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Research Article

SIMPLE HPLC METHOD FOR THE DETERMINATION OF CEFIXIME, OFLOXACIN AND LINEZOLID IN SOLID DOSAGE FORMS

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ABSTRACT

Cefixime, Ofloxacin and Linezolid three drugs can be used to treat bacterial infections. Each drug works with different mechanism. Stability indicating RP- HPLC method was developed for Cefixime, Ofloxacin and Linezolid quantification in tablet dosage form. RP-HPLC method was validated with precision, specificity, accuracy, ruggedness, robustness and linearity parameters. Liquid chromatographic conditions are mobile phase A: 0.5M KH_2PO_4 in HPLC grade water and mobile phase B: Acetonitrile, Agilent make Zorbax SB-C18, 100 x 4.6mm, 5µm, 280 nm, 1.0ml/min, 25 min (gradient program: mobile phase B at 0min 5%, 5min 5%, 10 min 16%, 14 min 16%, 17 min 34%, 20 min 5% and 25 min 5%. All validation results shown the accuracy results and % RSD for test area, %assay values were also within the limits. This HPLC method can be used to analyze the regular product quality control purpose.

Keywords: Cefixime, Ofloxacin, Linezolid, Tablets dosage form, Method development and validation.

INTRODUCTION

Cefixime is belongs to cephalosporins and it is an anti-biotic medicinal product. Cefixime fights for bacterial infections[1]. Cefixime is used to treat Gonorrhea, urinary and respiratory track bacterial infections and middle ear infection[2]. Cefixime inhibits the bio-synthesis of cell walls. Cefixime medicinal product was approved in United States in 1989. Brand names of this drug product are Suprax, Taxim O, Texit, Cef-3, Denvar, 3-C and Zifi. Side effects of Cefixime are headache, vomiting, diarrhea, abdominal pain, bloating, vaginal fungal infection, intestinal infection[3].

Ofloxacin is an antibiotic and used to treat bacterial infections like cellulitis, pneumonia, urinary tract infections, plague and prostatitis[4]. USFDA was approved this antibiotic drug in 1985 and world health organization listed as essential medicines[5]. Most frequent side effects are vomiting, diarrhea, insomnia, headache, dizziness, nausea and itching[5].

Linezolid is an antibacterial oxazolidinone class drug product and used to treat pneumonia and skin infections. But, linezolid cannot work for colds, flu and other viral infections[6]. Safe antibiotic if prescribed for short period and common side effects are diarrhea, rash, nausea and headache[7-8].

Chemical structures of Cefixime, Ofloxacin and linezolid were represented in figure-1. Table-1 represented the marketed combination products of Cefixime, Ofloxacin and linezolid.

Cefixime and Ofloxacin are available in the market in solid dosage form with multiple strengths. Ofloxacin and Linezolid are available in solid dosage combination form.

Literature survey reveals the few reported methods on HPLC, LCMS, TLC methods for the determination of cefixime-ofloxacin, cefixime-linezolid[9-14]. Naga M *et al.,* (2017), Ghimire S *et. al.,* (2018) and Hassouna ME *et. al.,* (2017), Prabhu S *et.al.,* (2010) were reported the RP-HPLC methods to determine cefixime-ofloxacin separately and cefixime-linezolid separately. There is no reported method to determine the three components by using simple HPLC method. Hence, the necessity of the HPLC method requirement was understood. The objective of this present research work is to develop a stability indicating HPLC method for the determination of three active components such as Cefixime, Ofloxacin, and Linezolid in combination solid dosage forms.

MATERIALS AND METHODS

MATERIALS

The Chromatographic system consisted of 1100 agilent separation module which provides quaternary solvent, 100 vial capacity, column heater and cooler module, VWD UV detector. In this research authors were tried with different makes of HPLC columns were checked but eventually, Agilent Zorbax SB-C18, 4.6x100 mm, 5 µm particle size was suitable. Cefixime, Ofloxacin, Linezolid standard materials were obtained from Aptuit Laurus Laboratroies Hyderabad.

MOBILE PHASE AND SOLUTIONS PREPARATION

Preparation of mobile phase A

Measured, 1000ml distilled water with class-A measuring cylinder and add 6.8 g of KH_2PO_4 resulting solution was degassed with 0.45µ filter paper.

Mobile Phase-B

HPLC grade Acetonitrile was used. Measured volume was sonicated for 5minutes using the sonicator and filtered using the vacuum pump.

Diluent solution

Put 250 mL of mobile phase A, 250 mL of Acetonitrile into a 1000ml beaker. The resulting solution was mixed for some time to get homogeneous dilution solution.

HPLC conditions

Column: Agilent Zorbax SB- C18, 100 x 4.6mm, 5µm

Flow rate	: 1.0 mL/minute
Detection	: 280 nm
Injection Volume	: 20 µL
Column temperature	: 30°C
Analysis time	: 25 minutes

Mobile Phase Elution Gradient Program

Standard solution

50 mg of Cefixime standard, 50 mg Ofloxacin standard and 150 mg of Linezolid were weighed accurately with calibrated analytical balance and transferred into a 100 mL volumetric flask. 50 mL of diluent was added to dissolve the contents and mixed well. Remaining volume was filled and mixed. 1.0ml of this solution was pipetted and transferred in to 50 ml class A volumetric flask and diluted with diluent.

Preparation of Cefixime and Ofloxacin Sample Solution

Randomly selected 20 tablets and weighed individually and calculated the average weight of one tablet and prepared the fine powder. Equivalent to 50 mg of Cefixime and Ofloxacin tablets powder was weighed and transferred into 100 mL volumetric flask. 50 ml of diluent was added and dissolve the content by using hand shake and sonication for 10 minutes. Further volume was diluted with diluent. Stock solution was filtered with what man filter. 1 mL of the above solution was transferred into a 50 mL volumetric flask and diluted.

Preparation of Cefixime and Linezolid Sample Solution

Randomly selected 20 tablets and weighed individually and calculated the average weight of one tablet and prepared the fine powder. Equivalent to 50 mg of Cefixime and 150 mg Linezolid tablets powder was weighed and transferred into 100 mL volumetric flask. 50 ml of diluent was added and dissolve the content by using hand shake and sonication for 10 minutes. Further volume was diluted with diluent. Stock solution was filtered with whatman filter. 1 mL of the above solution was transferred into a 50 mL volumetric flask and diluted.

% component (Cefixime, Ofloxacin and Linezolid) value calculation formula

$$\frac{\text{Tarea X Tweight X 1 X 100 X 50 X Label claim X Potency}}{\text{Sarea X 100 X 50 X Sweight X 1X Tablet weight X 100 X 100}}$$

In the above calculation formula, Tarea is Peak area from sample preparation; Sarea is Average peak area from standard solution; Tweight is weight of standard taken in mg; Sweight is the weight of standard solution.

RESULTS AND DISCUSSION

HPLC method optimization

Three components standard materials (Cefixime, Ofloxacin and linezolid) were analysed for solubility study, UV spectroscopic study and pKa estimation. UV absorbance was represented in figure-2 for Cefixime, Ofloxacin and linezolid. UV spectrums confirmed the wavelength absorbance values and based on the absorbance of three components, UV wavelength was measured at 280 nm.

Solubility results reveals that Cefixime has high polarity and Ofloxacin has medium polarity and linezolid has less polar than other two components. Based on the understanding of the literature published methods, development trails were initiated with acetate buffer and methanol composed mobile phase. Less carbon C8 250 mm column was used, 280 nm, 20µL injection volume, 30°C column oven temperature was used.

Development trial-1
Conditions
1. 0.25 M ammonium acetate used as buffer; 2. Buffer and Acetonitrile mixed in the ratio of 28:72 v/v, isocratic elution; 3. Intertsil C8 250x4.6mm,5µ column; 4. Flow rate 1.0ml/min, 30°C column temperature, 280 nm; 20µL injection volume.

Observation
All three peaks were eluted but Cefixime peak shape was eluted near void volume of the column with poor peak shape. Further optimization carried out by changing the HPLC column and gradient program. Development trial mixed sample chromatogram was represented in figure 3.

Development trial-2
Conditions
1. 0.5M of ammonium acetate used as mobile phase A; 2. Acetonitrile used as mobile phase B; 4. Intertsil ODS-3 250x4.6mm,5µ column; 5. 1.0ml/min flow rate, 40°C column oven temperature, wavelength 280 nm; 6. Gradient program at 0 min 20% mobile phase B, at 8 min 20%, at 15 min 70%, at 22 min 70%, at 23 min 20% and at 27 min 20%; 7. Diluent: mobile phase A and B 50:50 v/v.

Observation
All three peaks were eluted after the column void volume but blank interference was observed. Blank interference should be minimized with mobile phase buffer and gradient program. Development trial mixed sample chromatogram was represented in figure 4.

Development trial-3
Conditions
1. 0.5M of KH_2PO_4 used as mobile phase A; 2. Acetonitrile used as mobile phase B; 4. Zorbax C18 100x4.6mm,5µ column; 5. 1.0ml/min pump mobile phase flow rate, 40°C column oven temperature, wavelength 280 nm; 6. Gradient program at 0 min 5% mobile phase B, at 5 min 5%, at 10 min 16%, at 14 min 16%, at 17 min 40% 20 min 5% and at 25 min 5%; 7. Diluent: mobile phase A and B 50:50 v/v.

Observation
All three peaks were eluted with good peak shape and no interference was observed at all three product peaks. Slight modification required for linezolid peak early elution. Development trial mixed sample chromatogram was represented in figure 5.

Method validation
Optimized HPLC method procedure was evaluated with method validation parameters such as precision, linearity, specificity, accuracy, ruggedness and robustness. % RSD for replicate standard solutions and replicate test solutions were calculated, linearity correlation coefficient was evaluated, recovery %RSD was evaluated.

System suitability
System suitability was evaluated with freshly prepared standard solutions. Five replicate standard solution injections were performed and calculated the %RSD for retention time and peak area. Other parameters theoretical plates and tailing factor were measured. Peak purity of three components was checked. System suitability results were tabulated in table-3. Blank, placebo and standard solution chromatograms were represented in figure-6, 7 and 8. %RSD values were within the limit 2.0%.

Precision
Precision also called as repeatability. Precision parameter was performed with six replicate test solutions preparations. Six replicate solutions were injected in to the HPLC system. Peak area, %RSD results were calculated and tabulated in table-4. Test solution of cefixime and Ofloxacin, cefixime and linezolid were represented in figure-9 and 10. Precision results were satisfactory and %RSD values were below 2.0%.

Specificity
Specificity parameter is used to evaluate the interference from blank, placebo, known and stress study un-known impurities. Stress studies acid, base, peroxide, thermal and UV light conditions were evaluated. Figure-11 to 20 represented the all stress studies chromatograms for cefixime-ofloxacin and cefixime-linezolid test samples. Table-5, 6 and 7 represented the stress study conditions and results. Results were satisfactory and all un-known impurities were separated and have no interference with products.

Linearity
Linearity parameter was evaluated with standard solution by preparing five different concentrations. Linearity levels are 50%, 75%, 100%, 125% and 150% concentrations. All five linearity solutions were injected into the HPLC system and calculated the correlation coefficient values. Correlation coefficient was calculated for concentration versus peak area. Results were tabulated in table-8 and linearity solutions overlay chromatogram was

represented in figure-21 and linearity graphs were represented in figure-22 to 24. Results were satisfactory, correlation coefficient values were above 0.999.

Accuracy

Accuracy was evaluated to establish the recovery of the components. Different concentration of active components was added to the placebo (constant concentration for all accuracy levels). Accuracy levels 50%, 75%, 100%, 125% and 150% were evaluated. 50% and 150% were performed with six replicate preparations and remaining concentration levels were three replications. Accuracy recovery and %RSD were calculated and tabulated in table-9. % recovery results were between 97% to 103% and %RSD values were below 2.0%.

Ruggedness

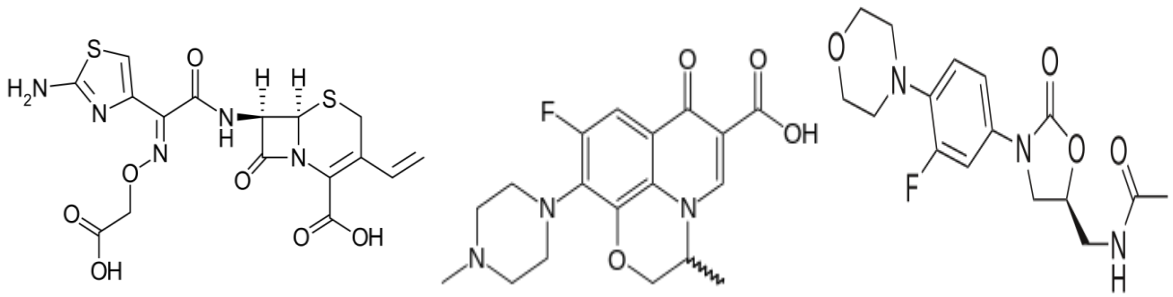
Sample solutions were used to perform ruggedness of the HPLC method. Precision test samples 1 and 2 were used to perform solution stability at room temperature and refrigerator storage conditions. Post analysis of precision 1 and 2 samples were kept at room temperature and refrigerator conditions. Analysis was performed at day-1 and day 3. Samples assay values were calculated and % assay difference found below 2.0%. Results were tabulated in table-10.

Robustness

Robustness of the method was evaluated by changing the chromatographic conditions like mobile phase flow rate, column oven temperature. System suitability was conducted to check the variation changes and results were satisfactory. Retention time, area %RSD, theoretical plates and tailing factor results were tabulated in table-11.

CONCLUSION

Stable and rugged HPLC method was developed for the quantitative determination of Cefixime, Ofloxacin and Linezolid in solid dosage form. Cefixime-Ofloxacin is available in tablet combination dosage form and Cefixime and Linezolid also available in tablets dosage form. Optimized method was evaluated with precision, linearity, specificity, ruggedness and robustness validation parameters. %RSD for area (not more than 2.0%), % recovery (between 97% - 103%), % of degradation, Correlation coefficient (not less than 0.999) and variation change difference (mobile phase flow rate, column oven temperature) were evaluated and results were satisfactory.



Cefixime **Ofloxacin** **Linezolid**

Fig. 1: Chemical structures of Cefixime, Linezolid and Linezolid

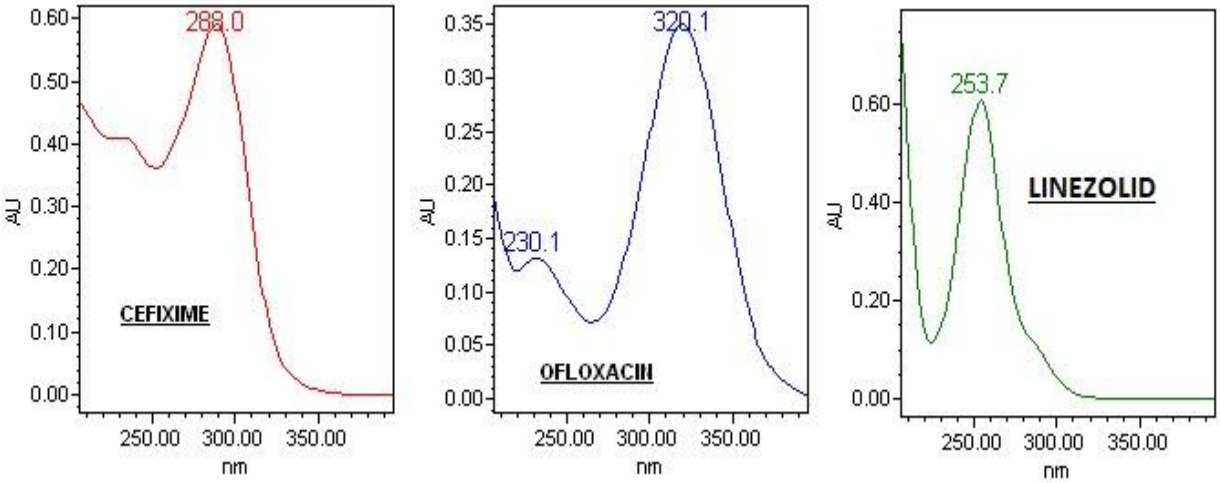


Fig. 2: UV spectrum of Cefixime, Ofloxacin and Linezolid

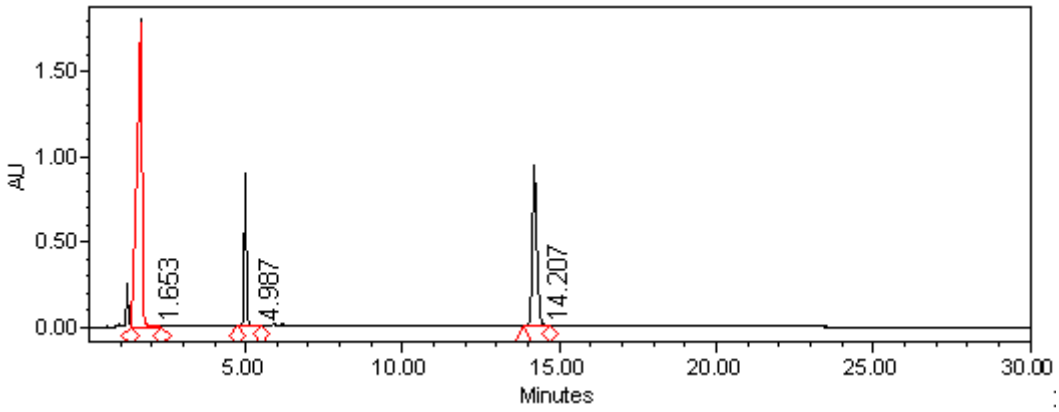


Fig. 3: Method development trial-1 chromatogram

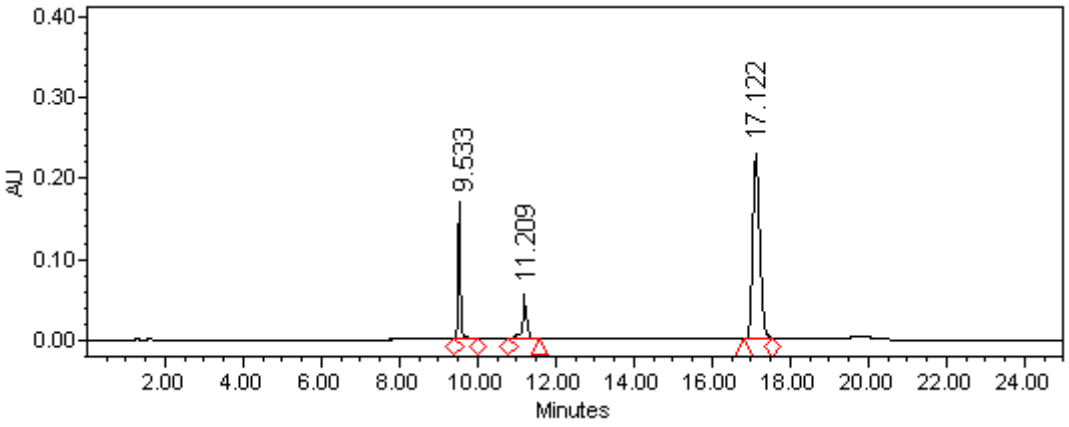


Fig. 4: Method development trial-2 chromatogram

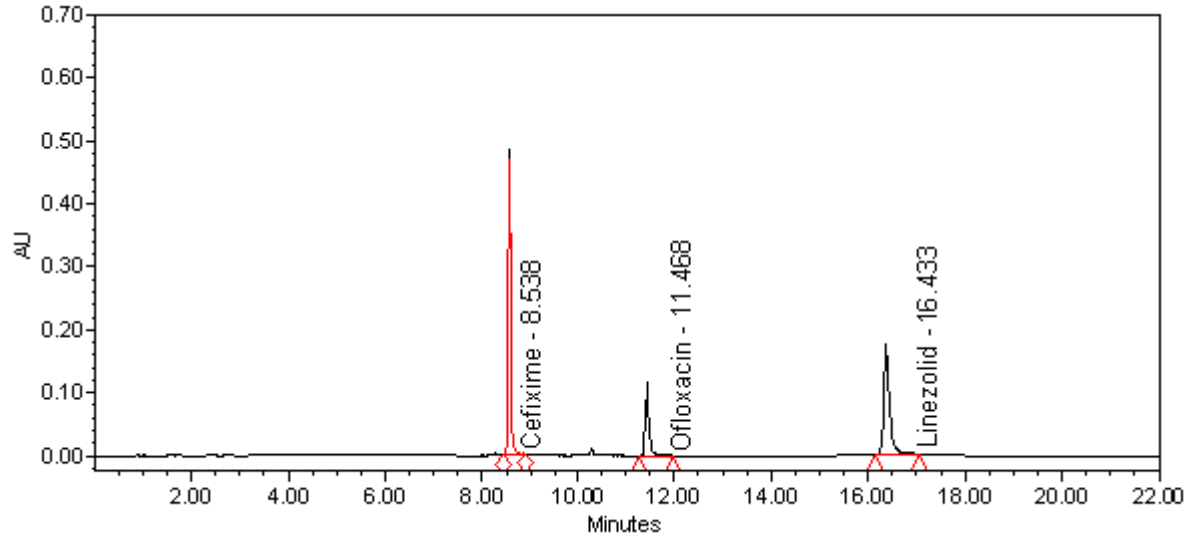


Fig. 5: Method development trial-3 chromatogram

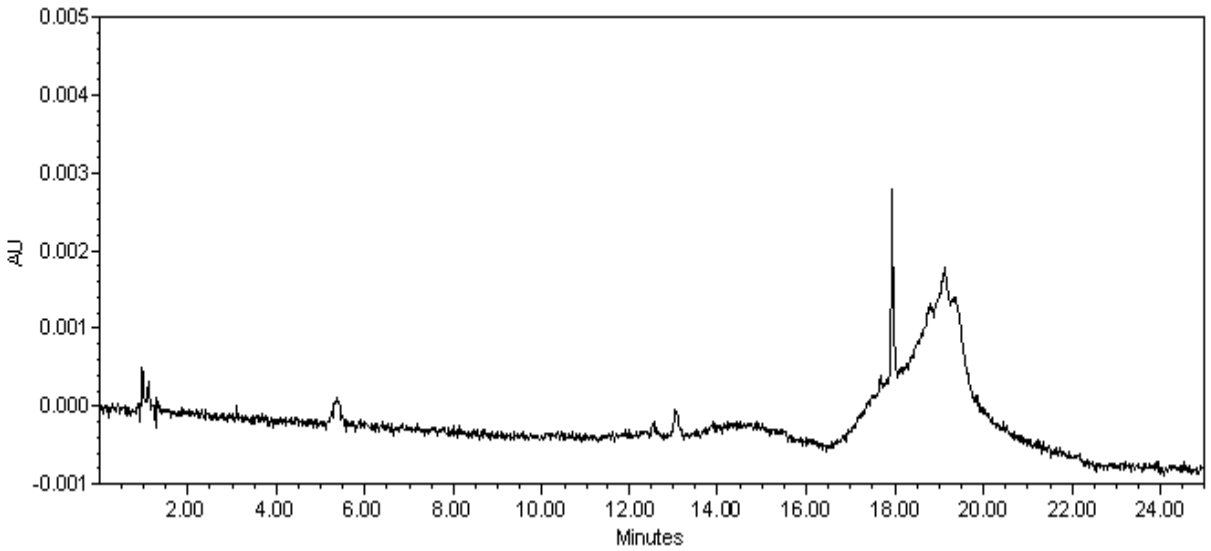


Fig. 6: Blank Chromatogram

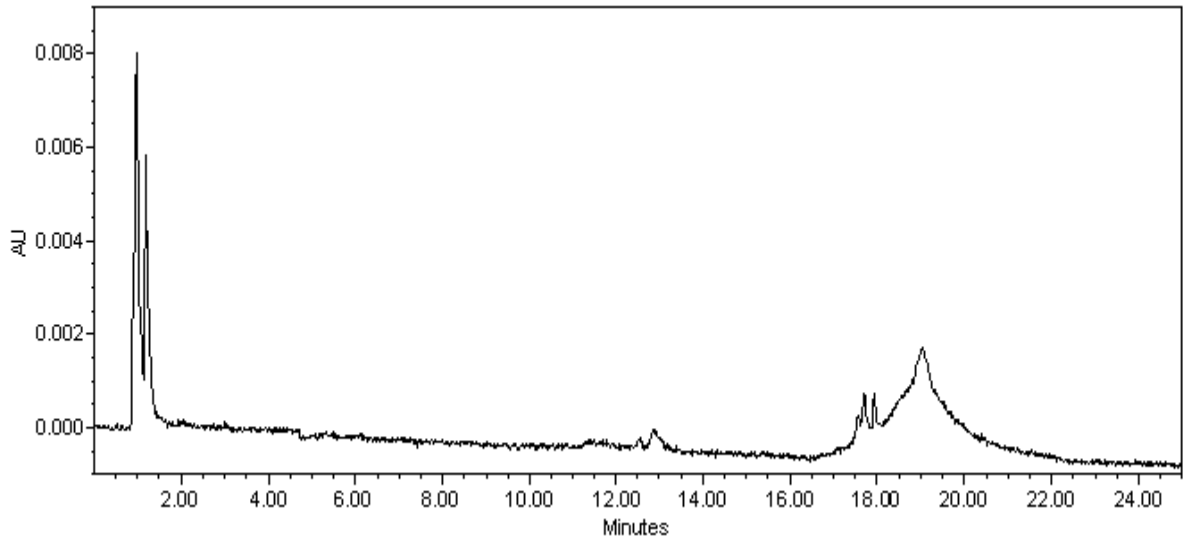


Fig. 7: Placebo Chromatogram

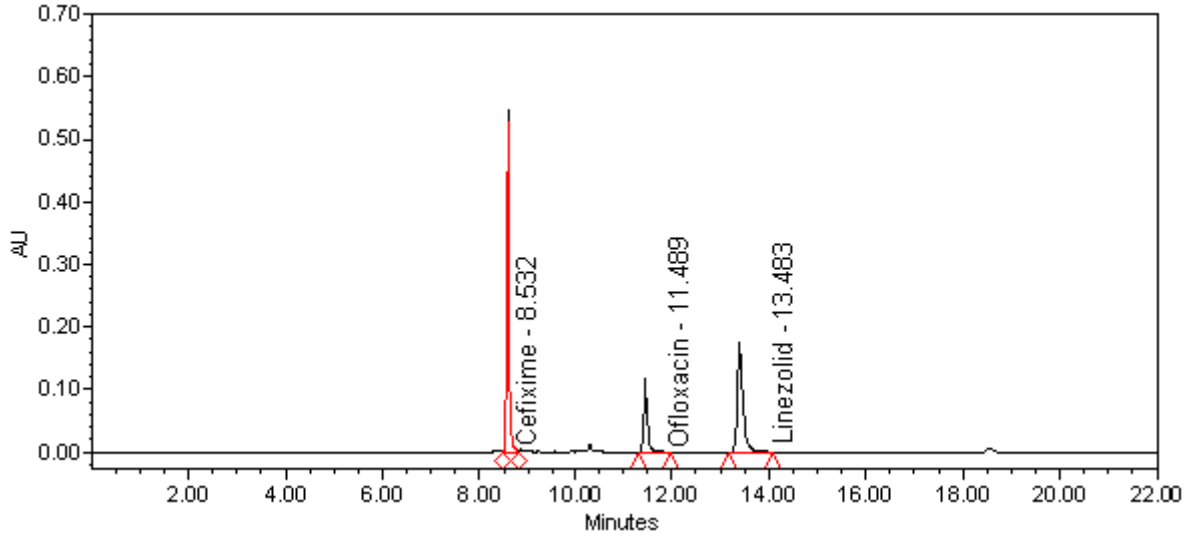


Fig. 8: Standard solution Chromatogram

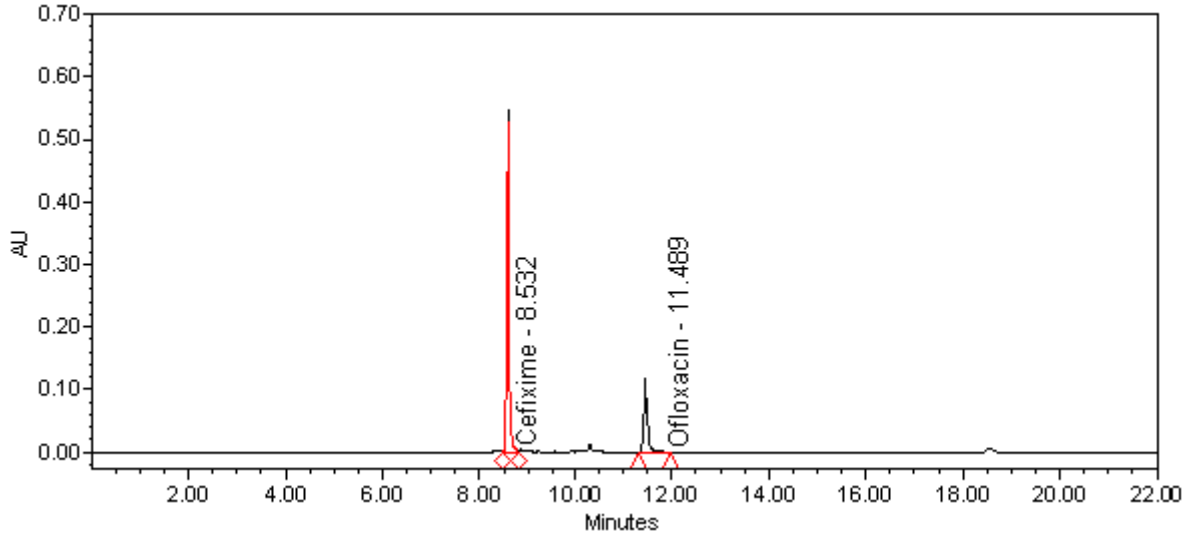


Fig. 9: Cefixime and Ofloxacin test sample chromatogram

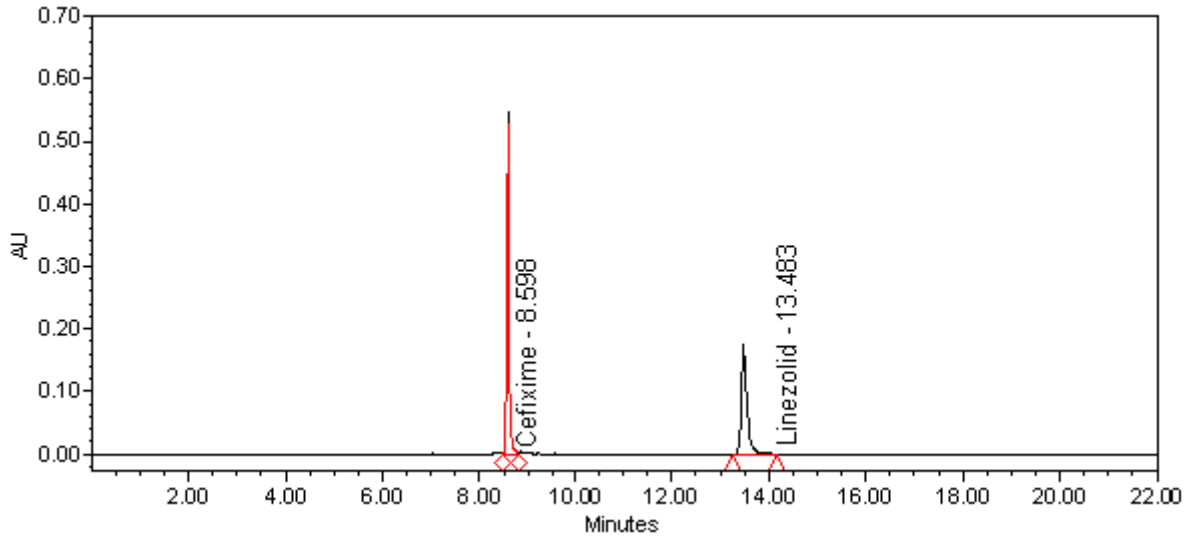


Fig. 10: Cefixime and Linezolid sample chromatogram

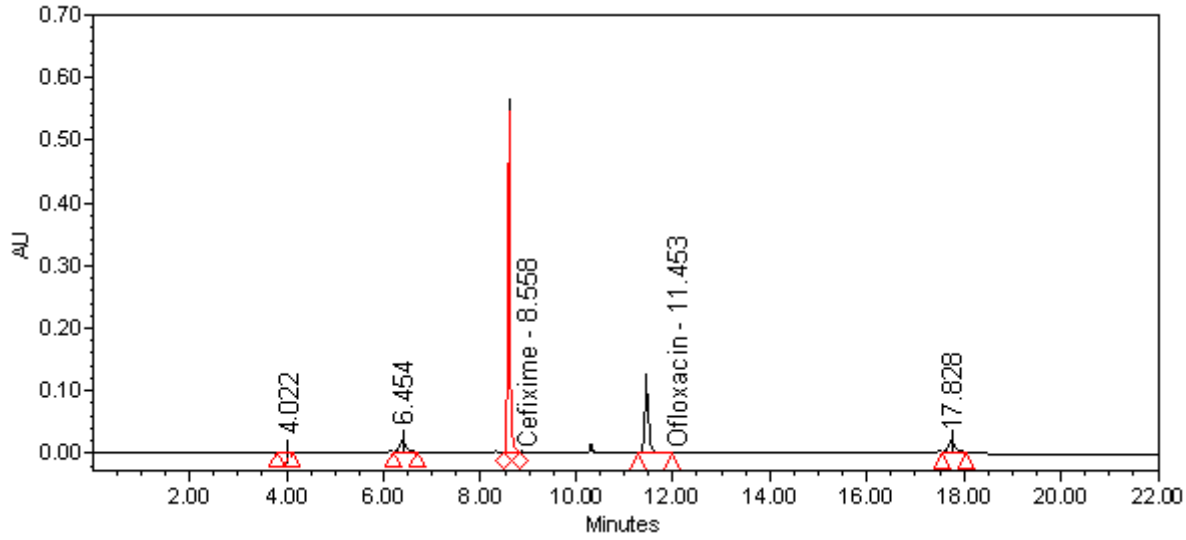


Fig. 11: Cefixime and Ofloxacin Acid stress study chromatogram

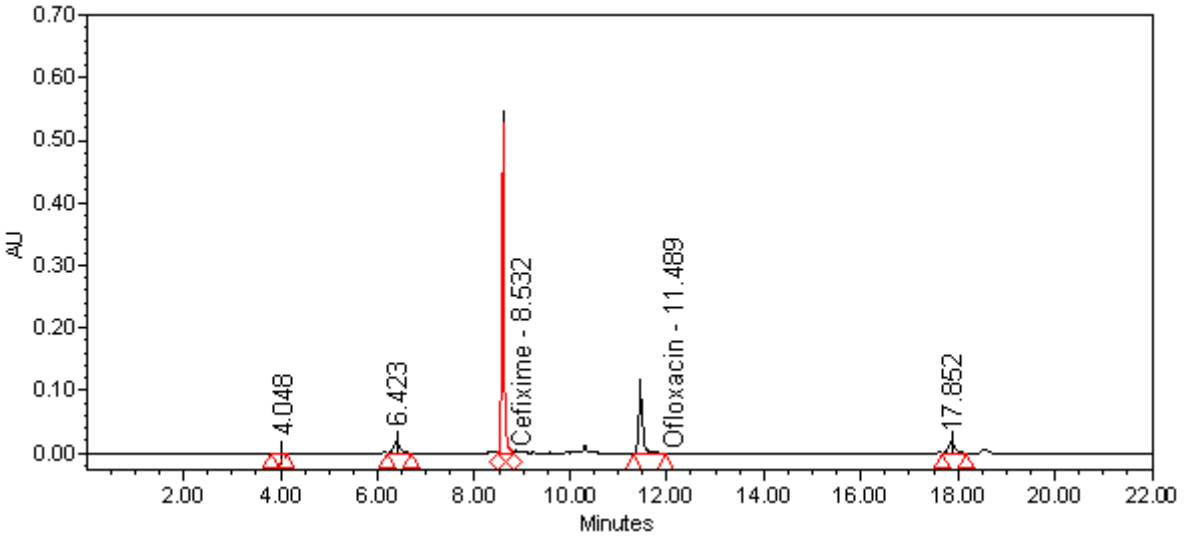


Fig. 12: Cefixime and Ofloxacin Base stress study chromatogram

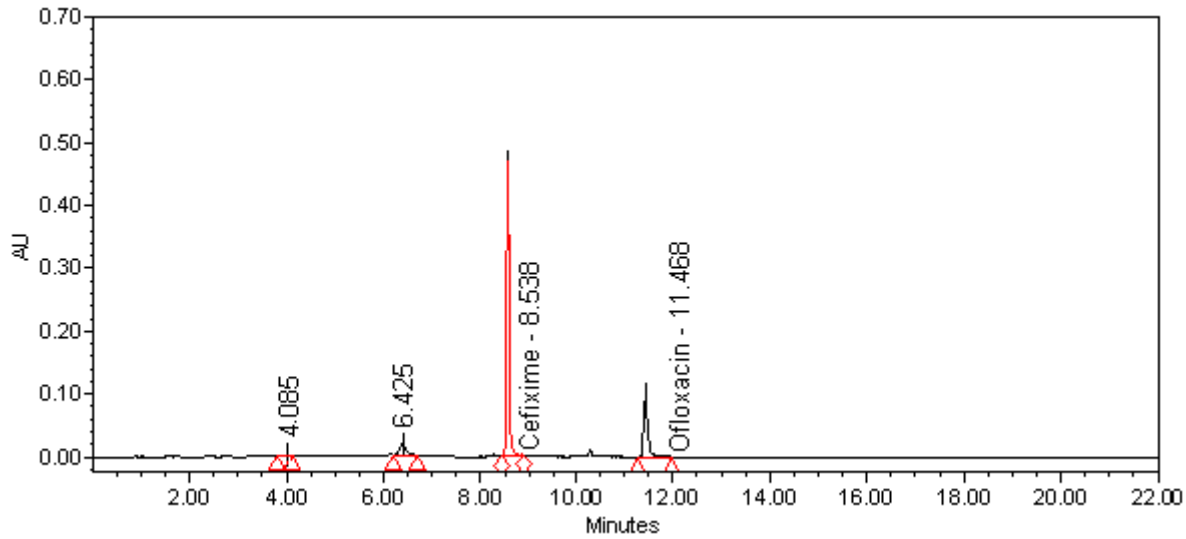


Fig. 13: Cefixime and Ofloxacin Peroxide stress study chromatogram

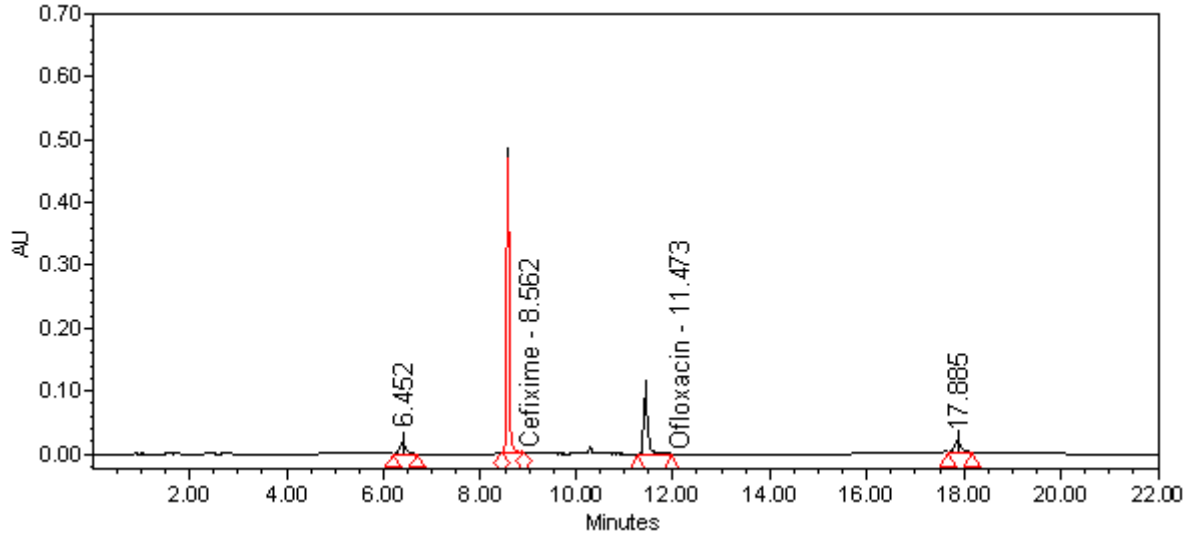


Fig. 14: Cefixime and Ofloxacin Thermal stress study chromatogram

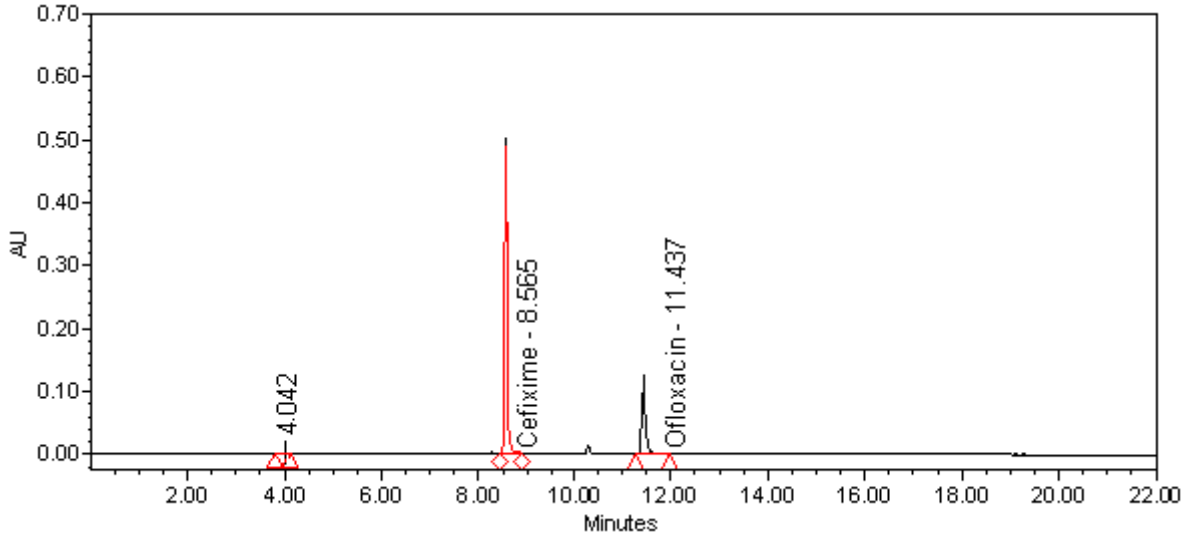


Fig. 15: Cefixime and Ofloxacin UV stress study chromatogram

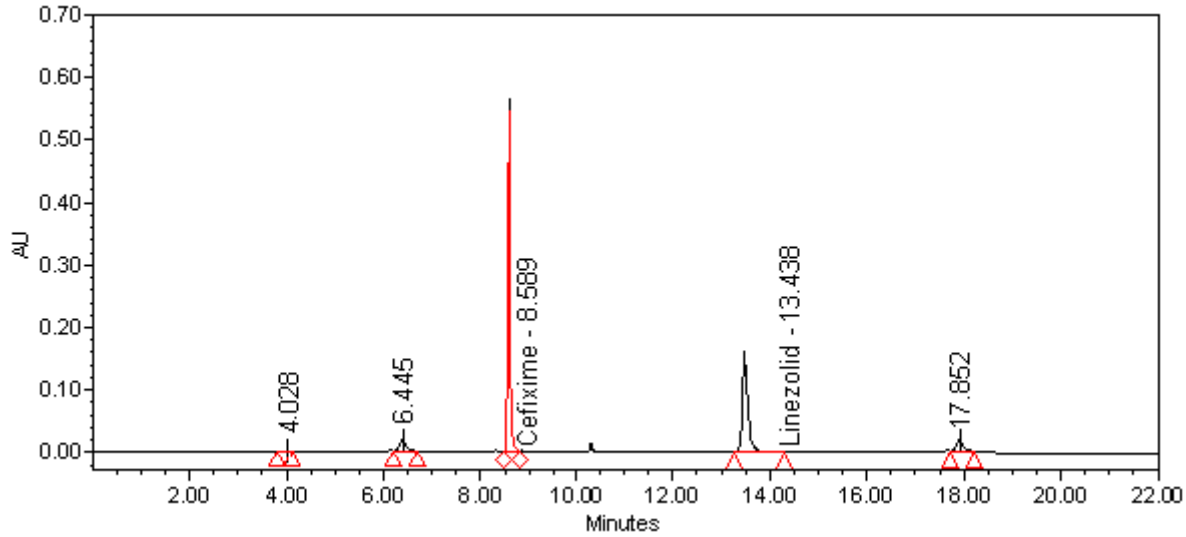


Fig. 16: Cefixime and Linezolid Acid stress study chromatogram

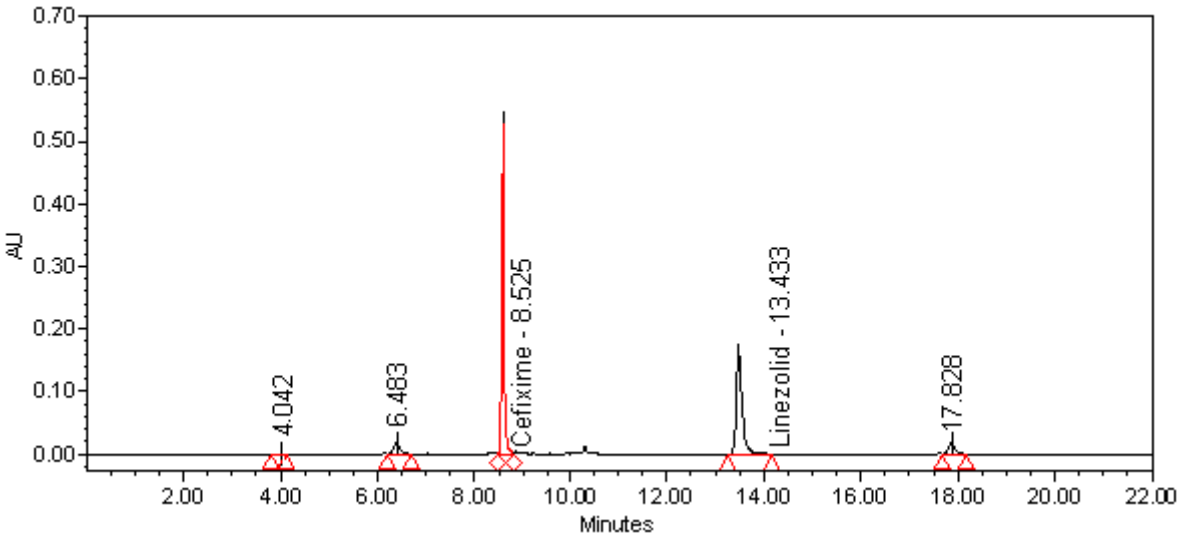


Fig. 17: Cefixime and Linezolid Base stress study chromatogram

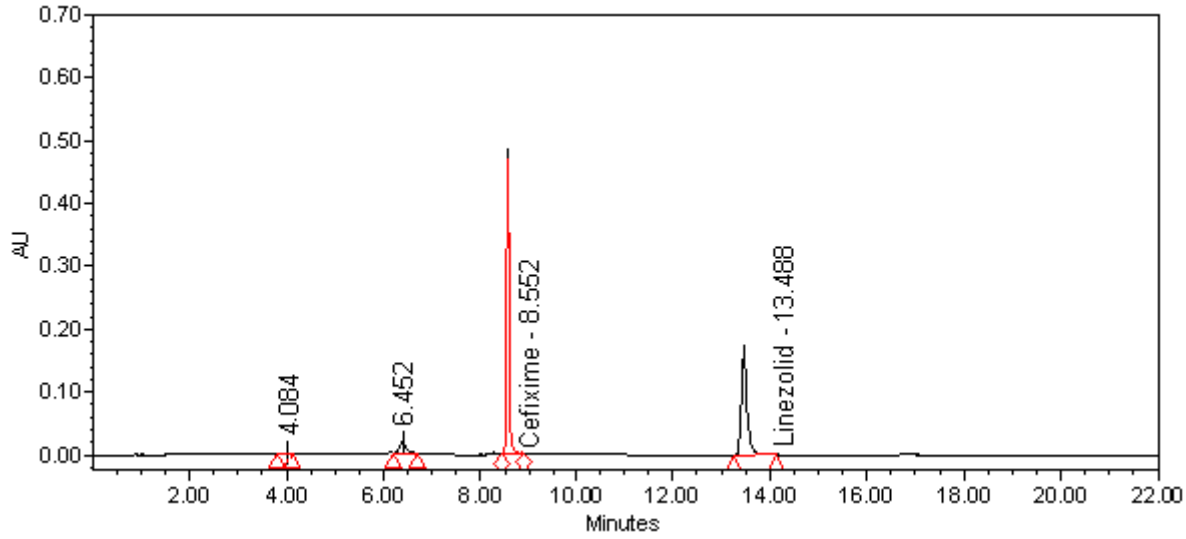


Fig. 18: Cefixime and Linezolid Peroxide stress study chromatogram

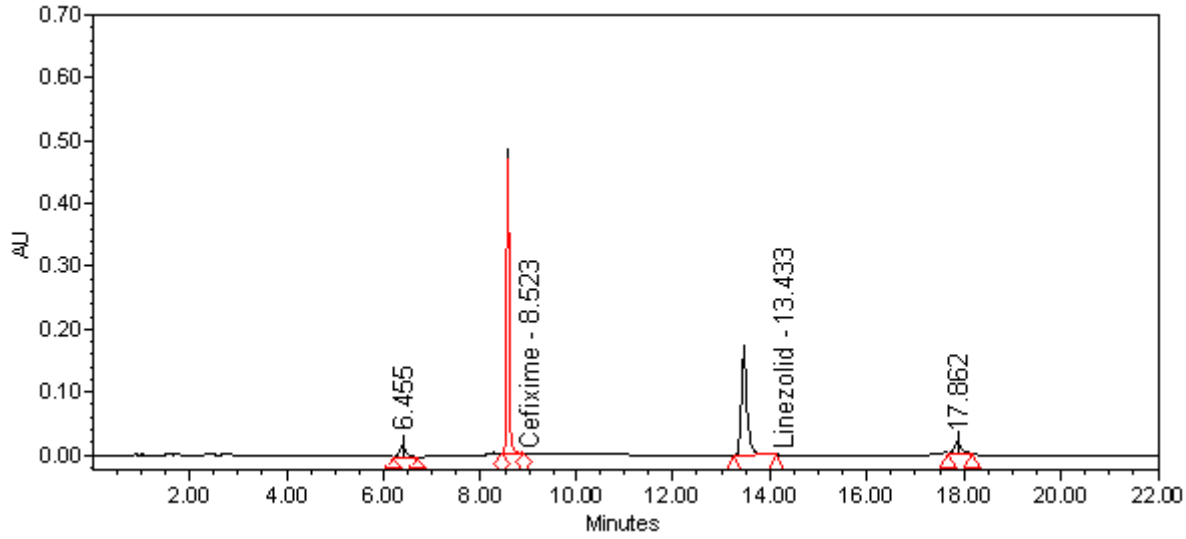


Fig. 19: Cefixime and Linezolid Thermal stress study chromatogram

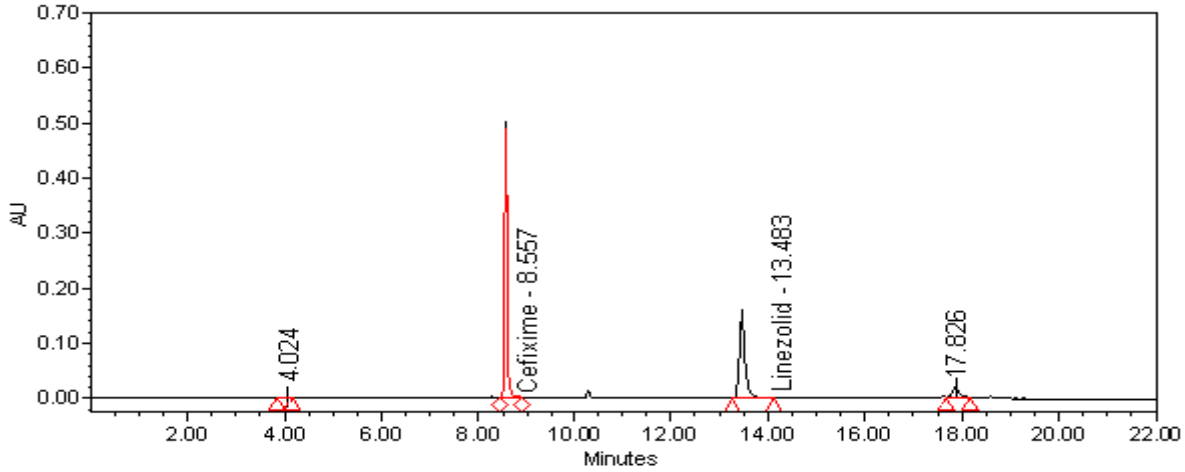


Fig. 20: Cefixime and Linezolid UV stress study chromatogram

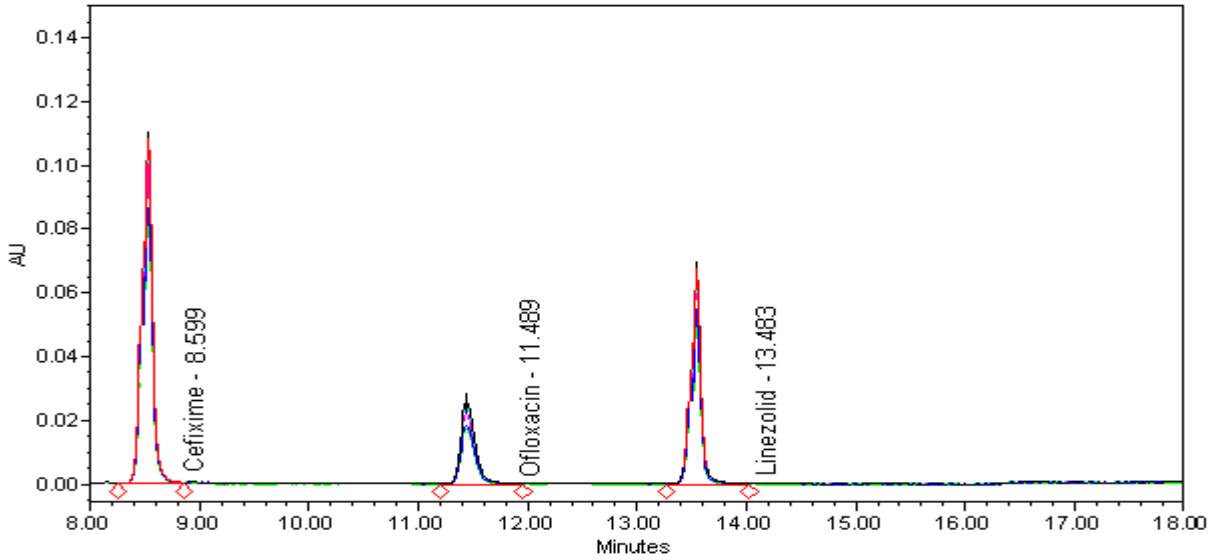


Fig. 21: Linearity overlay chromatogram

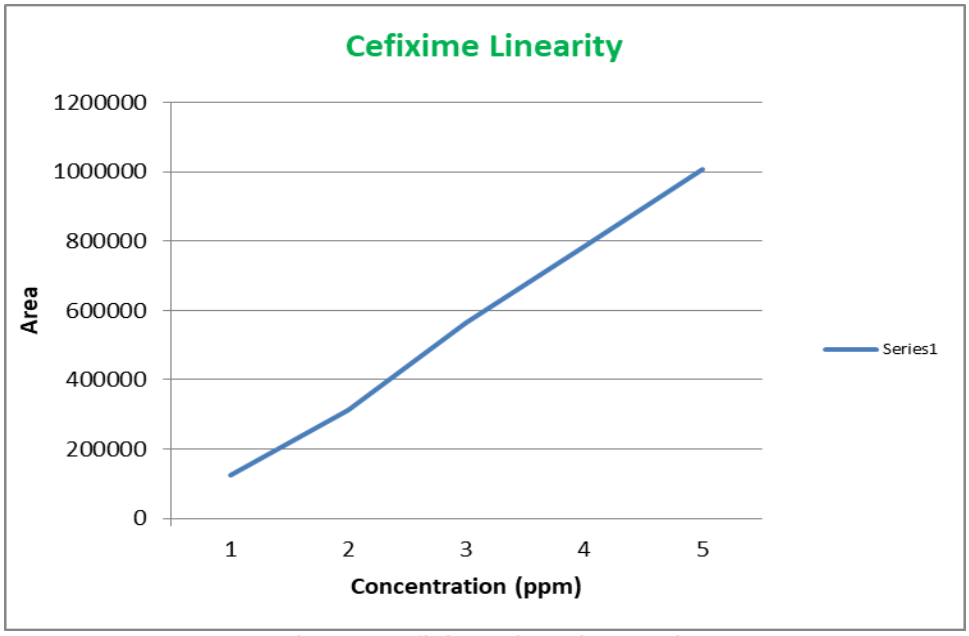


Fig. 22: Cefixime Linearity graph

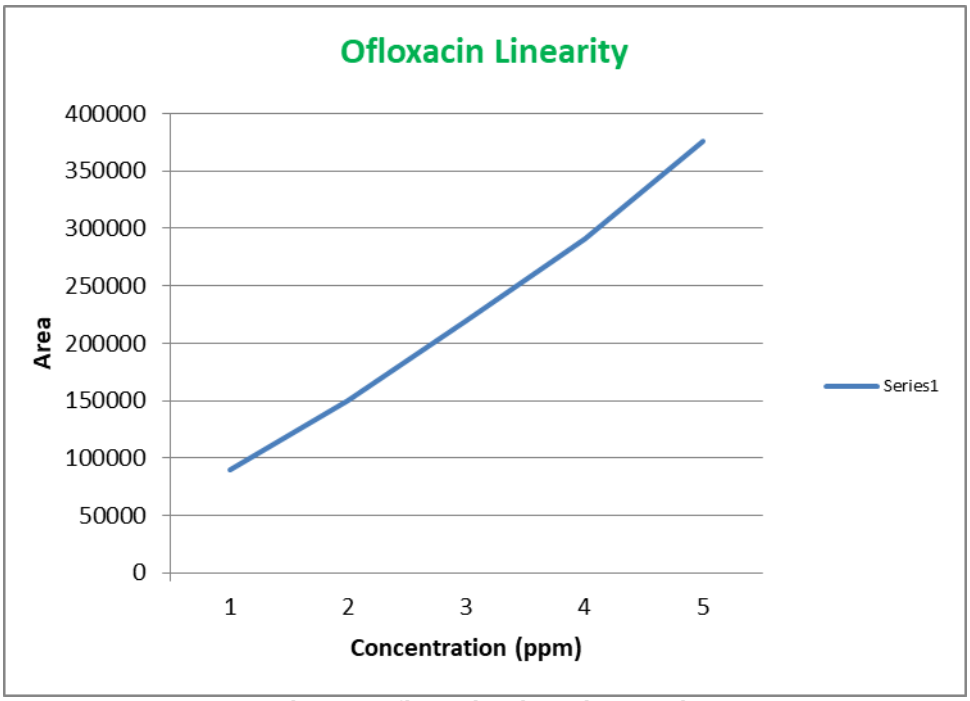


Fig. 23: Ofloxacin Linearity graph

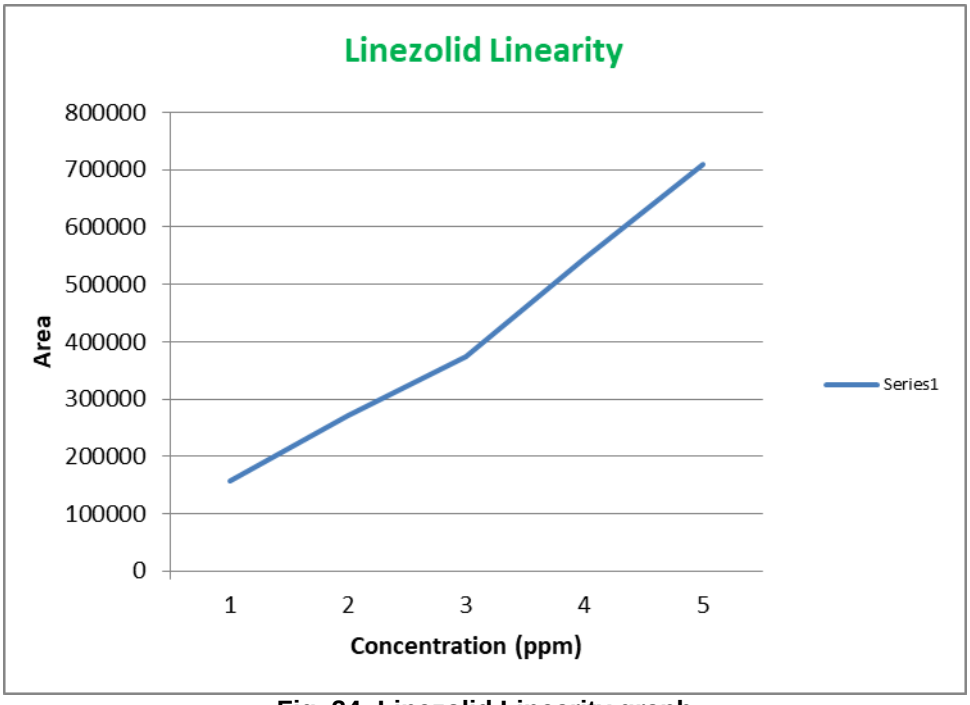


Fig. 24: Linezolid Linearity graph

Table 1: Marketed medicinal products

Brand name	Company name	Composition
EUROX-O tablets	Health guard	Cefixime 200 mg and Ofloxacin 200 mg Cefixime 100 mg and Ofloxacin 100 mg
MILIXIM-O tablets	Glenmark	
MYCEF PLUS tablets	Amro Pharma	
OFCEF tablets	JB chemicals	
RINTAX PLUS tablets	Octane biotech	
LINCEF tablets	Alkem	Cefixime 200 mg, Linezolid 600 mg
Linezonix –CF	Phoenix	
Lizomac-CX	Macleods	
Morbicef-L	Intra labs	

Table 2: Gradient program

Time (Minutes)	Mobile phase-A (%v/v)	Mobile phase-B (%v/v)
0.00	95	5
5.00	95	5
10.00	84	16
14.00	84	16
17.00	66	34
20.00	95	5
25.00	95	5

Table 3: System suitability results

Injection	Retention time (min)			Area		
	Cefixime	Ofloxacin	Linezolid	Cefixime	Ofloxacin	Linezolid
1.	8.53	11.48	13.48	566504	216345	371025
2.	8.52	11.48	13.47	567125	216314	370152
3.	8.53	11.49	13.49	567314	216781	370145
4.	8.54	11.48	13.47	559987	214987	371025
5.	8.53	11.49	13.47	561046	215164	370146
%RSD	0.08	0.05	0.07	0.63	0.37	0.13
	Theoretical plates			Tailing factor		
1.	5342	5468	5497	1.2	1.1	1.2
2.	5216	5900	5682	1.1	1.3	1.2
3.	5415	6102	5637	1.3	1.2	1.3
4.	5701	5803	5429	1.2	1.4	1.1
5.	5634	5269	5498	1.4	1.2	1.2
Average	5461	5708	5548	1.24	1.24	1.20

Peak purity Results			
Active component	Purity angle	Purity threshold	Peak purity Results
Cefixime	0.330	0.433	Pass
Ofloxacin	0.161	0.389	Pass
Linezolid	0.111	0.256	Pass

Table 4: Precision and intermediate results

S.No.	Precision % Assay				Intermediate precision % Assay			
	Cefi.	Oflo.	Cefi.	Line.	Cefi.	Oflo.	Cefi.	Line.
1	99.8	101.2	100.6	101.3	101.3	101.2	101.0	100.6
2	101.2	100.4	101.3	100.8	100.5	100.7	100.6	101.0
3	100.6	101.2	100.4	100.4	100.6	100.2	100.4	101.3
4	100.1	99.9	99.9	100.8	99.6	101.0	100.8	100.8
5	99.9	100.1	100.3	101.4	100.6	100.7	99.9	100.4
6	100.8	101.6	100.8	101.3	100.3	100.1	100.5	100.1
Average	100.4	100.73	100.5	101	100.48	100.65	100.5	100.7
% RSD	0.54	0.65	0.47	0.49	0.55	0.37	0.25	0.42

Table 5: Specificity stress study conditions

Cefixime Ofloxacin sample	Cefixime Linezolid sample
Acid stress/1N-60°C/60 minutes	Acid stress/1N-60°C/60 minutes
Base Stress/1N- 60°C/2 hrs	Base Stress/1N- 60°C/2 hrs
Peroxide stress/3%- 60°C/1 hrs	Peroxide stress/3%- 60°C/1 hrs

Thermal (80°C for 6 hrs)	Thermal (80°C for 6 hrs)
UV energy of 200-watt hrs/^{2}m	UV energy of 200-watt hrs/^{2}m

Table 6: Specificity Results

Stress condition	Cefixime			Ofloxacin			Linezolid		
	Purity angle	Purity threshold	Pass/ fail	Purity angle	Purity threshold	Pass/ fail	Purity angle	Purity threshold	Pass/ fail
Acid	0.332	0.412	Pass	0.113	0.251	Pass	0.121	0.236	Pass
Base	0.315	0.421	Pass	0.116	0.261	Pass	0.131	0.250	Pass
Peroxide	0.264	0.484	Pass	0.132	0.269	Pass	0.125	0.253	Pass
Thermal	0.269	0.428	Pass	0.223	0.278	Pass	0.120	0.243	Pass
UV	0.289	0.451	Pass	0.120	0.236	Pass	0.196	0.238	Pass

Table 7: Specificity results

Peak RT (min)	Cefixime and Ofloxacin samples degradation				
	Acid	Base	Peroxide	Thermal	UV
4.1	1.45	1.48	1.36	NA	1.40
6.4	1.61	1.50	1.42	1.41	NA
17.8	1.30	1.43	NA	1.46	NA
Cefixime and Linezolid samples degradation					
4.2	1.43	1.46	1.39	NA	1.40
6.4	1.29	1.38	1.40	1.42	NA
17.8	1.38	1.42	NA	1.40	1.39

Table 8: Linearity results

Linearity level	Cefixime		Ofloxacin		Linezolid	
	Conc.	Area	Conc.	Area	Conc.	Area
50%	5.21	125910	5.17	89910	15.48	155910
75%	7.52	313236	7.49	150236	22.59	270236
100%	10.10	565504	10.04	219345	28.9	375025
125%	12.45	785681	12.48	290681	37.8	545681
150%	15.2	1005610	15.15	375610	47.13	710610
Correlation coefficient.	0.9993		0.9992		0.9994	

Table 9: Accuracy samples preparations and recovery results

Recovery level	Sample Prepn.	Cefixime Recovery		Ofloxacin Recovery		Linezolid Recovery	
		% Recovery	Mean recovery/ %RSD	% Recovery	Mean recovery/% RSD	% Recovery	Mean recovery/% RSD
50%	1	99.6	100.31 /0.55	100.3	100.30/ 0.47	100.2	100.40/0.51
	2	101.2		99.7		101.3	
	3	100.3		101.0		100.4	
	4	100.5		100.3		99.9	
	5	99.9		100.6		100.0	
	6	100.4		99.9		100.6	
75%	1	100.8	101.06 /0.30	100.7	100.36/ 0.35	100.1	100.60/0.46
	2	101.0		100.0		100.7	
	3	101.4		100.4		101.0	
100%	1	99.9	100.26 /0.40	100.6	100.63/ 0.35	100.4	100.46/0.60
	2	100.2		101.0		101.1	
	3	100.7		100.3		99.9	
125%	1	101.0	100.43/ 0.55	100.6	100.63/ 0.35	100.3	100.06/0.21
	2	100.4		100.3		100.0	
	3	99.9		101.0		99.9	
150%	1	100.3	100.48 /0.37	99.9	100.16/ 0.44	100.4	100.28/0.32
	2	101.0		100.3		99.9	
	3	100.7		101.0		100.3	
	4	100.6		100.1		100.8	
	5	100.4		99.9		100.0	
	6	99.9		99.8		100.3	

Table 10: Sample solution stability results

Room Temperature								
Time interval	Cefixime-Ofloxacin sample				Cefixime-Linezolid sample			
	Cefixime		Ofloxacin		Cefixime		Linezolid	
	% Assay	% Diff.	% Assay	% Diff.	% Assay	% Diff.	% Assay	% Diff.
Initial-1	99.8	NA	101.2	NA	100.6	NA	101.3	NA
Intial-2	101.2		100.4		101.3		100.8	
Day-1	100.2	0.4	100.4	0.8	100.9	0.3	100.3	1.0
Day-1	100.4	0.8	100.8	0.4	100.0	1.3	100.6	0.2
Day-3	101.1	1.3	101.0	0.2	100.4	0.2	100.0	1.3
Day-3	100.5	0.7	100.6	0.2	100.6	0.7	100.5	0.3

Table 11: Flow rate variation, temperature variation system suitability results

Variation	Robust Parameters		RT (min)	5 inj. Area %RSD	USP Plate Count avg.	USP Tailing avg.
Flow variation	Actual (1.0ml/min)	Cefi.	8.53	0.32	5681	1.12
		Oflo.	11.41	0.25	5490	1.01
		Line.	13.46	0.21	5389	1.10
	Low (0.9ml/min)	Cefi.	8.63	0.40	5709	1.30
		Oflo.	11.56	0.34	6100	1.41
		Line.	13.64	0.29	6081	1.13
	High (1.1ml/min)	Cefi.	8.32	0.32	5937	1.10
		Oflo.	11.34	0.41	5890	1.15
		Line.	13.40	0.29	5687	1.31
Column oven temp.	Low 25°C	Cefi.	8.62	0.31	5909	1.25
		Oflo.	11.54	0.28	6012	1.01
		Line.	13.52	0.43	6081	1.15
	High 35°C	Cefi.	8.29	0.40	5964	1.12
		Oflo.	11.35	0.36	5937	1.32
		Line.	13.40	0.30	6106	1.30

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