

ESTIMATION OF CEPHALOSPORINS (CEFTRIAZONE, CEFTAZIDIME) ANTIBIOTICS AS PURE AND PHARMACEUTIC FORMS BY COLOR PRODUCED REACTION IN UV-VIS SPECTROPHOTOMETIC TECHNIQUE

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ABSTRACT

A new simple, accurate and low cost-effective UV-VIS spectrophotometric methods has been developed for the analysis of chosen cephalosporins (ceftriazone, ceftazidime) in bulk samples and pharmaceutical dosage forms by using a specific color-generated reaction. This method involves the Schiff's base formation reaction between selected cephalosporins with alcoholic 5-sulfo salicylaldehyde reagent 5SSA with heating to establish a yellow colored product displaying λ_{max} at 426 nm as well as 412 nm sequentially. These methods applied to the Beer's law through the range of concentration was (4 - 60 $\mu\text{g}\cdot\text{mL}^{-1}$), (5 -50 $\mu\text{g mL}^{-1}$) respectively for two drugs. The analysis results for these studies have been tested statistically by the studies of recovery. These methods were successfully applied to the determination of the cephalosporins in bulk form and in Pharmaceuticals additionally it was shown that these methods have equivalent accuracy with the common method(BP)estimation procedures for the studied drugs. The interferences from frequently taken excipients were no influence on the estimation process .The study could discover a good as an employment cost-influence and speed method which that possibility used for making quality control for these cephalosporin antibiotics.

Keywords: UV-VIS Spectrophotometric, Cephalosporins, Pharmaceutics, Ceftriazone and Ceftazidime

INTRODUCTION

Cephalosporins medicines are one type from b-lactam antibiotics appeared in the 1950's as well as they are made by different species of the matrix cephalosporium additionally they are taken from semi-synthetic approaches [1]. Cephalosporins are wide antibiotics spectrum, through the strong effectiveness of various bacteria (broad spectrum). These are bacteria highly averse to deactivation through b-lactamases, extremely those made by bacteria (broad spectrum).They besides have comparatively little serum protein

connecting potentially as well as nearly each one are evacuated during the nephritic route [2]. These medicines are ordinarily utilized in the dealing with urinary tract as well as upper respiratory infections. These medicines besides ordinarily utilitarian for the scarce sick person who is reactive penicillin even if sensitiveness to cephalosporin medicines is besides as some point discover [3, 4]. The essential nucleus of the cephalosporins is (7-ACA)7-amino-cephalosporanic acid, that be composed a di-hydro thiazine nucleus into a β -lactam ring. These medicines are conventional separated (1-2-3 and 4 initiation performers, depended forcefully on their time realization as well as their antimicrobial characterizes i.e. spectrum activeness [5,6] Ceftriaxone (M.wt = 662) was a third- initiation cephalosporin antibiotic. Chemically Ceftriaxone ceft is (6R,7R,Z)-7-(2-(2-amino thiazol-4-yl)-2-(methoxy imino) acetamido)-3-((6-hydroxy-2-methyl -5-oxo - 2,5- dihydro -1,2,4-triazine-3-ylthio)methyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid [7]. Like other third- initiation cephalosporins, it has broad spectrum activity against Gram-positive and Gram-negative bacteria [8]. Ceftazidime (M.wt = 637) penta hydrate cfz is (Z)-(7R)-7-[2-(2- amino thiazol-4-yl)-2-(1- carboxy-1- methoxy imino) acetamido]-3-(1-pyridiniomethyl)-3-cephem-4-carboxylate penta hydrate. thecfz is a third generation of cephalosporin antibiotic represented through a wide broad spectrum antibiotic additionally averse to β -lactamase making by bacteria in addition to its antimicrobial activeness opposition, Staphylococci, Pneumococci additionally Streptococci [9, 10]. The chemical structures of (Ceftriaxone are $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3\frac{1}{2}H_2O$, as well as Ceftazidime $C_{22}H_{22}N_6O_7S_2 \cdot 5H_2O$) Figure (1).

Chemical properties of ceft is freely soluble in water, sparingly soluble in methanol, very slightly soluble in anhydrous ethanol, cfz, white or nearly white, fine crystal clear, a little soluble in methyl alcohol as well as water, virtually insoluble ethyl alcohol additionally in acetone. It disperses in alkali as well as acidic solutions. The common approaches for the cephalosporins analysis were HPLC proficiencies in the back phase manner [11, 12]. Diverse additional replacement approaches have been recorded for the analyzes of the cephalosporins, The approaches were contained spectrophotometric [1, 2, 13], spectrofluorometric [14-16], chemiluminescence [17-19], chromatographic [20-23], and electrochemical methods [24-27]. This paper reports a study on the development of new validated UV-spectrophotometric methods for the quantitative determination of Cephalosporins: Ceftriaxone and Ceftazidime as bulk and solid dosage form. By a specific color-generated reaction. This method involves the Schiff's base formation reaction between

selected cephalosporins with alcoholic 5-sulfo salicylaldehyde reagent (5SSA) with heating to form yellow colored chromogens with high accuracy and precision.

MATERIAL AND METHOD

Materials and reagents

Everyone of spectra as well as absorbance appreciations was made through applied a UV-Visible double-beam (160 digital) reporting spectrometer (Japan). Cooling–Heating water bath (Haake, Fe3), sensitive balance (Sartorius BL 210S). The chemicals which were used in the approach with high degree of purity and did not need to purification, all reagents in the research was given from (BDH) (reagent Laboratory, Chemicals Ltd), their solutions were prepared by the following:

Ceftriaxone sodium drug: 500 ppm standard concentration solution of ceft was prepared by dissolution 0.05g of ceft in 100ml with deionized water in a volumetric flask.

Ceftazidime pentahydrate drug: 500ppm standard concentration solution of cfz was prepared by dissolution 0.05 g of cfz in 100 ml with deionized water in a volumetric flask and heating for 20 min to complete the dissolution of cfz drug in water. The drug solutions were transferred to a dark flask and it is stable for at least one week the solution was stayed stable for more of one month after keeping away from the light. the working solution prepared from this solution.

An alcoholic solution of 5-sulfo salicylaldehyde reagent (5SSA) 0.04 M: was prepared by dissolving 2.02gm from reagent in 25ml of ethanol absolute in the volumetric flasks.

General procedure [28]

Aliquots of (0.2 ml – 4.0 ml) ceft as well as cfz were transported into a sequence of volumetric flasks 25 ml. To each flask, alcoholic solution 2.0ml for 5-sulfo salicylaldehyde was utilized as well as warmed at 70 °C for 50 min for ceft and 60 min for cfz. The volumes were as weakened to the mark with ethyl alcohol additionally the yellow colored agents absorbance was checked at 426 nm as well as 412 nm averse to the blank agent solution. The colored agents were as stable for high than 1 hour. The ceft as well as cfz quantities are examined was checked from the calibration curve. The colors were was discovered that be stable for more from 2 days.

Assay procedure for Ceftriaxone sodium and Ceftazidime sodium in Pharmaceutical preparations: A number of preparations containing ceft and cfz as ingredient active were analyzed. These are summarized in Table 1 and 2.

Injection vial preparation:

0.05% gm/ml from the powder of each type of vials which was containing ceft and cfz as ingredient active was taken into 100ml flasks volumetric and weakened up to the imprint with ethanol solvent. At that point, we computed the concentration by using the calibration curve [11].

RESULT AND DISCUSSION

Various circumstances were contemplated that are influencing on the absorbance for the resultant compound that leads to increase it.

Effect of (5SSA) reagent Concentration

The study the reagent effect of 5SSA on the absorbance. It was making by utilizing 1 ml of 500 ppm from ceft and cfz drugs were transferred into a sequence of 25 ml volumetric flasks, varying volumes for 5SSA 0.04 M from 0.5 - 8ml was taking from alcoholic solution of 5-sulfo salicylaldehyde was taken and warmed at 70 °C for 50 minutes for ceft and 60 minutes of cfz, for the formation the Schiff base and complete the volumes by utilizing ethanol, the final volume was 2ml for the reagent of both drugs, that volumes produce the large absorption, that was utilized in the next experiments [29].

Effect of heating

The heating effect was checked for the range wide of temperature from (20- 120) °C. It was found the color activity expanded with warming up to 25 °C, and it was slightly increased at higher temperatures. The highest absorbance was at 70 °C for 50 minutes for ceft and 60 minutes of cfz, the next experiments were performed at this temperature that need to Schiff bases formation to simplify the analytical procedure [30].

Effect of the time for completing the Schiff base reaction

After heating and mixing well in 70 °C boiling water bath at room temperature for drug and reagent It was found 50 minutes for ceft and 60 minutes of cfz that the best times for completing the Schiff base reaction which selected in subsequent experiments. The resulted color products were as stabilized at over than 24 hour [28].

Absorption Spectra

The spectral scan was directed to get the more absorption wavelength of coming about the Schiff base compounds that result from two drugs subsequent to introducing the perfect circumstances for this reactions. against blank solution ethanol solvent 98% ,after that,the spectral scan was obtained the greater wavelength absorption for the colour complexes which was resulted from the reaction between the drugs and the reagent.

Quantification :

Applying the perfect circumstances was showing by the procedure, a calibration curves linear for ceft drug and cfz drug is showed in figure 3, from this curve the Beer's law is applied between the range of concentrations of (4 - 60 $\mu\text{g/ml}$) (5 - 50 $\mu\text{g/ml}$) for two drugs respectively, with ceft drug the correlation coefficient was 0.9992, the slope of curve was 0.0301, and an intercept of 0.0344. The highly molar absorptivity of the yellow product was founding (1.9926×10^4) $\text{L.mol}^{-1}.\text{cm}^{-1}$. The sensitivity Sandal was (4.5×10^{-5})($\mu\text{g} .\text{cm}^{-2}$). The limit detection (LOD) was 1.121 $\mu\text{g}.\text{ml}^{-1}$ as well as the LOQ was 1.943 $\mu\text{g} .\text{ml}^{-1}$.and showing in table (3).

Interferences

The specificity of the suggested kinetic spectrophotometric procedures (fixed time procedure) for investigation of the ceft and cfz drugs within the sight of often experienced excipients like, talc, lactose, acacia, starch, glucose, sucrose, polyvinylpyrrolidone (PVP), magnesium stearate, and aspartate by the presented study. The solutions of studied drugs was framed and everyone from the studied excipients was given independently by ten-times concentrations more than of studied drugs were prepared by the self-procedure in the Calibration curve. 1 ml of 500ppm ceft, cfz solutions and 1ml of every excipients solutions was connected for the study of interferences after that dilution to the sign of volumetric flask 25 ml. A grade of impedance was believed to make the procedure more satisfactory if the mistake was not more than $\pm 2\%$ in respect to the normal no obstructions were seen on the investigation of drugs within a sight of the studied excipients (Three determinations Average) [31] Table(4).

The stoichiometry of reaction

The stoichiometry of the reaction of two drugs ceft and cfz with 5SSA was performed by mole ratio method and Job's method. The methods applied by using the solution $1 \times 10^{-3}\text{M}$ of every one of the medicines as well as the reagent to determine the colour products stoichiometry. The solutions absorbance were calculated at maximum wave lengths 426 nm, 412nm for to the color products. From these methods the results are showing that 1:1 new

compound (Drug : 5SSA) compounds was formed at 426 nm, 412nm alternately. The products formed was ethanol soluble. A reactions mechanism based on the above reactions is shown in Schemes figure (5 and 6) [24-26]. The stability constant for the product compounds was figured by looking and measuring the absorbance of a solutions which including stoichiometric measure of Drugs with 5SSA with the perfect quantity 1 ml $2 \times 10^{-3} \text{M}$ from medicines and 5SSA solution with other solution containing a five-fold excess from the starting concentration. The average for calculated stability constant for the colour results in ethanol under the characterized experimental circumstances was $3.11 \times 10^5 \text{ l}^2 \cdot \text{mol}^{-2}$ for ceft drug and $1.26 \times 10^5 \text{ l}^2 \cdot \text{mol}^{-2}$ for cfz drug[32-34]. The interaction may be happened as obtained by the next Schemes Figure (6 and 7).

Effect of solvent

The type of solvent that was dissolving the drug substances employed affects both the wavelength and intensity of maximum absorption. Table (5) shows the effect solvent, ethanol was the best solvent, which gives very high intensity of maximum absorption which was in the case of using 5SSA as the aromatic aldehyde with two drugS. Ethanol is appeared to be a decent solvent from the point perspective of economy and sensitivity [29].

Application of the procedure [35-37]

The procedures was applied for the assay of pharmaceutical preparations of the two drug, was studied. The consequence of examining for accessible formulations of ceft and cfz drugs are appeared by following Table (6 and 7). Wherever the three normal determinations. also, the standard strategy was gotten from (2009) British Pharmacopeia. The outcomes were replicable and the determination procedures of formulations were through examined by the Standard procedure the studied approaches was felicitously utilized to estimate ceft and cfz as pure form and in its pharmaceuticals forms. The results given were checked statistical comparison by an *F*-test variance ratio for precision additionally for accuracy by utilizing Student's *t*-test with the common approach [5]. The results appeared that The values of the *F*-test and *t*-test. Were ($F=1.72$, $t=1.03$) for ceft medicine and ($F=2.12$, $t=0.88$) for cfz medicine, these values were little from the theoretical amount ($F=5.05$, $t=2.29$) for ceft and ($F=9.29$, $t=2.45$) for cfz drug, pointing there was no clear distinction between the tested approaches and common approaches. Three estimations average ultimately, *F*-test as well as *t*-test values (statistical analysis) seem that there is no considerable variation in accuracy between the tested procedure additionally the common BP procedures.

CONCLUSION

The present spectrophotometric procedures was a rapid, easily, sensitive and precise procedures has been created for the investigation of trace quantities of ceft and cfz drugs relevant for the investigation of two drugs in pure forms and injection samples. The proposed procedures are free from basic exploratory conditions and muddled systems, for example, extraction step. The reagents utilized as a part of the procedures are shabby, promptly accessible and the methods don't include any dreary sample preparation. These points of interest empower the utilization of the presented techniques in quality routine control investigation of ceft and cfz drugs in pharmaceutical preparations.

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Table 1. Pharmaceutical preparation studied for Ceftriaxone sodium

Pharmaceutical preparation	Composition	Company
Ceftriaxone sodium vial	Per vial 1g Ceftriaxone sodium	Sanaita,PharmaceuticalG MBH company (Werne Germany)
Ceftriaxone sodium Vial(Philtriaxone)	Per vial 1g Ceftriaxone sodium	Binh duong company, Vietnam
Ceftriaxone sodium Vial(Rameceftrix)	Per vial 1g Ceftriaxone sodium	Tenth of Ramadan for pharm.industries company (Egypt)
Ceftriaxone sodium Vial(Roth)	Per vial 1g Ceftriaxone sodium	Pharma Roth Gmbh company (Germany)
Ceftriaxone sodium Vial(Enoxirt)	Per vial 0.5g Ceftriaxone sodium	Gulf Pharmaceutical industries (UAE)

Table 2. Pharmaceutical preparation studied for Ceftazidime sodium

Pharmaceutical preparation	Composition	Company
Ceftazidime I.M-I.V	Per vial 1g Ceftazidime pentahydrate	Laboratorios Torlan Ctra (Barcelona Spain)
Negacef Ceftazidime I.V.	Per vial 1g Ceftazidime pentahydrate	Gulf Pharmaceutical Industries (U.A.E)
Ceftazidime Roth IV/IM	Per vial 1g Ceftazidime pentahydrate	Pharma Roth Gmbh (Wiesbaden Germany)

Table 3. Analytical Data for the time fixed procedure of the kinetic spectrophotometric procedures for investigation of ceft and cfz drugs

Parameter	Value with (ceft)	Value with (cfz)
λ_{max} , nm	426	412
Correlation coefficient , r^2	0.9992	0.9989
Slope(a)	0.0301	0.0226
The Molar absorptivity (L .mol ⁻¹ .cm ⁻¹)	1.9926 x 10 ⁴	1.4396 x 10 ⁴
The law of Beer limits ($\mu\text{g/ml}$)	(4 - 60)	(5 -50)
the sensitivity of Sandell ($\mu\text{g.cm}^{-2}$)	4.5 x 10 ⁻⁵	3.5 x 10 ⁻⁵
Intercept (b)	0.0344	0.0052
The detection Limit (LOD) ($\mu\text{g.ml}^{-1}$)	1.121	1.883
The quantification Limit (LOQ) ($\mu\text{g.ml}^{-1}$)	1.943	2.421
Average recovery	% 100.42	% 99.92
*RSD	% 1.26	% 1.51

Table 4. Excipients eEffect at 200 ppm on the recovery of ceft and cfz drugs at 20 ppm for the fixed time method

Interference	% Error With (ceft)	% Recovery With (ceft)	% Error With (cfz)	% Recovery With (cfz)
Talc	- 1.180	98.820	- 0.991	99.009
lactose	+ 1.140	101.140	-1.021	98.979
Acacia	+ 1.030	101.030	- 0.772	99.228
Starch	- 1.640	98.360	- 0.551	99.449
Glucose	- 1.300	98.700	- 1.101	98.899
Sucrose	+1.150	101.150	- 1.411	98.589
magnesium stearate	- 1.600	98.400	- 1.521	98.479
Aspartate	+ 1.010	101.010	- 0.821	99.179
PVP	+ 1.450	101.450	- 0.765	99.235

Table 5. Spectrophotometric attributes of the colored products in different organic solvents

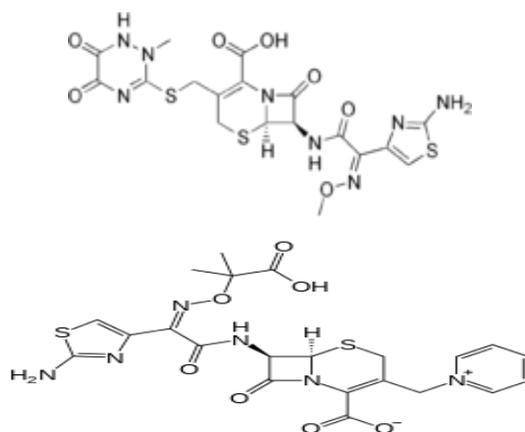
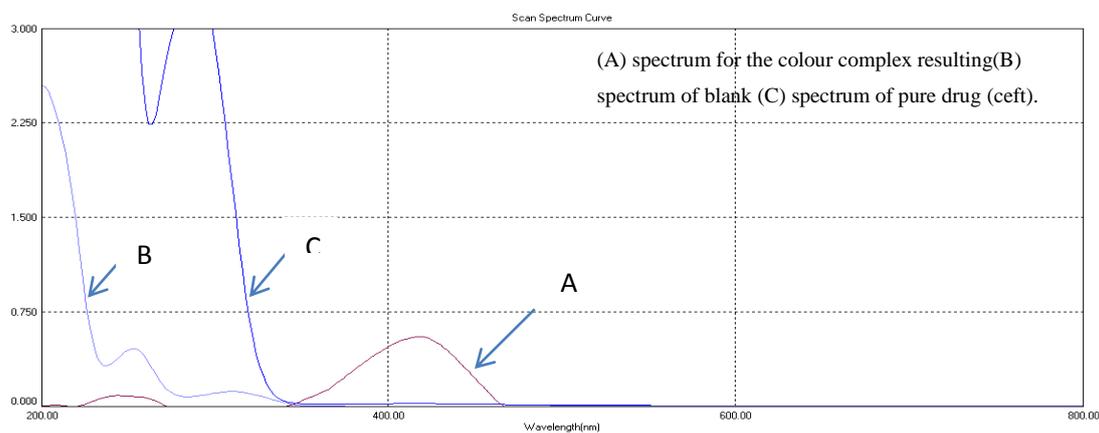
Solvent	λ_{\max} , nm (ceft)	λ_{\max} , nm (cfz)	ϵ , L.mol ⁻¹ .cm ⁻¹ (ceft)	ϵ , L.mol ⁻¹ .cm ⁻¹ (cfz)
Acetone	378	372	1.146 × 10 ³	1.228 x10 ³
Chloroform	402	380	1.3368 x10 ³	2.425 x10 ²
2- propanol	368	376	4.321 x10 ²	1.721 x10 ³
Acetic acid	346	350	1.871 x10 ²	1.278 x10 ²
Dimethyl sulphoxide	370	368	2.262 x10 ²	1.410 x10 ³
CCl ₄	380	372	1.005 x10 ³	1.201x10 ²
Dioxine	382	390	1.412 x10 ³	1.211 x10 ²
Dimethyl formamide	402	350	1.510 x10 ³	1.612 x10 ³
Ethanol	426	412	1.667 x 10 ⁴	1.233 x 10 ⁴
Benzene	330	340	2.301 x10 ²	1.308 x10 ²
Methanol	408	402	1.252 x10 ⁴	1.161 x10 ⁴
Teri butyl alcohol	406	394	1.138 x10 ⁴	1.020 x10 ⁴
Formic acid	390	386	2.961 x10 ²	1.712 x10 ³
Pyridine	360	362	1.213 x10 ³	1.420 x10 ³
Di ethyl ether	372	366	1.712 x10 ²	1.310 x10 ³

Table 6. The recovery % and average RSD% of ceft drug pure and pharmaceutical forms

Pharmaceutical preparations including ceft	Average recovery % and average RSD%			
	Proposed procedure		Standard procedure ⁽¹¹⁾	
Pure ceft	100.42	1.26	100.88	1.41
Ceftriaxone sodium Vial (1g)Germany) ceft	101.16	1.33	99.13	1.11
Ceftriaxone sodium (1g) Vietnam Vial(Philtriaxone)ceft	99.31	1.87	100.47	0.89
Ceftriaxone sodium (1g)Eygpt Vial(Rameceftrix)) ceft	100.22	1.57	100.12	1.65
Ceftriaxone sodium(1g))ceft Germany Vial(Roth)	99.77	0.89	99.54	1.07
Ceftriaxone sodium (1g) U.A.E Vial(Enoxirt)) ceft	100.4	0.78	100.32	1.31

Table 7. The recovery % and average RSD% of cfz drug pure and pharmaceutical forms

Pharmaceutical preparations including cfz	Average recovery % and average RSD%			
	Proposed procedure		Standard procedure ⁽¹¹⁾	
Pure cfz	99.92	1.51	99.33	0.91
Ceftazidime I.M-I.V(1g)Spain cfz	99.56	1.22	99.51	1.03
Negacef Ceftazidime I.V.(1g)U.A.E cfz	99.12	0.82	99.17	1.46
Ceftazidime RothIV/IM(1g)Germany cfz	98.88	1.12	99.23	0.96

**Figure 1.** The chemical structures of (Ceftriaxone as well as Ceftazidime) antibiotics**Figure 2.** Appears the spectra of the color complex made by the reaction between the ceft drug 1ml of 500 ppm and reagent against blank solution, the absorption was maximum at 426 nm where (A) spectrum gives the color for complex resulting by the reaction, (B) is obtaining the spectrum of the blank 2ml of 0.04M reagent, (C) spectrum represents the spectrum for the pure drug ceft

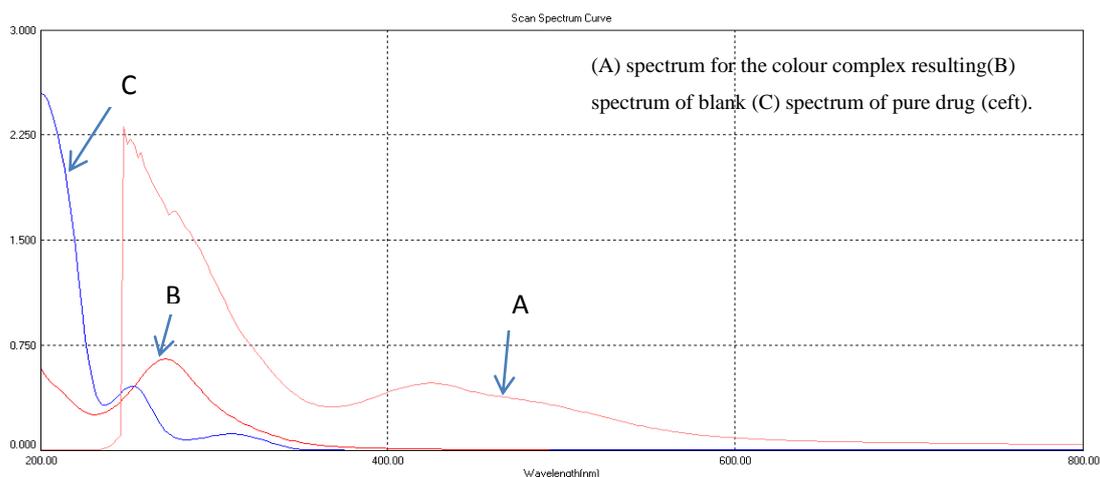


Figure 3. The spectra of the color complex formed by the reaction between the cfz drug 1ml of 500 ppm and reagent against blank solution, the absorption was maximum at 412 nm where (A) spectrum gives the color for complex resulting by the reaction, (B) is obtaining the spectrum of the blank 2ml of 0.04M reagent, (C) spectrum represents the spectrum for the pure drug cfz

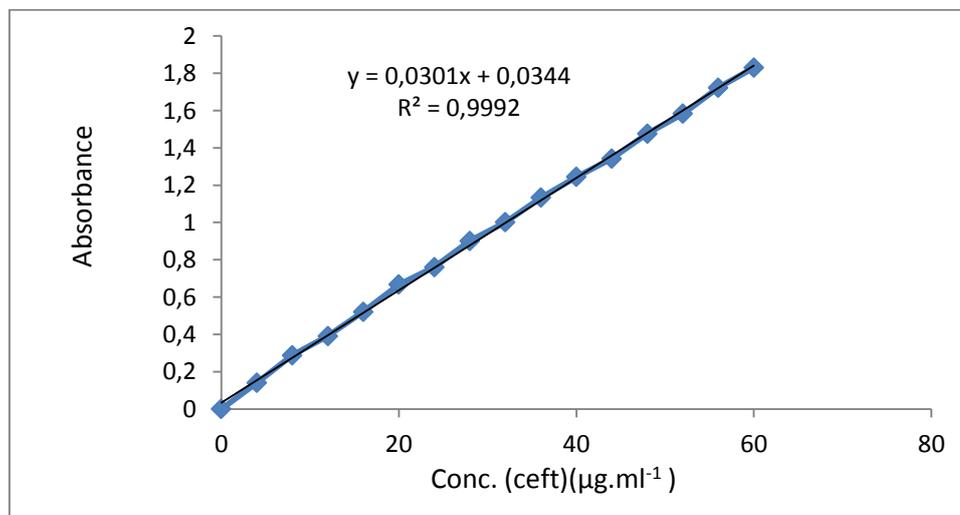


Figure 4. The Calibration curve of ceft

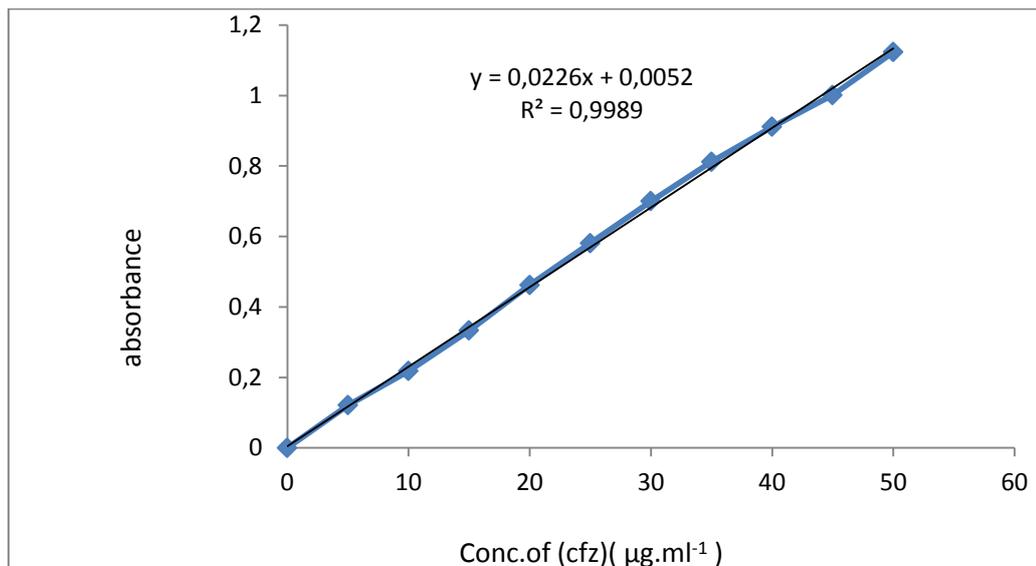


Fig 5. The Calibration curve of cfz

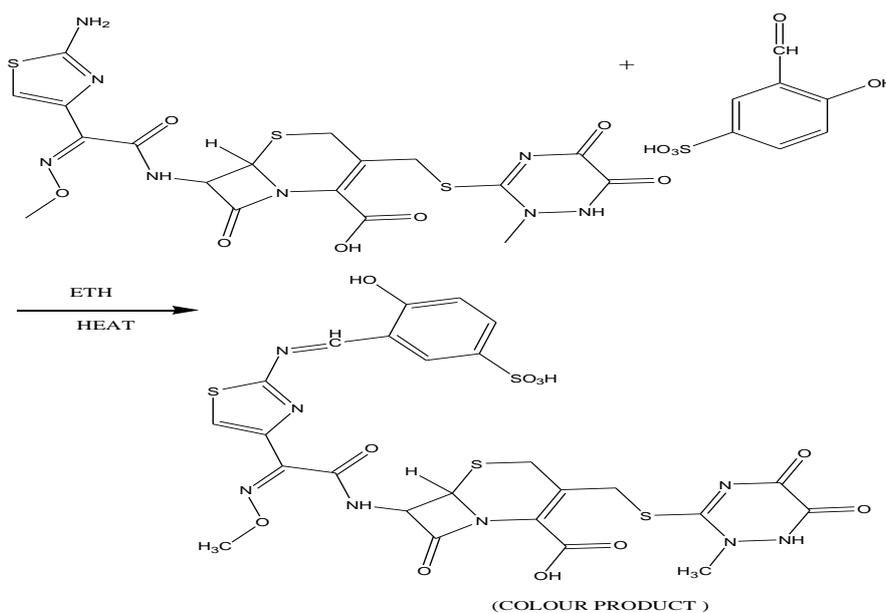


Figure 6. Scheme of probable interaction pathway for the figuration of the color product of ceft medicine with 5SSA

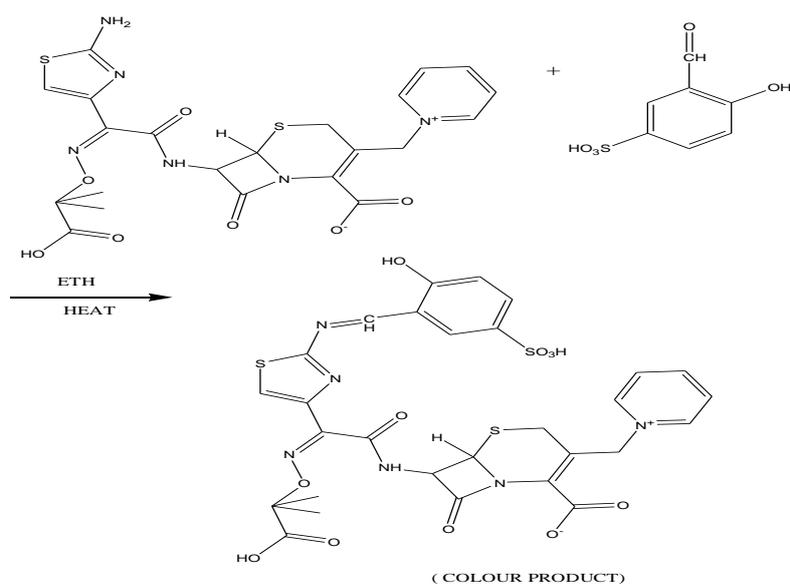


Figure 7. Scheme of probable interaction pathway for the figuration of the color product of cfz medicine with 5SSA