^{-1})

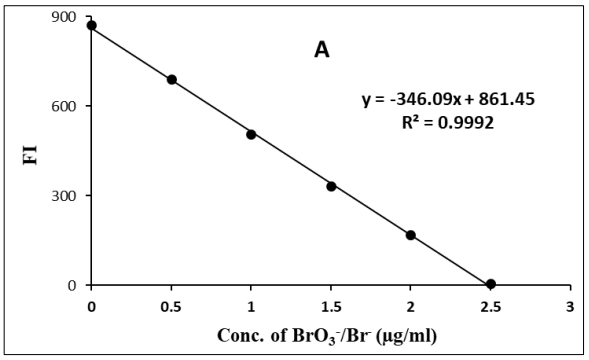

Figure 4. Effect of bromate-bromide concentration on AF fluorescence quenching

Effect of acid

Three types of acids were tested, hydrochloric acid medium was found to be an ideal medium for both oxidation of drug and quenching of AF by bromate (Table 1). In addition, one ml of 1 mol l^{-1} HCl was selected as optimum amount for all drugs as shown Fig. 5.

Table 1. Effect of acid kind

Acid* (1M)	Fluorescence intensity/ 2.6 µg ml^{-1} drug		
	Cefotaxime sodium	Ciprofloxacin HCl	Famotidine
HCl	616.1	567.1	478.7
H_2SO_4	601.8	527.3	455.5
HNO_3	584.2	492.2	446.1

* 1.0 ml of acid added

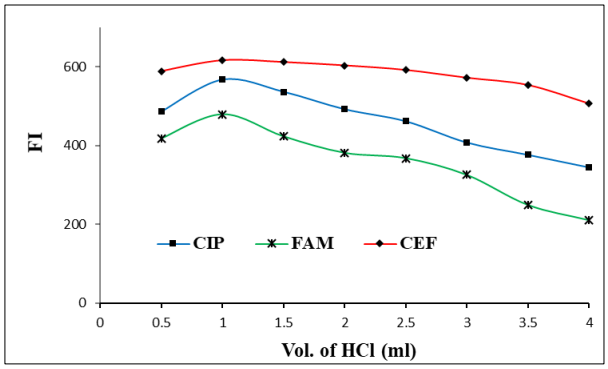

Figure 5. Effect of HCl volume

Effect of oxidation time and temperature

Time is important for oxidation reactions. It has been studied in both cases for drugs and AF. Oxidation time of drugs has been determined by adding reaction components before adding AF. After shaking the flasks and waiting for suitable time, AF was added. The flasks were shake again for several minutes to complete oxidation process of AF. Results were listed in Table 2 and show that 15 min is the perfect time for oxidation of CEF and 10 min for CIP and FAM. Also 10 min was a suitable time for oxidation of AF using bromate-bromide mixture. The stability study of the reaction mixture in different temperatures (0-60 ^{o}C) shows that the fluorescence intensity is stable for 24 hours at the room temperature (27^{o}C ±2). Figure 6 (for CIP as an example) reveals the negative effect of temperature at 0 ^{o}C and more than room temperature.

Table 2. Effect of oxidation time

Standing time before adding AF (min)	Fluorescence Intensity/ Standing time after adding AF & dilution (min)										
	5	10	15	20	30	40	50	60	120	240	Over night
Cefotaxime sodium											
After addition	510.8	507.6	513.4	520.5	515.9	511.7	509.0	518.2	501.2	506.3	488.0
5	568.4	568.6	559.2	549.3	553.4	550.0	543.4	539.1	538.9	547.1	519.0
10	613.7	618.2	628.6	619.7	621.3	616.3	607.3	609.9	617.3	622.7	591.2
15	738.0	761.3	759.1	746.8	760.6	757.5	754.3	759.8	753.6	740.0	737.3
20	722.8	719.0	723.9	720.1	721.9	719.3	716.2	712.1	719.3	711.7	693.9
Ciprofloxacin HCl											
After addition	501.7	504.3	506.3	503.6	502.5	500.5	503.8	501.0	498.3	501.1	518.3
5	542.5	547.8	543.6	547.1	545.0	548.3	543.9	549.4	544.6	544.0	560.7
10	573.8	632.2	630.1	631.4	630.7	628.9	629.4	624.5	620.5	629.1	636.8
15	552.4	565.1	568.5	564.8	559.0	560.4	563.6	558.5	559.8	556.2	543.6
20	566.2	580.6	582.5	579.4	581.7	576.0	577.3	581.4	584.6	573.0	552.2
Famotidine											
After addition	448.3	443.1	440.3	445.0	444.8	452.5	445.5	453.6	459.3	456.3	451.7
5	512.7	512.4	513.3	510.0	511.1	506.7	506.2	511.1	512.2	510.8	501.9
10	485.8	567.5	566.9	564.1	566.6	562.3	567.9	563.4	559.7	563.2	551.3
15	541.5	541.8	530.4	544.6	531.3	539.5	535.4	535.9	545.8	541.8	515.5
20	522.8	527.5	528.9	525.1	524.6	527.3	526.9	520.4	523.7	520.6	496.6

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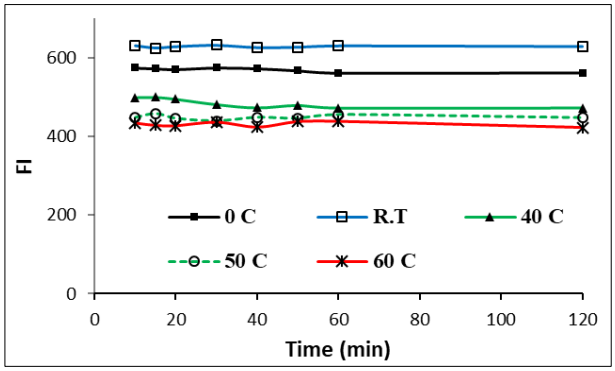

Figure 6. Effect of temperature on CIP determination (RT=27°C ±2)

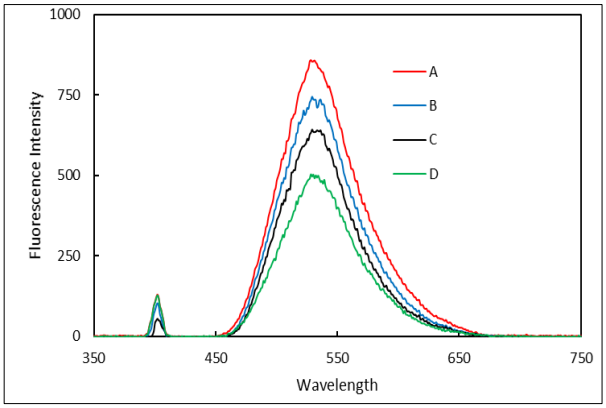

Figure 7. Fluorescent spectrums of AF only (A) and in the presence of 2.6 µg ml^{-1} CEF and CIP (B and C respectively) and 2.2 µg ml^{-1} FAM (D)

Order of addition

Order of addition in such reaction is very effective due to the competition between drug and dye towards oxidizing agent. Different order of addition of reaction components were examined. The order which involved addition sequence of acid, bromate-bromide mixture, drug and AF gives best fluorescence intensity (with optimum oxidation time for drug and AF).

After optimization procedure, final fluorescence spectrum of AF in the presence of studied drugs was scanned as shown in Fig. 7.

Method validation

Under the optimal conditions described above, standard calibration graphs for CEF, CIP and FAM were constructed by plotting fluorescence intensity against concentration (Fig. 8). The linearity was represented by the regression equation and the corresponding correlation coefficient for drugs determined by the proposed method representing excellent linearity (Table 3). Limit of detection (LOD) and limit of quantitation (LOQ) calculated according to ICH guidelines (41) are also present in Table 3 and revealed very high sensitivity of the proposed method.

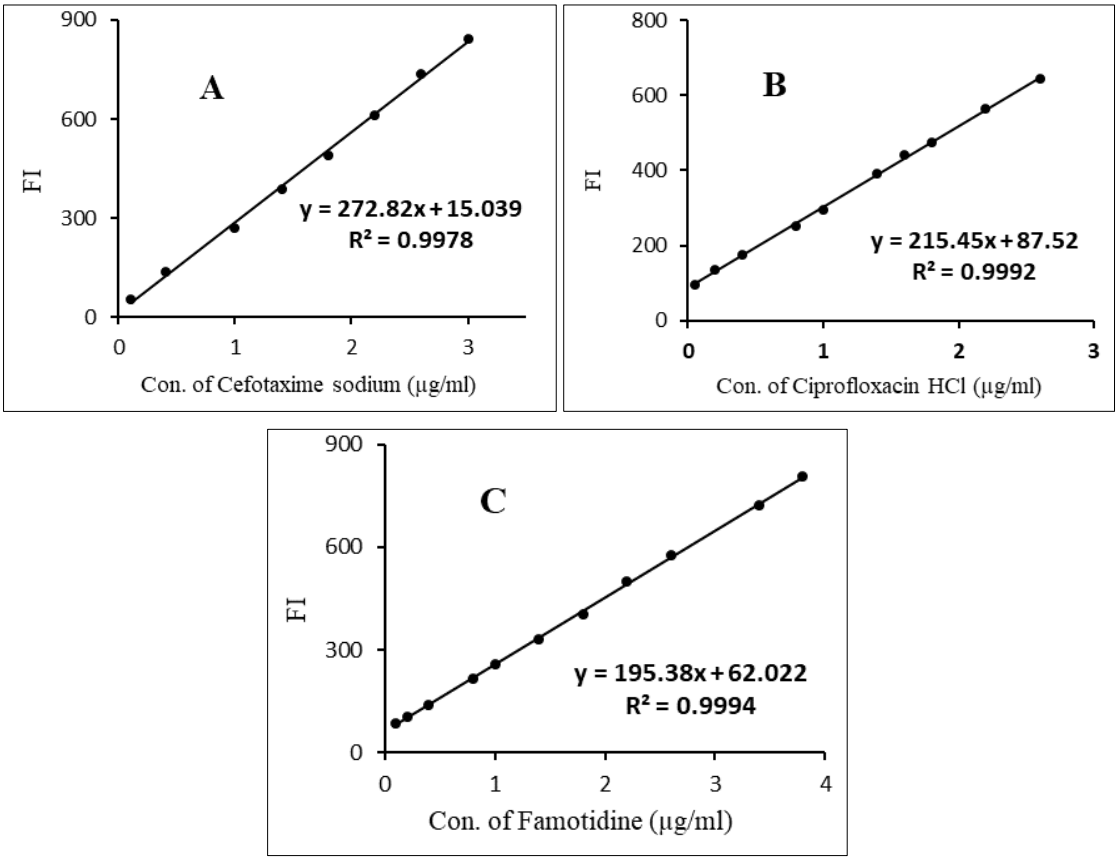

Figure 8. calibration graphs of studied drugs; CEF (A), CIP (B) and FAM (C).

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Table 3. Analytical parameter of calibration curve, LOD and LOQ

Parameter	Drug		
	Cefotaxime sodium	**Ciprofloxacin HCl**	**Famotidine**
Linearity range (µg ml^{-1})	0.1-3.0	0.05-2.6	0.1-3.8
Slope	272.82	215.45	195.38
Intercept	15.039	87.52	62.022
R^2	0.9978	0.9992	0.9994
Standard deviation of slope	5.274	2.217	1.547
Standard deviation of intercept	9.684	3.229	3.116
LOD* (µg ml^{-1})	0.019	0.002	0.006
LOQ* (µg ml^{-1})	0.063	0.006	0.021

*Average of ten determinations of drug's low concentration

Accuracy and precision:

The accuracy and precision of the method were evaluated by performing six replicates analysis on pure drug solutions at four different concentration levels. The relative standard deviation (RSD) and average recovery (%) indicated that the method is precise and accurate (Table 4).

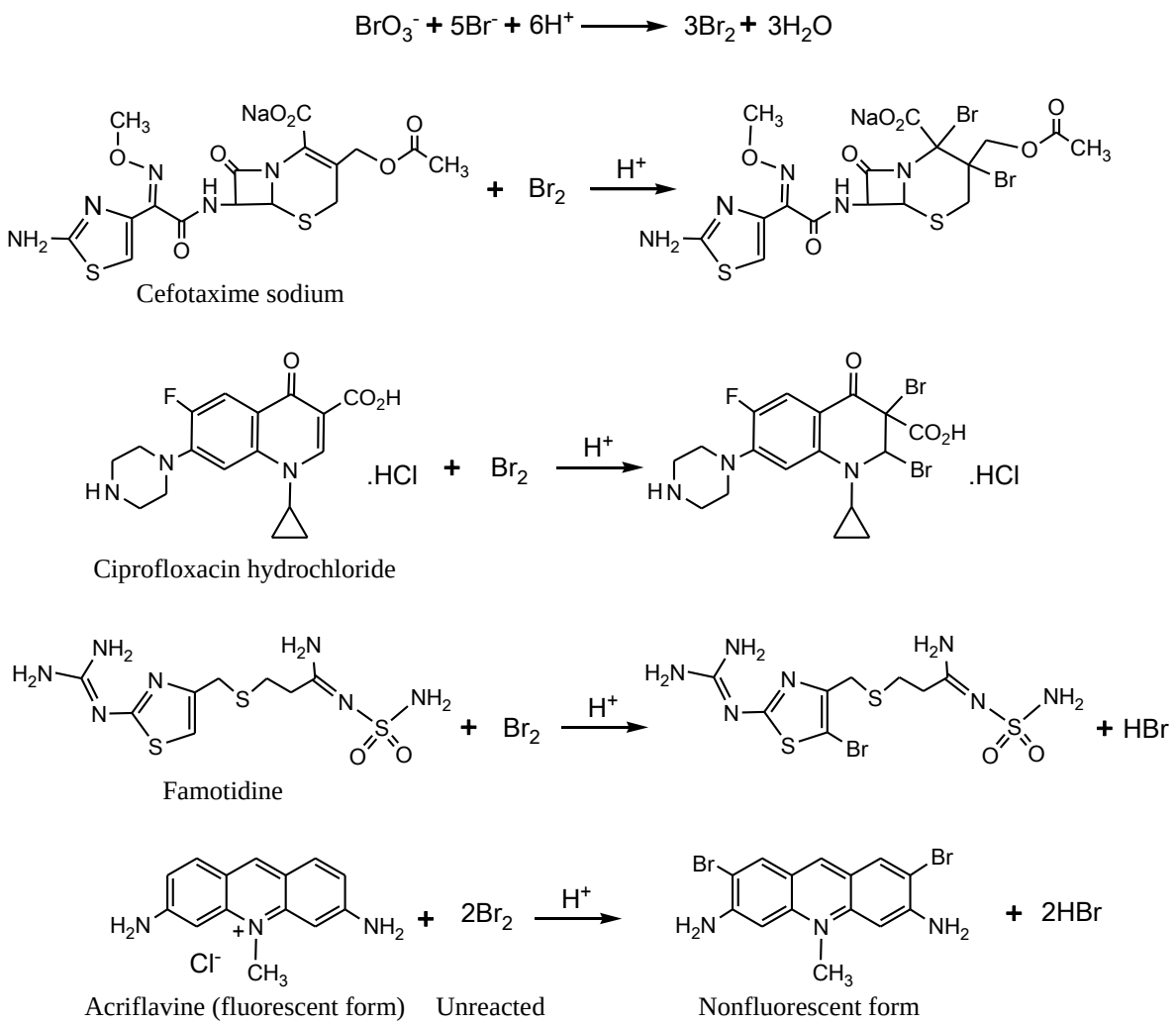
Table 4. precision and accuracy of suggested method

Drug	Amount taken (µg ml^{-1})	Recovery* (%)	Average recovery (%)	RSD %
Cefotaxime	0.4	101.15	100.21	1.93
sodium	0.8	98.51		0.94
	1.2	100.17		2.25
	2	101.01		2.07
Ciprofloxacin	0.4	99.67	99.69	3.90
HCl	0.8	99.13		3.47
	1.2	98.64		2.93
	2	101.31		2.71
Famotidine	0.4	99.39	99.60	2.26
	1	101.70		1.53
	1.8	97.71		1.12
	2.6	99.60		1.22

*Average of six determinations.

Suggested mechanism of the reaction

The Bromate-bromide mixture in acidic medium generates bromine equivalent to bromate concentration. The excessed known amount of liberated bromine led to bromination of drug (42). Then the unreacted oxidant brominates AF (as acridine molecule) to give product (43) with nonfluorescent properties. So, the fluorescence intensity increased linearly with increasing of concentration the determined drug. The proposed mechanism of reaction is shown in Scheme 1.



Scheme 1. Suggested mechanism of the proposed method

Effect of interferences

Seven drug's additives were added separately to four different amounts of each to flasks containing 1 µg ml^{-1} CIP, the results were listed in Table 5 which show that no significant effect of these materials on determination method.

Table 5. Interferences effect on recovery of 1 µg ml^{-1} of CIP

Foreign compound	Recovery (%) of 1 µg ciprofloxacin HCl per µg of foreign compound added			
	100	250	500	1000
Acacia	99.87	102.38	103.77	104.32
Starch	98.25	99.36	102.75	100.80
NaCl	96.86	101.27	99.60	101.41
Lactose	98.90	102.61	103.17	102.89
Sucrose	100.66	101.96	101.68	99.87
Glucose	101.68	100.85	102.06	99.32
Fructose	99.36	101.27	98.16	101.55

Determination of pharmaceutical preparations

According to the suggested method, different pharmaceutical preparations of studied drugs were examined (Table 6). The obtained results showed good agreement of found values with certified values which indicate that the proposed method is precise and accurate.

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Table 6. determination of pharmaceuticals of studied drugs by suggested method

Pharmaceutical preparation	Certified value	Amount Taken (µg ml^{-1})	Drug content found* (mg or g)	Recovery* (%)	Average recovery (%)
Cefotaxime sodium					
Cefotaxime Normon injection Spain	1 g	0.4	0.993 g	99.30	99.34
		0.8	1.007 g	100.67	
		1.2	0.991 g	99.15	
		2	0.982 g	98.23	
Cefagen injection Turkey	1 g	0.4	1.018	101.83	100.31
		0.8	0.997	99.72	
		1.2	1.009	100.89	
		2	0.988	98.81	
Brucitax injection India	1 g	0.4	0.975	97.52	98.50
		0.8	0.981	98.11	
		1.2	0.991	99.09	
		2	0.993	99.25	
Ciprofloxacin HCl					
Ciproneer tablets Iraq	500 mg	0.4	493.50	98.70	100.67
		0.8	503.08	100.61	
		1.2	509.79	101.96	
		2	506.99	101.40	
Cipronatin ablets Turkey	500 mg	0.4	508.12	101.62	100.74
		0.8	504.58	100.92	
		1.2	497.37	99.47	
		2	504.76	100.95	
Alcipro tablets India	500 mg	0.4	494.08	98.82	98.37
		0.8	489.85	97.97	
		1.2	494.59	98.92	
		2	488.88	97.78	
Famotidine					
Gastrofam ablets Turkey	40 mg	0.4	40.39	100.98	99.99
		0.8	40.25	100.64	
		1.2	39.51	98.76	
		2	39.83	99.57	
Ulceran tablets Cyprus	20 mg	0.4	20.22	101.08	100.49
		0.8	20.16	100.82	
		1.2	20.08	100.38	
		2	19.93	99.67	
Famodar tablets Jordan	20 mg	0.4	20.03	100.16	101.42
		0.8	20.05	100.26	
		1.2	20.75	103.75	
		2	20.30	101.48	

* Average of five determinations

Evaluation of the suggested method

The proposed method has been evaluated either by comparing its results with standard method of British Pharmacopeia (2), or standard addition procedure. For FAM pharmaceutical preparations, British Pharmacopeia procedure which involved potentiometric titration was applied and compared with obtained results of the suggested methods (Table 7). According to t and F tests values which were less than their statistical listed values at confidence level of %95 (2.45 and 9.28 respectively), there is no significant difference in the precision between proposed and standard methods.

Table 7. Comparing standard method results with proposed for the determination of FAM preparations

Pharmaceutical preparation	Recovery* (%)		t-test	F-exp
	Present method	Standard method		
Gastrofam ablets Turkey	99.99	100.17	0.16	4.01
Ulceran tablets Cyprus	100.49	98.41	1.42	0.05
Famodar tablets Jordan	101.42	100.17	0.95	0.68

* Average of four determinations.

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Standard addition procedure was applied for the determination of CEF and CIP preparations (Fig. 9 and 10). Parameter of the tests were listed in Table 8, which exhibit a good agreement between standard addition procedure and proposed method.

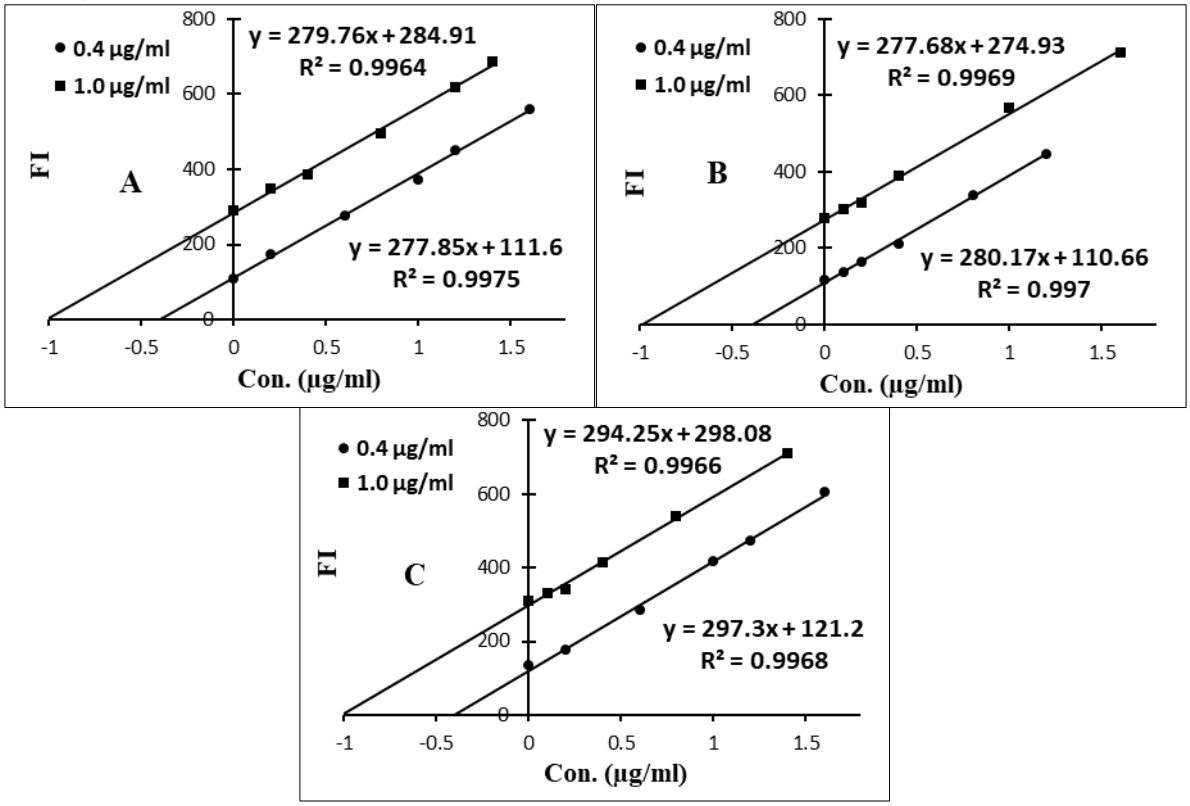

Figure 9. Standard addition curves for determination of CEF preparations A: Cefotaxime Normon injection-Spain, B: Cefagen injection-Turkey and C: Brucitax injection-India

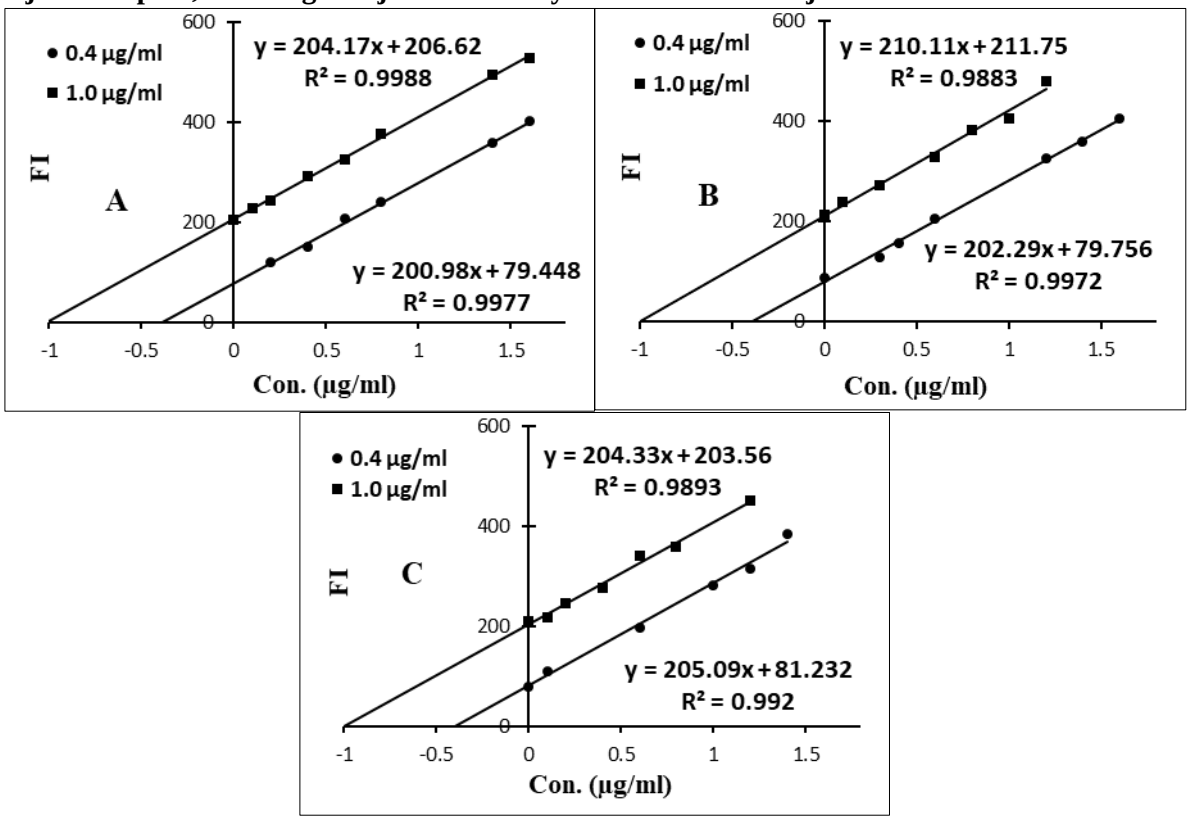

Figure 10. Standard addition curves for determination of CIP preparations A: Ciproneer tablets-Iraq, B: Cipronatin ablets-Turkey and C: Alcipro tablets -India

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Table 8. Determination of CEF and CIP preparation by standard addition procedure and suggestion method

Drug	Pharmaceutical prepration	Certified value	Amount present (µg ml^{-1})	Drug content found	
				Present Method*	Standard Addition procedure
Cefotaxime sodium	Cefotaxime injection-Spain Normon	1 g	0.4	0.993 g	1.004
			1.0	0.987 g	1.018
	Cefagen injection Turkey	1 g	0.4	1.018 g	0.987
			1.0	0.999 g	0.990
	Brucitax injection India	1 g	0.4	0.975 g	1.019
			1.0	1.001 g	1.013
Ciprofloxacin HCl	Ciproneer tablets Iraq	500 mg	0.4	493.50 mg	494.12
			1.0	503.69 mg	506.01
	Cipronatin ablets Turkey	500 mg	0.4	508.12 mg	492.82
			1.0	495.57 mg	503.92
	Alcipro tablets India	500 mg	0.4	494.08 mg	495.09
			1.0	499.79 mg	498.11

* Average of three determinations

Conclusion:

A new simple sensitive and precise spectrofluorometric method has been developed for the determination of CEF, CIP and FAM. The method involves an oxidation of drugs with excessed known amount of bromate-bromide mixture in acidic medium. The surplus of oxidizing agent was determined by quenching fluorescence of AF dye. Fluorescence intensity of residual AF was measured at 528 nm after excitation at 402 nm. So, the fluorescence intensity increases linearly with increasing of drug concentration. The method is applicable and no extraction is needed. Different pharmaceutical formulations of studied drugs were estimated using proposed method with an excellent agreement.

Conflicts of Interest: None.

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طريقة فلورومترية غير مباشرة لتقدير السيفوتاكسيم صوديوم وهيدروكلوريد السيبروفلوكساسين والفاموتيدين باستخدام برومات-بروميد وصبغة الأكريفلافين

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الخلاصة:

تم تطوير طريقة فلورومترية غير مباشرة، بسيطة وحساسة وقابلة للتطبيق لتقدير المركبات الدوائية السيفوتاكسيم صوديوم، هيدروكلوريد السيبروفلوكساسين والفاموتيدين باستخدام نظام التفاعل برومات-بروميد وصبغة الأكريفلافين المتفلورة اعتمدت الطريقة على مبدأ أكسدة المركبات الدوائية في وسط حامضي بإضافة زيادة معلومة من برومات-بروميد ثم مفاعلة المتبقي من العامل المؤكسد مع كمية ثابتة من صبغة الأكريفلافين وقياس الاخماد في شدة تفلور الصبغة عند 528 نانوميتر بطول موجة إثارة 402 نانوميتر. ووجد أن شدة انبعاث الصبغة تزداد خطياً بزيادة تركيز المركبات الدوائية ضمن المدى 0.1-3.0 و0.05-2.6 و0.1-3.8 مايكروغرام/ مللتر، بحدود كشف 0.013 و0.018 و0.021 مايكروغرام/ مللتر، وتقدير كمي 0.044 و0.060 و0.069 مايكروغرام/ مللتر لكل من السيفوتاكسيم صوديوم، هيدروكلوريد السيبروفلوكساسين والفاموتيدين على التوالي، كما وجد أن الطريقة المقترحة لا تعاني من تداخلات مواد السواغ في التقدير. طبقت الطريقة بنجاح على المستحضرات الصيدلانية، وكانت الطريقة متفقة مع الطريقة القياسية المعتمدة في دستور الأدوية البريطاني وطريقة الإضافة القياسية.

الكلمات المفتاحية: أكريفلافين، سيفوتاكسيم صوديوم، هيدروكلوريد السيبروفلوكساسين، فاموتيدين، فلورومتري.