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Newer RP-HPLC method development and validation of cefixime and linezolide in bulk drugs and combined dosage form

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Abstract

Newer RP-HPLC method was developed for simultaneous determination of cefixime (CEFI) and linezolide (LINZ) in bulk drugs and combined dosage form. Mobile phase consisting of mixture of methanol and water (pH 3.2 adjusted with 1% O-phosphoric acid) in the ratio 40: 60 at flow rate of 1.0 ml/min using C18 Grace (250mmX 4.6mm) column at 252 nm. The retention time of CEFI and LINZ was found to be 4.81 min and 7.16 min, respectively. The linearity range for CEFI with LINZ observed was 1-5 µg/ml and 3-15 µg/ml, respectively. Method was validated as per ICH guidelines. Validation parameters studied were linearity and range, recovery study, precision, LOD, LOQ and robustness. Statistical data obtained was found to satisfactorily.

Keywords: RP-HPLC, Cefixime , Linezolide, Validation

Introduction

Cefixime (CEFI) is an oral third generation cephalosporin class of antibiotic. Chemically it is (6R,7R)-7-[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-[carboxymethoxy)imino]acetamido]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (**Fig. 1**).[1] It is used in the treatment of susceptible infections including gonorrhea, otitis media, pharyngitis, lower respiratory-tract infections such as bronchitis, and urinary-tract infections.[2-3] It is official in Indian Pharmacopoeia.[4]

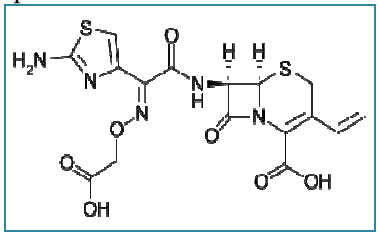

Fig. 1 Chemical structure of cefixime

Linezolide (LINZ) is first of the oxazolidinone class of antibiotic drug.[5] Chemically it is N-{[(5S)-3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (**Fig. 2**). It is useful as Antibacterial Agents.[6-7] It is official in British Pharmacopoeia.[8]

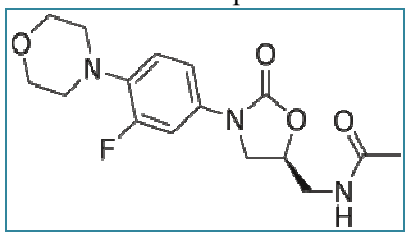

Fig. 2 Chemical structure of linezolide

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There are number of analytical methods for the analysis of pharmaceutical drugs from different formulations.[9-31] Literature review revealed different analytical methods have been reported for estimation of CEFI alone and in combination with other drugs including LINZ. Similarly, in literature there are two UV-spectroscopic method and three RP-HPLC methods available for simultaneous analysis of CEFI and LINZ in tablet dosage form.[32-36] Nonetheless, no one has enclosed the complete validation of developed methods as per ICH guidelines. For that reason, attempt were made to develop new RP-HPLC method for simultaneous determination of CEFI with LINZ in combined dosage form.

Material and Methods

Instrumentation and chemicals

Chromatography was performed with Youngline ACME 9000 (Autochro-3000 software) system coupled with Grace (4.6 mm I.D x 250 mm) C18 column and UV 730 detector. A Rheodyne injector (manual loading) with a 20 µL external loop was used. Chemicals used in method were of HPLC grade. Standard drugs were obtained as gift samples from Alkem Laboratories Ltd and tablet formulations (**LINCEF®**, contents- CEFI - 200 mg & LINZ - 600 mg were purchased from local pharmacy shop.

Selection of wavelength and chromatographic conditions

All the solutions used in work contained concentration in the ratio of 1:3 (CEFI : LINZ) based on amount ration in used marketed formulation. Wavelength for analysis of both the drugs was selected by scanning the individual drug's standard solutions in methanol (i.e. CEFI 5 µg/ml, LINZ 15 µg/ml). From overlain spectra, wavelength 252 nm was selected for further experimental work. Mobile phase for separation of drugs from mixed standard solution (containing CEFI 3 µg/ml & LINZ - 9 µg/ml) was consists of mixture of methanol and water (pH 3.2 adjusted with 1% O-phosphoric acid) (40:60 v/v) in isocratic mode with flow rate 1 ml/min using 20 µl injection volume.

Assessment of system suitability parameters

The system suitability test was performed by collecting data from six replicate injections (20 µl) of mixed standard solution (containing CEFI-3 µg/ml & LINZ-9 µg/ml in methanol) at selected chromatographic conditions. The studied parameters includes retention time, theoretical plates, area under curve and tailing factor.

Assay of tablet formulation

Average weight of 20 tablets was determined and were then crushed to fine powder. Average power equivalent to 300 mg of LINZ (also contain 100 mg of CEFI) was weighed accurately and was transferred to 100 ml volumetric flask. To this 20 ml of methanol was added and shaken for 30 min and sonicated for 10 min. Final volume was added up to 100 ml with same solvent. The solution was filtered the Whatman filter paper. Above solution was further diluted to get final concentration of solution containing 3 µg/ml of CEFI and 9 µg/ml of LINZ. About 20µl sample solution was injected into the system and concentration of each drug was calculation from respective regression equation prepared for individual drug using area under curve prepared by using mixed standard solutions.

Validation of method

Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice.[37] Studied validation parameters includes accuracy and precision, linearity & range, LOD (limit of detection) & LOQ (limit of quantitation) and robustness.[38-39]

(a) Accuracy & precision

Accuracy. The accuracy of an analytical method is the closeness of test results obtained by that method to the true value. The accuracy of an analytical method should be established across its range.[40] To study the accuracy and precision, recovery study was carried out by addition of standard drugs solutions to preanalysed sample. Recovery study was undertaken at three levels i.e. 80%, 100% and 120%.

Sensitivity is the ability to detect small changes in the concentration of the analyte in the sample. The sensitivity or precision as measured by multiple injections of a homogeneous sample (prepared solution) indicates the performance of the HPLC instrument under the chromatographic conditions and day tested. Precision of a method is the degree of agreement among individual test results when

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the procedure is applied repeatedly to multiple samplings. Precision is measured by injecting a series of standards or analyzing series of samples from multiple samplings from a homogeneous lot.[41]

(b) Linearity & range

Linearity was studied by injecting a series of dilutions of mixed standard stock solution in the concentration range 1-5 µg/ml (CEFI) and 3-15 µg/ml (LINZ) into the HPLC system using 20µl volume. Calibration graph was plotted as concentration versus area under curve.

(c) LOD & LOQ

LOD is lowest amount of analyte in a sample that can be detected but not necessarily quantitated. LOQ is the lowest amount of analyte in a sample that can be quantified with suitable accuracy and precision. The LOD & LOQ were confirmed by diluting known concentrations of drug until the average area under curve were approximately 3 or 10 times the standard deviation of AUC of the blank for five replicate determinations. The signal/noise ratios 3:1 and 10:1 were taken as the LOD and LOQ, respectively .

(d) Robustness

The ruggedness of an analytical method can generally be described as the ability to reproduce an analytical method in different laboratories or in different circumstances without the occurrence of unexpected differences in the obtained results.[42]

Robustness is the evaluation of an analytical method wherein the results obtained are found to be reliable even when performed in a slightly varied condition. It is the ability of a method to remain unaffected when slight variations are applied. Robustness was studied by making changes in the chromatographic conditions, such as slight change in wavelength (± 1 nm), flow rate (±0.1 ml/min), ratio of mobile phase (±1%), days (intra- and inter-day variations), different lots of reagents, column to column variations, variation in pH of mobile phase (±0.1), assay temperature variation (±1°c). Percent contents of drugs were measured in preanalysed tablet formulation.

Results and Discussion

On the basis of literature survey, combination of CEFI and LINZ was selected for RP-HPLC method development for simultaneous estimation of both from tablet dosage form. Solvent methanol was used to prepare standard and sample solutions as it dissolved both the drugs at selected concentration. Wavelength for detection selected was 252 nm because at this wavelength both the drug showed better sensitivity **(Fig. 3)**.

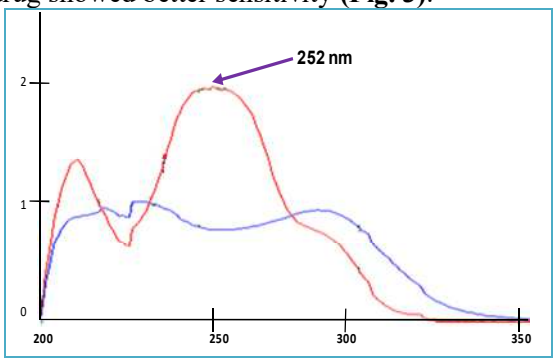

Fig. 3. Overlain UV-vis spectra of CEFI and LINZ in methanol

The linearity range for CEFI with LINZ observed was 1-5 µg/ml and 3-15 µg/ml, respectively. From calibration curve, concentration selected were 3 µg/ml for CEFI and 9 µg/ml for LINZ **(Fig. 4 & 5)**.

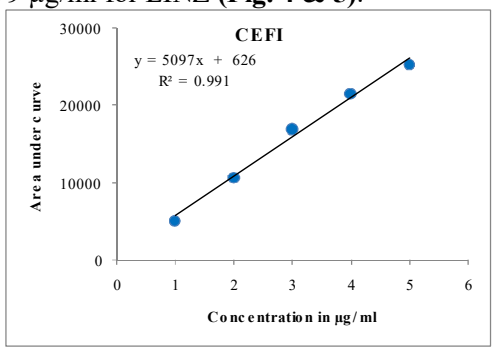

Fig. 4 Calibration curve for CEFI

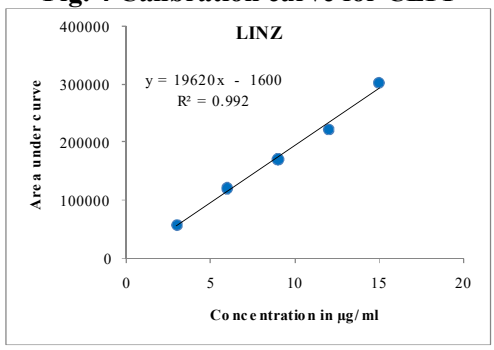

Fig. 5 Calibration curve for LINZ

At selected chromatographic conditions i.e. mobile phase consisting of mixture of acetonitrile and potassium phosphate buffer (pH 7.0 with triethylamine) in the ratio 60: 40 at a flow rate of 1 ml/min with Grace C18(4.6 mm I.D x 250 mm) column at 27°C temperature, retention time

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obtained for CEFI and LINZ was 2.96 and 6.98 min, respectively **(Fig. 6)**. 1% o-phosphoric acid was used to correct the pH so as to get sharp peak with minimum tailing and fronting. Herein, CEFI elutes first because of it is more polar in nature followed by less polar LINZ.[43]

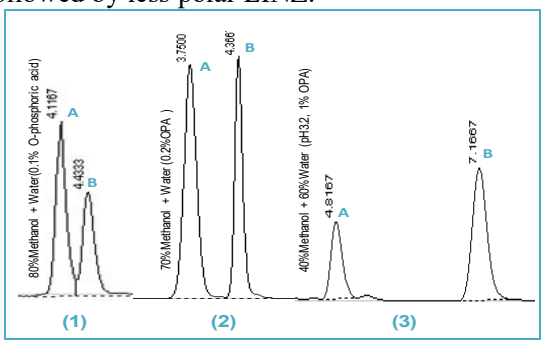

Fig. 6. Chromatograms (1-3) obtained upon using various mobile phases (A. CEFI & B. LINZ). Chromatogram (3) is selected for separation of CEFI (t_R 4.81 min) and LINZ (t_R 7.16 min).

The validation study was performed as per ICH guidelines. Linearity and range was studied by using the series of dilution of each drug solution. Both the drugs shows linear response over the studied range. From this, concentration for CEFI and LINZ were selected. The LOD & LOQ were checked by diluting known concentration of standard drug until the mean responses were approximately 3 or 10 times the standard deviation of the responses of the blank for five replicate measurements. The signal/noise ratios 3:1 and 10:1 were considered as the LOD and LOQ, respectively. LOD and LOQ values obtained are given in Table 1. Precision of the method was checked by measuring system suitability parameter by replicate injection of mixed standard solution. The results are expressed % RSD.

Recovery study was performed to determine the recovery of pure drugs from sample solution. Recovery study by standard addition method at three levels i.e. 80,100 and 120 %. The percentage recovery for both the drug was closed to 100% w/w for both drugs. The percent contents of drugs were measured in preanalysed tablet formulation (Table 1). Precision was determined by studying system suitability parameters by injecting standard solution (Table 1).

Robustness studies also are used to establish system suitability parameters to make sure the validity of the entire system (including both the instrument and the method) is maintained throughout implementation and use. The capacity of developed method was checked by performed robustness study. The conditions changed deliberately were change in wavelength (± 1 nm), flow rate (±0.1 ml/min), ratio of mobile phase (±1%), days (intra- and inter-day variations), different lots of reagents, column to column variations, variation in pH of mobile phase (±0.1), assay temperature variation (±1°c) and retention time or percent contents in formulation were estimated. The result showed develop method remain unaffected. Results of robustness study is represented in **Table 1**.

Conclusion

Novel RP-HPLC method for simultaneous analysis of CEFI with LINZ from combined dosage form is simple, accurate and precise. It does not get affected upon smaller variation in experimental condition. Thus, It be used for routine quality control analysis of bulk drugs and marketed tablet dosage forms.

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Table 1: Results of the validation of method*

Parameter	Level / Term	Results					
		CEFI			LINZ		
		Observation	SD	%RSD	Observation	SD	%RSD
Label claim	-	200 mg	-	-	600 mg	-	-
Assay of tablet	-	100.33	4.41	1.01	99.97	3.32	0.13
% Recovery ♣	80% level	107.08	0.12	0.428	100.41	0.43	0.324
	100% level	107.4	0.10	0.89	102.26	0.17	0.55

	120% level	100.14	0.16	1.23	101.56	0.09	0.23
Linearity & range	Range (µg/ml)	1-5	-	-	3-15	-	-
	Slope	5097	-	-	19620	-	-
	R^2	0.991	-	-	0.992	-	-
	LOD	0.31	-	-	0.93	-	-
	LOQ	0.005	-	-	0.015	-	-
System suitability parameters	Ret. time (min)	4.81	2.32	1.20	7.16	1.20	1.25
	Theor. plates	3445	2.47	2.58	3465.8	2.17	2.15
	Area under curve	16053	2.22	2.33	171380	2.33	2.39
	Tailing	1.18	1.58	1.65	1.16	1.84	2.18
Robustnes							
1) Wavelength ♣	251 nm	99.77	1.65	1.35	100.32	1.41	1.22
	252 nm	100.37	1.73	1.89	100.35	1.88	0.47
	253 nm	100.63	1.67	1.82	98.92	1.47	1.26
2) Flow rate ψ	0.9 ml/min	5.88	2.43	0.83	8.93	1.27	0.07
	1 ml/min	4.81	1.93	0.83	7.16	1.38	0.07
	1.1 ml/min	3.16	1.77	0.81	6.93	1.11	0.07
3) Mobile phase (a: b) **,ψ	62:38	3.58	1.12	0.92	5.45	1.33	1.12
	60:40	3.32	1.65	0.82	5.08	1.44	0.9
	58:42	3.35	1.74	0.76	5.27	1.71	0.77
4) Days ψ	Intra-day	4.80	1.16	0.77	7.14	1.41	0.52
	Inter-day	4.81	2.17	0.99	7.16	1.65	0.98
5) Diff. lots of reagents ψ	Rankem	4.81	2.11	0.83	7.15	1.38	1.02
	Alfa chemika	4.81	2.37	0.99	7.16	2.25	0.11
	Pure chemicals Co.	4.81	1.93	0.62	7.15	2.18	0.97
6) Diff. Columns ψ	Grace (4.6 mm I.D x 250 mm)	4.80	2.33	1.93	7.15	1.42	1.11
	Nucleosil (4.6 mm I.D x 250 mm)	4.81	2.37	1.02	7.16	2.07	0.45
	Hypersil BDS (4.6 mm I.D x 250 mm)	4.81	1.88	0.68	7.15	2.33	0.91
7) pH of mobile phase ψ	pH 3.1	4.81	2.43	1.93	7.17	1.42	1.13
	pH 3.2	4.81	2.31	1.02	7.16	2.11	0.77
	pH 3.3	4.83	1.78	0.68	7.17	2.33	1.93
8) Diff. assay temperature ♣	26°c	100.20	1.87	0.35	99.62	1.51	0.98
	27°c	101.33	1.93	0.87	100.25	1.98	0.48
	28°c	99.65	1.77	0.81	98.99	1.44	1.25

* Mean of six results; ** a- methanol, b- water; ♣ Amount is expressed in percentage, w/w; ψ Results in retention time in min.

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