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Research Article

Development And Validation Of Rp-Hplc Method For Combination Of Cefuroxime Axetil And Linezolid In Pharmaceutical Dosage form

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Abstract

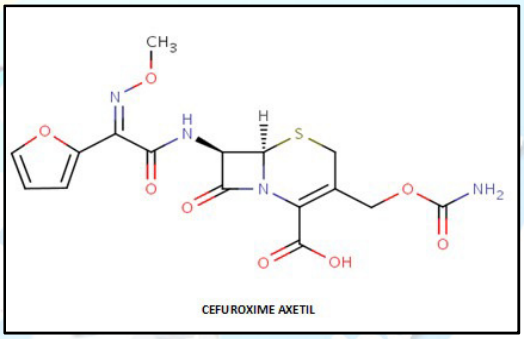
A simple, rapid, accurate and economical RP-HPLC method has been developed for simultaneous estimation of Cefuroxime Axetil& Linezolid pharmaceutical dosage validated as per ICH guideline.For the analysis, HPLC LC- 20 AT SPD 20A UV detector at 240 nm and C_{18} (250mm x 4.6 mm) column was used. The selected mobile phase was Potassium phosphate (pH 5.0) and Acetonitrile (60:40v/v) in isocratic mode at a flow rate of 1 mL/min. Retention time of Linezolid and Cefuroxime Axetil were found to be 3.713 min and 6.107 min respectively.

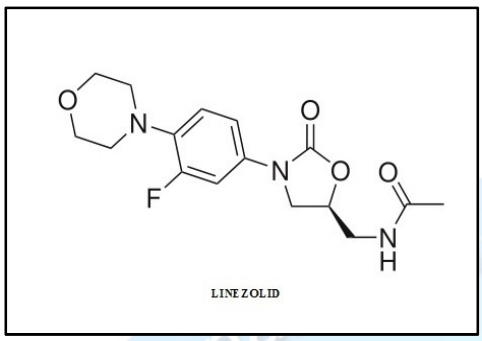
Key words: Cefuroxime Axetil, Linezolid, RP-HPLC, Validation.

INTRODUCTION[1-7]

Cefuroxime axetil (CFA) is a second-generation cephalosporin that contains the classic β-lactam ring structure. Cefuroxime axetil is an ester prodrug of cefuroxime, which is rendered more lipophilic by esterification of carboxyl group of the molecule by the racemic 1- acetoxyethyl bromide, thus enhancing absorption. The absorbed ester is hydrolysed in the intestinal mucosa and in portal circulation. Products of hydrolysis are active cefuroxime, acetaldehyde and acetic acid. Cefuroxime is chemically (1RS)-1-[(acetyl) oxy] ethyl- (6R, 7R)-3-(carbamoyloxy) methyl]-7-[(Z-2-furan- 2yl)-2-(methoxyimino) acetyl) amino]-8-oxo-5-thia-1-azabicyclo- (4.2.0)-oct-2-ene-2-carboxylate. It is used as an antibiotic for the treatment of many type of bacterial infections such as bronchitis, sinusitis, tonsillitis, ear infections, skin-infections, urinary tract infections.

Linezolid(LNZ) is chemically (*S*)-*N*-({3-[3-fluoro-4-(morpholin-4-yl) phenyl] - 2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide. It is member of oxazolidinone class. It is used for the treatment of serious infection caused by Gram positive bacteria that resistance to other antibiotics. The main uses are infections of the skin and pneumonia although it may be use for a variety of other infections. Oxazolidinone bind to the 50S subunit of the prokaryotic ribosome, preventing it from complexing with the 30S subunit, mRNA, initiation factors and formyl-methionyl-tRNA. The net result is to block assembly of a functional initiation complex for protein synthesis, thereby preventing translation of the mRNA.





LINEZOLID

Literature review reveals that numbers of individual analytical methods available for estimation of Cefuroxime Axetil and Linezolid intheir individual dosage forms.But HPLC method has been not reported for simultaneous estimation of Cefuroxime Axetil and Linezolid in solid dosage forms. So it is developRP-HPLC method for simultaneous estimation of Cefuroxime Axetil and Linezolid in Pharmaceutical Dosage Form and validated as per ICH guideline.[8-36]

MATERIALS AND METHODS

Apparatus and Software

HPLC was performed on isocratic Shimadzu (Shimadzu Corporation, Kyoto, Japan) chromatographic system equipped with Shimadzu LC-20AT pump and Shimadzu SPD-20AV absorbance detector Data acquisition and integration was performed using spinchrome software.

Reagents and materials

Cefuroxime Axetiland Linezolid were procured from Gujarat laboratory, Ahmedabad, Gujarat.Tablet samples were purchased from local pharmacy (**Stafcure-LZ**- Labelled claim: 500mg Cefuroxime and 600 mg Linezolid). HPLC grade methanol (Merck Ltd., Mumbai, India) and acetonitrile (Finar Chemicals Ltd., Mumbai, India) were used during study. Double distilled water (Purified HPLC grade water) was obtained by filtering double distilled water through nylon filter paper 0.2 µm pore size and 47 mm diameter (Pall Life Sciences, Mumbai, India). Potassium dihydrogen orthophosphate purified was procured from S D Fine Chem. Ltd, Mumbai.

Chromatographic Condition

Chromatographic separation was performed using C18 (25cm x 0.46 cm) Hypersil BDS, at ambient temperature, eluted with mobile phase at a flow rate of 1.0 ml/min. The mobile phase consisted of Potassium phosphate (pH 5.0): Acetonitrile (60:40 v/v). Measurements were made with an injection volume of 20 µL and UV detection at 240 nm, as both components showed reasonably good response at this wavelength.

Selection of wavelength

Standard solution of CefuroximeAxetil (10 µg/mL) and Standard solution of Linezolid (12 µg/mL) were scanned between 200-400 nm using UV-visible spectrophotometer. Wavelength was selected from the overlay spectra of above solutions.Both Cefuroxime Axetil and Linezolid show reasonably good response at 231nm.

Preparation of mobile Phase

Take 6.8 gmPotassium Hydrogen Phosphate in 1000 ml water and dissolve, adjust pH 5.0 with 10 M potassium hydroxide. Filter it with 0.45 micron filter paper and mix with Acetonitrile. The mobile phase composition is Buffer:Acetonitrile 60:40(v/v). Sonicate the solution for 15 min.

Preparation of standard stock solution

Standard solution of Cefuroxime Axetil (100 µg/ml) and linezolid (120µg/ml) was prepared by transferring accurately weighed Cefuroxime Axetil (10 mg) and linezolid (12 mg) in 100 ml volumetric flask separately and dissolving in methanol. The solution was diluted to 100 ml with methanol in separate volumetric flask to inject in chromatographic system.

Preparation of standard solution of binary mixtures of Cefuroxime Axetil (10 µg/mL) and Linezolid (12 µg/mL)

Take 1 mL from the Cefuroxime Axetil stock solution and 1mL from Linezolid stock solution and transferred to 10 mL volumetric flask and volume made up to the mark by mobile phase.

Preparation of sample solution

Take Tablet Powder equivalent to 10 mg of Cefuroxime Axetil and 12 mg of Linezolid was transferred to a 100 ml volumetric flask, and made up volume up to the mark with mobile phase. The solution was filtered through whatman filter paperno. 42 and first few drops of filtrate were discarded. 1 ml of this solution was diluted to

10 ml with mobile phase.

Validation Studies

The following parameters were considered for the analytical method validation for the quantification of Cefuroxime Axetil and Linezolid in tablet dosageform as per ICH guideline.

System suitability test

System suitability was performed by preparing solutions per the test method and analysed before performing any validation parameters to verify that the system is adequate for the analysis. The parameter used to verify in this test were retention time, theoretical plate, tailing factor and resolution.

Acceptance criteria:

%RSD of area of five replicate standard injection should not be more than 2.0; Theoretical plates for the analysis peak should not be less than 2000; Tailing factor for the analyte peak should not be more than 2.0. Data is show in Table 1.

Specificity

Specificity of an analytical method is its ability to measure the analyte accurately and specificity in the presence of component that may be expected to be present in the sample matrix. Chromatogram of standard and sample solution of Cefuroxime Axetil and Linezolid were compared, and peak purity spectra obtained from using photo diode array detector (PDA) were recorded in order to provide an indicated of specificity of the method. Chromatograms are Shows in Figure1 to 5.

Acceptance criteria: There must be no interference

Linearity & Range

Linearity response was determined by analyzing different concentration for calibration curve in the range 5-15 g/ml for Cefuroxime Axetil and 6-18 g/ml for Linezolid. Peak area was measured at each level. Peak area was plotted against concentration and equation of straight line and correlation co-efficient was determined.

Acceptance criteria: value of R^2should be ≥0.99. Linearity data are given in table 2. Chromatogram and calibration curve in shown in figure Figure6to 8 respectively.

Precision

The precision of an analytical expresses the closeness of agreement (degree of scatter) between a series of measurement obtained from multiple sampling of the same homogeneous sample under the prescribed condition. Precision considered at three levels: Repetability, intermediate (intraday) Precision and Reproducibility (Interday) Precision.

Repetability

Method precision of experiment was performed by preparing the standard solution of Cefuroxime Axetil (10µg/ml) and Linezolid (12µg/ml) for six times and analysed as per proposed method and % RSD was calculated.

Acceptance Criteria: %RSD of area should not be more than 2.0%/ Data is show in Table 3.

Intraday Precision

Solution containing 5, 10, 15 µg/ml of Cefuroxime Axetil and 6, 12, 18µg/ml of Linezolid were analysed for three times in same day and % RSD was calculated. Data is show in Table 4.

Interday Precision

Solution containing 5, 10, 15µg/ml of Cefuroxime Axetil and 6, 12, 18µg/ml of Linezolid were analysed for three times on three different successive days and % RSD was calculated. Data is show in Table 5.

Accuracy

The accuracy of the method was determined at 80%, 100%, and 120% by calculating recoveries of Cefuroxime Axetil and Linezolid by the standard addition method. Known amount of standard solution of Cefuroxime Axetil (10, 20, 30 g/ml) and Linezolid (5, 10, 15 g/ml) were added to pre-qualified sample solution of Cefuroxime Axetil (20 g/ml) and Linezolid (10 g/ml). Each solution was injected in triplicate and the percentage recovery was calculated by measuring the peak areas and fitting these values into the regression equation of the respective calibration curves.

Acceptances Criteria: % Recovery at each should be between 98.00% to 102.00%. % recovery data show in Table 6-7.

Roubstness

The Roubstness was studies by analysing the sample of Cefuroxime Axetil and Linezolid by delibe-

rate variation in the method parameters. The change in the response of Cefuroxime Axetil and Linezolid was noted. Roubstness of the method was studied by changing flow rate by +-0.2 ml/min, and mobile phase composition +-2ml. the change in the response of Cefuroxime Axetil and Linezolid were noted and compared with the original one. Flow rate: 0.8ml/min &1.2 ml/min; Mobile phase composition: 58:42 and 62:38

Acceptance criteria

Number of theoretical plates for the analyte peak should not be less than 2000, Asymmetry value for theanalyte peak should not more than 2.0, and % RSD for the analyte peak should not be more than 2.0 %. Data of Robusness are shown in Table 8-9

Limit of Detection and Limit of Qualification

According to the ICH recommendation, the approach based on the standard deviation (SD) of the response and slop was use of the determining the LOD & LOQ value.

LOD &LOQ values:

$$LOD = 3.3\sigma/S$$

$$LOQ = 10\sigma/S$$

Where σ = standard deviation of response; S = slop of calibration curve; Data of LOD &LOQ are shown in Table 10-11.

Table 1. System suitability test Linezolid for Cefuroxime Axetil.

Parameters	Data observed	
	Linezolid	Cefuroxime Axetil
Theoretical plates per column	6714	6376
Symmetry factor/Tailing factor	1.375	1.439
Resolution	9.825	

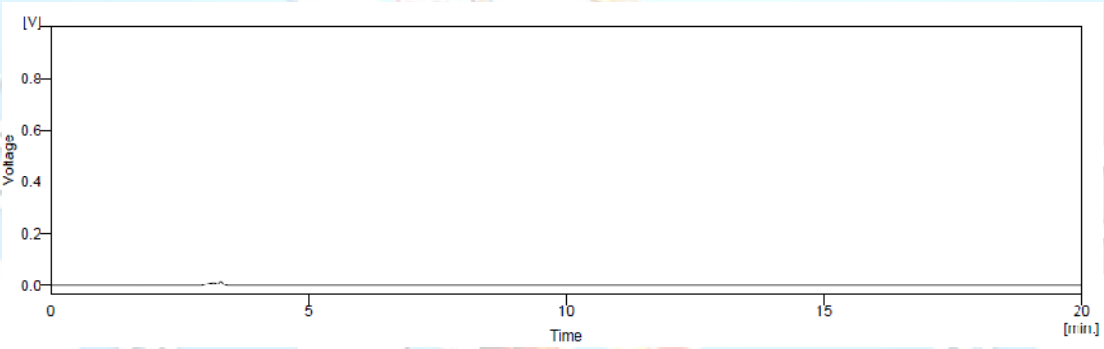


Fig. 1. Chromatogram of Blank

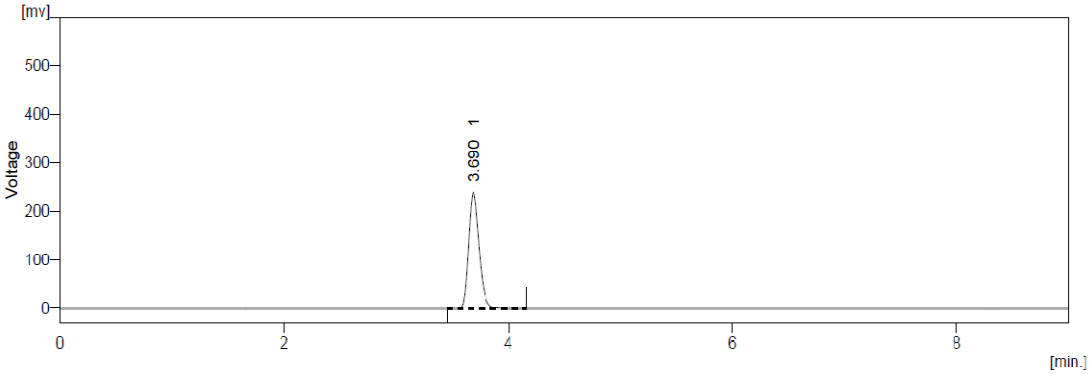


Fig. 2. Chromatogram of Cefuroxime Axetil std

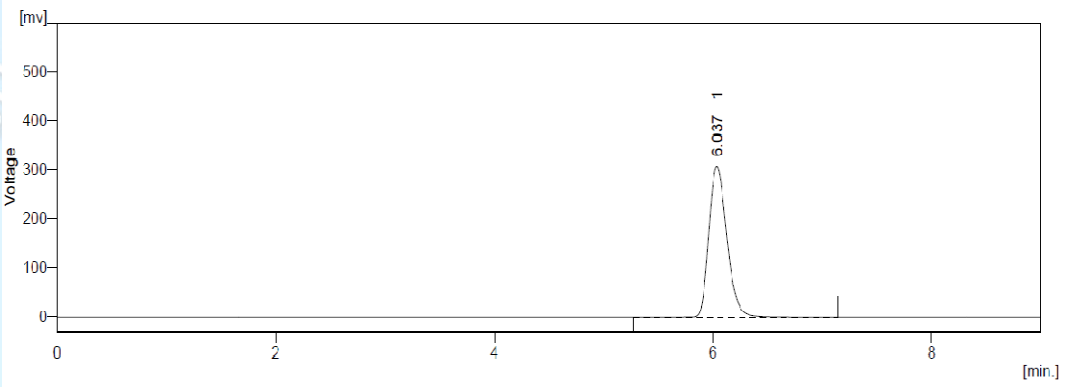


Fig.3. Chromatogram of std Linezolid

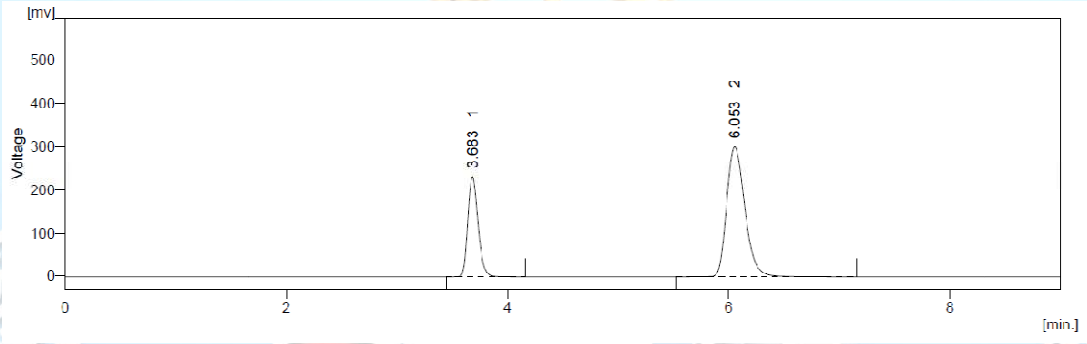


Fig. 4. Chromatogram of Linezolid and Cefuroxime Axetil STD

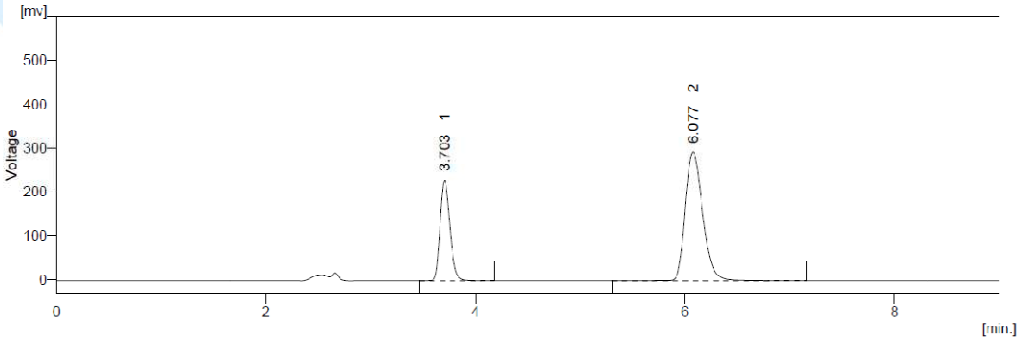


Fig. 5. Chromatogram of Linezolid and Cefuroxime Axetil sample

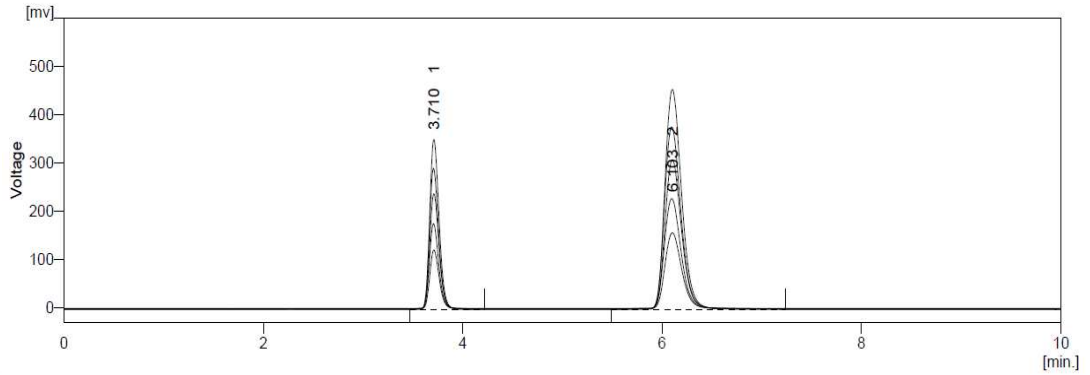


Fig.6. Overlain chromatogram of different concentrations of binary mixtures of Cefuroxime Axetil and Linezolid

Table 2. Linearity Data

Sr. No.	Linezolid		Cefuroxime Axetil	
	Concentration (µg/ml)	Area	Concentration (µg/ml)	Area
1	6	1715.814	5	788.914
2	9	2641.259	7.5	1147.108
3	12	3586.424	10	1557.216
4	15	4378.060	12.5	1900.763
5	18	5194.468	15	2297.691

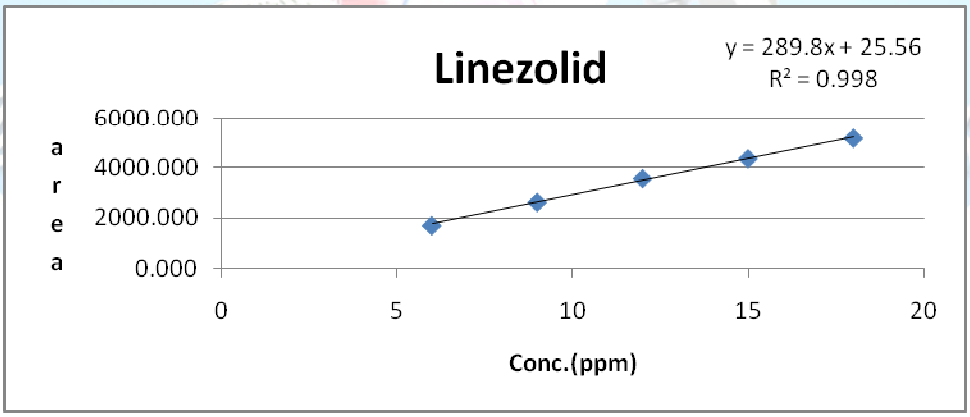


Fig.7. Calibration Curve of Linezolid (6-18µg/ml)

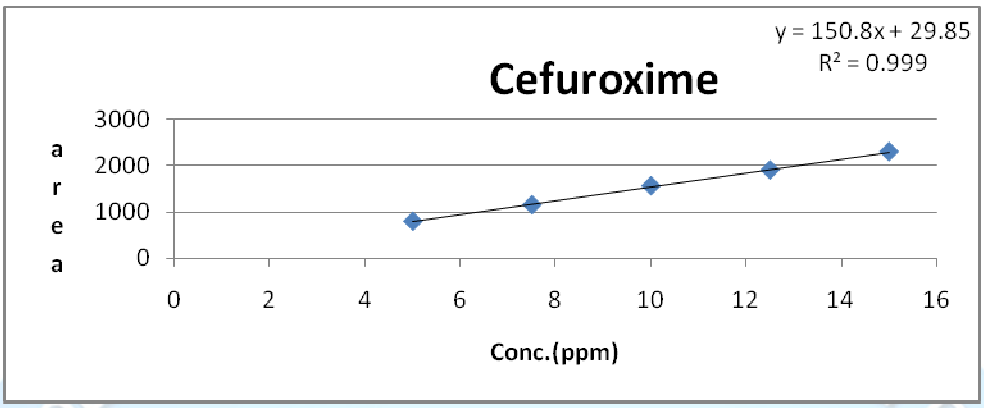


Fig.8. Calibration Curve of Cefuroxime Axetil (5-15 µg/ml)

Table 3. Repeatability Data for Cefuroxime Axetil & Linezolid

Sr No.	Conc.(µg/ml)	Area of Cefuroxime Axetil	Mean ± SD (n=6) of Cefuroxime Axetil	%RSD of Cefuroxime Axetil	Area of Linezolid	Mean ± SD (n=6) of Linezolid	%RSD of Linezolid
1.	10	1514.329	1513.595±3.135	0.207	3491.047	3476.51±27.688	0.796
		1508.290			3477.098		
		1512.866			3421.438		
		1517.429			3494.591		
		1512.885			3484.053		
		1515.771			3490.821		

Table 4. Intraday precision for estimation of Cefuroxime Axetil and Linezolid.

	Cefuroxime Axetil			**Linezolid**		
SR. NO.	**Conc. (µg/ml)**	**Area Mean ± SD (n=3)**	**%RSD**	**Conc. (µg/ml)**	**Area Mean ± SD (n=3)**	**%RSD**
1	5	756.305±4.938	0.653	6	1747.377±5.434	0.311
2	10	1513.430±8.048	0.532	12	3481.259±10.659	0.306
3	15	2260.461±22.580	0.999	18	5223.842±30.832	0.590

Table 5.Interday precision for estimation of Cefuroxime Axetil and Linezolid

	Cefuroxime Axetil			Linezolid		
SR. NO.	Conc. (µg/ml)	Area Mean ± SD(n=3)	%RSD	Conc. (µg/ml)	Area Mean ± SD (n=3)	%RSD
1	5	766.738±1.178	0.154	6	1761.403±6.804	0.386
2	10	1517.764±3.810	0.251	12	3492.041±11.002	0.315
3	15	2283.195±15.149	0.663	18	5250.840± 24.925	0.475

Table 6. Recovery Data for Cefuroxime Axetil

SR. NO.	Conc. Level (%)	Sample Amount	Amount Add-ed	Amount recovered (µg/ml)	% Recovery	% Mean Recovery ± SD
1	80 %	5	4	4.05	101.21	100.27 ± 1.50
2		5	4	3.94	98.54	
3		5	4	4.04	101.06	
4	100 %	5	5	5.08	101.62	100.95 ± 0.65
5		5	5	5.02	100.32	
6		5	5	5.05	100.92	
7	120 %	5	6	6.10	101.74	100.29 ± 1.25
8		5	6	5.98	99.63	
9		5	6	5.97	99.50	

Table 7. Recovery Data for Linezolid.

SR. NO.	Conc. Level (%)	Sample amount (µg/ml)	Amount Add-ed (µg/ml)	Amount recovered (µg/ml)	% Recovery	% Mean Recovery ± SD
1	80 %	6	4.8	4.83	100.64	99.99± 0.70
2		6	4.8	4.80	100.06	
3		6	4.8	4.76	99.26	
4	100 %	6	6	6.07	101.19	101.46 ± 0.32
5		6	6	6.08	101.39	
6		6	6	6.11	101.81	
7	120 %	6	7.2	7.17	99.63	100.68 ± 0.95
8		6	7.2	7.31	101.49	
9		6	7.2	7.27	100.90	

Table 8. Robustness Data for Cefuroxime Axetil

SR. NO.	Area at Flow rate (- 0.2 ml/min)	Area at Flow rate (+ 0.2 ml/min)	Area at pH (-0.2)	Area at pH (+0.2)	Area at Mobile phase(-2)	Area at Mobile phase(+2)
1	1670.85	1358.85	1537.07	1482.66	1580.31	1424.21
2	1665.87	1348.05	1521.75	1475.28	1588.26	1431.40
3	1669.25	1356.16	1524.82	1482.72	1596.28	1434.29
%RSD	0.15	0.41	0.53	0.29	0.50	0.36

Table 9. Robustness Data for Linezolid.

SR. NO.	Area at Flow rate (- 0.2 ml/min)	Area at Flow rate (+ 0.2 ml/min)	Area at pH (- 0.2)	Area at pH (+ 0.2)	Area at Mobile phase(-2)	Area at Mobile phase(+2)
1	3852.13	3129.69	3539.73	3414.32	3643.15	3280.23
2	3840.61	3104.69	3504.56	3400.84	3661.53	3296.68
3	3828.30	3123.36	3501.66	3434.52	3680.00	3323.40
%RSD	0.31	0.42	0.60	0.50	0.50	0.66

Table 10. Limit of Detection Data for Cefuroxime Axetil and Linezolid.

Cefuroxime Axetil	Linezolid
LOD = 3.3 x (SD / Slope) = 3.3 x (16.540/150.8) = 0.362 µg/ml	LOD = 3.3 x (SD / Slope) = 3.3 x (62.267/289.8) = 0.709µg/ml

Table 11.Limit of Quantitation Data for Cefuroxime Axetil and Linezolid.

Cefuroxime Axetil	Linezolid
LOQ = 10 x (SD / Slope) = 10 x (16.540/150.8) = 1.097µg/ml	LOQ = 10 x (SD / Slope) = 10 x (62.267/289.8) = 2.149µg/ml

Table 12. Method Validation Study

Parameters	Cefuroxime Axetil	Linezolid
Specificity	Peak purity index near about 1	Peak purity index near about 1
Linearity and range	5-15 µg/ml	6-18 µg/ml
Regression line Equation	y=150x+29.85	y=285x+25.56
Correlation co-efficient	0.999	0.998
Precision (%RSD)		
Repeatability	0.207%	0.796%
Intraday	0.154-0.6635%	0.315-0.475%
Interday	0.532-0.999%	0.306-0.590%
Accuracy(%Recovery)		
80%	99.99±0.70	100.27±1.50
100%	101.46±0.32	100.95±0.65
150%	100.68±0.95	100.29±1.25
Robustness	Within acceptance criteria as per system suitability.	Within acceptance criteria as per system suitability.
Limit of Detection	0.362 µg/ml	0.709 µg/ml
Limit of Quantitation	1.097 µg/ml	2.149 µg/ml
% Assay	98.66± 0.195	97.68± 0.195

Discussion

A RP-HPLC method has been developed for simultaneous estimation of Cefuroxime Axetil and Linezolid in tablet dosage form was rapid, accurate, precise, specific, sensitive & robust.

Linearity of the development method followed beer`s law and was near to. If found to be linear in range of 5-15µg/ml for Cefuroxime Axetil and 6-18 µg/ml for linezolid.

%RSD was found to be less than 2 for precision.

% Recovery were found to be 100.27-100.95% and 99.99-100.68% for Cefuroxime Axetil and linezolid respectively. Hence, this method can be used for analysis of Cefuroxime Axetil and Linezolid in bulk drug and pharmaceutical dosage form in Quality control department of routine analysis.

REFRENCES

1. "Drug profile for Cefuroxime", September 2015, http://www.drugbank.ca/drugs/DB01112
2. "Drug profile for Cefuroxime", September 2015, http://en.wikipedia.org/wiki/Cefuroxime
3. "Drug profile for Linezolid", September 2015, http://www.drugbank.ca/drugs/DB00601
4. Expert Committee, Monograph Development-Antibiotics USP31–NF26 (MDANT05), pp 1698
5. European Pharmacopoeia, 6th Edition; Medicinal and Pharmaceutical Substances, 2009, pp 1462-1464.
6. British Pharmacopoeia 2009, Volume I &II,Monographs; Medicinal and Pharmaceutical Substances, Cefuroxime Axetil, pp 1173-1175.
7. Indian Pharmacopoeia 2010, Government of India, Ministry of Health and Family Welfare, Ghaziabad, Volume No-2,pp 263-264, 1590-1591.
8. Validation of Analytical Procedures: Methodology ICH, Q2 (R1). International Conference on Harmonization, IFPMA, Geneva, 1996.
9. Shinde MV, Pishawikar SA, and More HN, "Spectrophotometeric Determination of Cefuroxime Axetil from bulk and in its tablet dosage form." *Ind. J. Pharm. Sci*. 2008, *70(2),* 249–251.
10. Shelke S, Dongre S, Rathi A, Dhamecha D, Maria S, and Hassan M, "Development and Validation of UV Spectrophotometric Method of Cefuroxime Axetil in Bulk and Pharmaceutical Formulation." *Asian. J. Research Chem.*, 2009, *2(2),* 222-224.
11. Jain P, Patel M and Surana S, "Development and validation of UV Spectrophotometric method for determination of Cefuroxime Axetil in bulk and in Formulation." *Inter. J. Drug Devel. & Rese.*2011, *3(4),* 318-322.
12. Sengar MR, Gandhi SV, Rajmane V, Patil UP and Gandhi BB, "Simultaneous Determination of Cefuroxime Axetil and Potassium Clavulanate in Tablet Dosage Form by Spectrophotometry." *Res. J. Pharm. and Tech*, 2010,*3(1),* 260-262.
13. Ranjane PN, Gandhi SV, Kadukar SS and Ranher SS, "Simultaneous determination of Cefuroxime axetil and Ornidazole in tablet dosage form using reversed-phase high performance liquid chromatography." *Chinese. J. Chroma.* 2008, *26(6),* 763–765.
14. Sengar MR, Gandhi SV, Rajmane V, Patil UP and Gandhi BB, "Reverse phase High performance liquid chromatography for simultaneous determination of Cefuroxime axetil and Potassium clavulanate in tablet dosage form." *Inter. J. Chem. Tech. Res.* 2009, *1(4),* 1105-1108.
15. Ingale PL, Dalvi SD, Jadav DD, Gudi SV, Patil LD, And Kadam YA, "Simultaneous determination of Cefuroxime axetil and Potassium Clavulanate in pharmaceutical dosage form by RP- HPLC." *Inter. J. Pharm and Pharm. Sci*. 2013, *5(4),* 179-181.
16. Maste MM, Mandavkar YD and Bhat AR, "High Performance Thin Layer Chromatographic Estimation of Cefuroxime Axitel in Bulk and Pharmaceutical Formulation." *International J. Pharm Research.*2012, *4(1),* 26-28.
17. Sengar MR, Gandhi SV, Rajmane V and Patil UP, "HPTLC Determination of Cefuroxime Axetil and Ornidazole in Combined Tablet Dosage Form."*J. Chroma. Sci*. 2010, *48(1),* 26-28.
18. The United State Pending Monograph, Correspondence Number C97768, 2013.
19. Naik AD and Pai SP, "Spectrophotometric Method for Estimation of Linezolid in Tablet Formulation." *Asi. J. Biomed. andPharma. Sci.* 2013, *3(21),* 4-6.
20. Saikiran BH, Johny SK, Madhuri PL, "UV Spectroscopic Method for Estimation Of Linezolid In Tablets." *Int. j Pharma. Chem. and Bio Sci.* 2013, *3(3),* 729-731.
21. Gadhiya DT and Bagada HL, "Simultaneous Equation Method for the estimation of cefiximetrihydarte and linezolid in Their Combined Tablet Dosage Form By UV-visibleSpectrophotometry." *Int. Bul. Drug. res.* 2013,*3(5),* 29-38.
22. Sangshetty JN, Rashid BS, Bhojane S and Zaheer Z, "Simultaneous Estimation of Cefixime and Linezolid in bulk and tablet dosage form." *Am. J. Pharma Tech. Res.* 2013, *3(5),* 350-358.
23. Clos A and Kus K, "Determination Of Linezolid In Human Serum By Reversed-Phase High-Performance Liquid ChromatographyWith Ultraviolet And Diode Array Detection." *Actapoloniea. Pharma.* 2013, *70(4),* 631-641.

24. Prasanti KJ and Sundar BS, "A Validated RP-HPLC Method For The Determination Of LinezolidIn Pharmaceutical Dosage Forms." *Int. J. Pharma. and Bio Sic.* 2012, *3(3),* 44-51.
25. Patel SA and Patel JV, "RP-HPLC Method For Simultaneous Estimation Of CefiximeTrihydrate And Linezolid In Tablet Dosage Form." *Int. J. Phram. chem. and Bio. Sci.* 2013, *3(2),* 372-379.
26. Mohpatra S, Annapurna MM, Kumar RV and Anwar M, "Validated Stability Indicating Rphplc Method For The Estimation Of Linezolid In A PharmaceuticalDosage Form." *J. liq. Chr. and Tech.* 2011, *34(18),* 2185-2195.
27. Patel NS, Tandel FB, Patel YD and Thakkar KB, "Development and Validation of Stability indicating HPLC Method for Simultaneous Estimation of Cefixime and Linezolid." *Ind. J. Pharm. Sci.* 2014, *76(6),* 535-540.
28. Patel SA, Patel PU, Patel NJ and Patel MM, "High performance thin layer chromatographic method for estimation of linezolid in tablets." *Ind. J. Pharm. Sci.*, 2007, *69(4),* 571-574.
29. Philips OA, Abdel-Hamid ME and Al-Hassawi LA, "Determination of linezolid in human plasma by LC-MS MS." *Analyst.* 2001, *126(5),* 609-614.
30. Chen L, Borba BD and Rohrer J, "Determination of Morpholine in Linezolidby Ion Chromatography." *Thermo. Sci.* 2013.
31. Prajapati BN and Mashru RC, "Quantification Of Linezolid And Cefuroxime Axetil By Chemometrics Assisted And RP-HPLC Methods Development And Validation." *Int. J. pharm. Sci. and res.* 2016, *7(7),* 3028-3038.
32. Kshirsagar RS, Menjogea A and SenH.Rapidly disintegrating sustained release cefuroxime axetil composition. European Patents EP1330250, 2003.
33. Raman JV, Rathod D, Vohra I, Chavan M and PonnaiahR.Process for the preparation of Linezolid. European Patents EP2516408 A1, 2012.
34. Rao DM, Reddy PK.Process for the preparation of linezolid and related compounds. The United State US7741480 B2, 2010.
35. Yan Z, Deng B, Huang Y, Zeng H and Li J.Cefuroximeaxetil granule and preparation method of same.WO2013097305, 2003.
36. Aggrarwal KV, Goel S and Mishra U.An optimized bilayered tablet dosage form with high rate of bioavailability of two active antibiotics cefuroxime and clavulanic acid.WO2013001541, 2013.