

Analytical Method Development and Validation on Liquid Chromatography for Determination of the Drug Cefdinir by Using Tinidazole as an Internal Standard in Bulk and Pharmaceutical Dosage Forms

Gadapa Nirupa^{1*} and Upendra M. Tripathi²

¹Department of Chemistry, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad, A.P 500085, India.

²R and D Department Startech Labs Pvt Ltd, 2nd Floor, S M R Chambers, H. No 1-58/7 Madinaguda, Hyderabad, A.P, 500050, India.

Authors' contributions

The work was carried out in collaboration between both the authors. The author GN has designed the study, managed the literature searches, wrote the protocol, executed the analysis and wrote the manuscript under the guidance of the author UMT. Both the authors read and approved the final manuscript.

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ABSTRACT

The present work involves a rapid and reproducible HPLC method which was developed and validated for the estimation of the drug cefdinir in the bulk drug and pharmaceutical dosage forms. Tinidazole was used as an internal standard. In this method, the estimation was done by using C18 column (100 mm x 4.6 mm, 5 μ m); mobile phase consisting of buffer and Methanol (80:20). Buffer was prepared by dissolving 0.025M of Potassium dihydrogen orthophosphate in 1000 ml of water. The pH was adjusted to 2.5 with Orthophosphoric acid; the flow rate of 1.8 mL/min and ultraviolet

*Corresponding author: E-mail: niroopa.ramesh@yahoo.co.in;

detection at 290 nm. The retention time of Cefdinir was found to be 2.9 min. The method was partly validated with respect to Precision, Linearity, Accuracy, Ruggedness and Robustness as per ICH guidelines. The validated method was successfully applied to the commercially available pharmaceutical dosage forms.

Keywords: Cefdinir; tinidazole; HPLC; LC; method development and validation.

1. INTRODUCTION

We are contributing to the field of basic analysis since quite a few years. We have developed analytical methods for the determination of various drugs [1-4]. The results were quite interesting and have encouraged us to continue with the development of methods for other drugs also. In the present work sincere efforts were made to develop a rapid and user-friendly method for the quantification of the drug Cefdinir and we were very much successful in our attempt. This time we have used Tinidazole as an internal standard, which will help the analyst in providing error free analytical results.

Cefdinir is a semi-synthetic oral antibiotic belonging to the cephalosporin family of antibiotics. Cefdinir prevents the bacteria from forming the walls that surround them. The bacteria cannot survive without a cell wall because, these walls are necessary as they protect the bacteria from their environment and they also keep the contents of the bacterial cell together. Cefdinir is active against a very wide spectrum of bacteria, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* (the cause of strep throat), *Hemophilus influenza*, *Moraxella catarrhalis*, *E. coli*, *Klebsiella*, and *Proteus mirabilis* and it is not active against *Pseudomonas*. Cefdinir was approved by FDA in December 1997. Therapeutic uses of cefdinir include otitis media, soft tissue infections, and

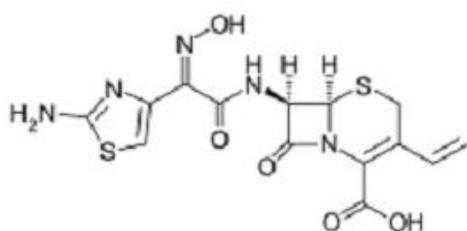
respiratory tract infections, including sinusitis, strep throat, community-acquired pneumonia, *E. coli*, staph infections, *streptococcus* infections, middle ear infections, tonsillitis and acute exacerbations of bronchitis [5,6]. The IUPAC name of Cefdinir is 8-[2-(2-amino-1,3-thiazol-4-yl)-1-hydroxy-2-nitroso- ethenyl] amino-4-ethenyl-7-oxo-2-thia-6- azabicyclo [4.2.0]oct-4-ene-5-carboxylic acid and the structure of the same is represented in Fig. 1.

For the estimation of the drug Cefdinir, several methods are available in the literature [7-12]. But our aim was to develop a faster method for eluting Cefdinir at about 3 minutes, which is a highly challenging task. Cefdinir is a highly sensitive molecule and great efforts were made to develop the method. The present method is a rapid and user- friendly method for the estimation of Cefdinir in the presence of an internal standard, Tinidazole.

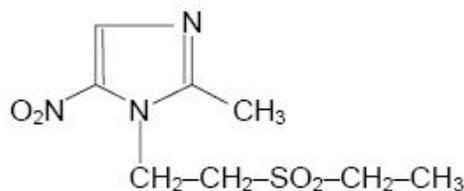
2. MATERIALS AND METHODS

2.1 Materials, Reagents and Chemicals

Startech Labs provided the standards of Cefdinir and Tinidazole. Tablets (dosage forms) used for the experiment, Cefdiel were manufactured by Ranbaxy laboratories and Adcef DT was manufactured by Torrent pharmaceuticals. HPLC grade Methanol, Potassium dihydrogen Orthophosphate and Orthophosphoric acid were obtained from Merck.



Cefdinir



Tinidazole

Fig. 1. Chemical structures of Cefdinir and Tinidazole

2.2 Equipments

UV Visible spectrophotometer used was Shimadzu, model UV-2450. The HPLC instrument used was Shimadzu make, model LC 2010 CHT. For data acquisition Class VP Software was used.

2.3 Preparation of Standard Solution

Stock solution of Cefdinir was first prepared. 25 mg of Cefdinir was taken in a 25 mL volumetric flask and the solution was made up to the mark with mobile phase. Standard solution of 100% (0.1 mg/mL) of Cefdinir was prepared by taking 1 mL of the prepared Cefdinir stock solution in 10 mL volumetric flask and the solution was made up to the mark with mobile phase. Stock solution of Tinidazole was also prepared. 25 mg of Tinidazole was taken in a 25 mL volumetric flask and the solution was made up to the mark with mobile phase. Standard solution of 100% (0.1 mg/mL) of Tinidazole was prepared by taking 1 mL of the prepared Tinidazole stock solution in 10 mL volumetric flask and then the solution was made up to the mark with mobile phase.

2.4 Preparation of Linearity Solutions

150%, 125%, 100%, 75%, 50% & 25% solutions were prepared for Linearity. 15 mL each of Cefdinir and Tinidazole stock solution was taken in 100 mL volumetric flask and diluted up to the mark with mobile phase to get 150% solution. In a 25 mL volumetric flask, 20.83 mL of 150% solution was taken and diluted up to the mark with mobile phase for preparing 125% solution. In a 25 mL volumetric flask, 16.7 mL of 150% solution was taken and diluted up to the mark with mobile phase for preparing 100% solution. In a 25 mL volumetric flask, 12.5 mL of 150% solution was taken and diluted up to the mark with mobile phase for preparing 75% solution. In a 25 mL volumetric flask, 8.3 mL of 150% solution was taken and diluted up to the mark with mobile phase for preparing 50% solution. In a 25 mL volumetric flask, 4.2 mL of 150% solution was taken and diluted up to the mark with mobile phase for preparing 25% solution.

2.5 Preparation of Accuracy Solution

Three spiked solutions were prepared to measure the accuracy. For the first solution,

1 mL of stock solution of cefdinir and 1 mL of stock solution of Tinidazole as prepared in section 2.3, was taken in a 25 mL volumetric flask and diluted up to the mark with 50% linearity solution. For the second solution, 1 mL of stock solution of cefdinir and 1 mL of stock solution of Tinidazole as prepared in section 2.3, was taken in a 25 mL volumetric flask and diluted up to the mark with 100% linearity solution. For the third solution, 1 mL of stock solution of cefdinir and 1 mL of stock solution of Tinidazole as prepared in section 2.3, was taken in a 25 mL volumetric flask and diluted up to the mark with 150% linearity solution.

2.6 Preparation of Sample Solution for Batch Analysis

The average weight of ten tablets was calculated and found to be 415.86 mg and 259.58 mg of Cefdiel and Adcef DT respectively. The tablets were crushed to get a homogeneous mixture and equivalent to 10 mg of Cefdinir in 100 mL volumetric flask and diluted up to the mark with mobile phase and 10 mg of Tinidazole was transferred in 100 mL volumetric flask and diluted up to the mark with mobile phase. 14.36 mg and 22.28 mg of the tablets Cefdiel and Adcef DT respectively were dissolved in 100 mL of the mobile phase. The solutions were sonicated for 5 minutes and then cyclomixing was done for 5 minutes so that the drug gets extracted in the solution. The solutions obtained were filtered by using Millipore syringe filter (0.42 μ). The clear solutions obtained were injected in HPLC in duplicate as per the method.

2.7 Method Development

The maxima for the drugs, Cefdinir and Tinidazole were obtained after scanning both the drugs by UV, individually, in a wavelength range of 200-400 nm. The maxima for Cefdinir was found to be 283.4 nm whereas, for Tinidazole maxima found at 315.2 nm. The corresponding UV spectrum graphs of Cefdinir and Tinidazole are as shown in Fig. 2. To optimize the UV maxima, various HPLC experiments were performed at various wavelengths starting from 230 nm to 350 nm. The best response has been observed at 290 nm. The average of the UV maxima was done and keeping in mind the main interest Cefdinir, 290 nm was selected for carrying out the experimental work. The respective chromatogram is shown in Fig. 2.

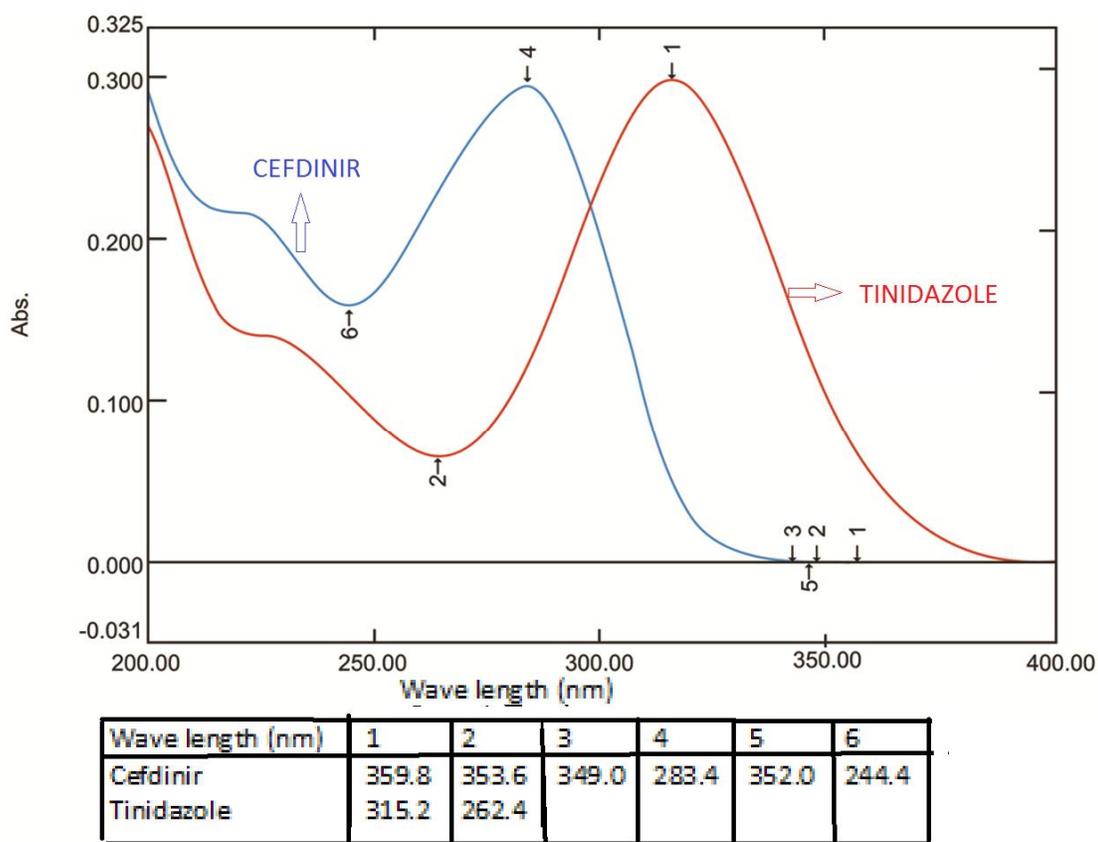


Fig. 2. UV spectrum of Cefdinir and Tinidazole

While optimizing the mobile phase composition, experiments were done with different mobile phase compositions with an intention to develop a method comprising of mobile phase which is user-friendly and environmental-friendly. After many trials Potassium dihydrogen orthophosphate and Methanol mixture was selected as the mobile phase to be used for the experiment. Different compositions of this mixture were tried. Initially 90:10 ratio of Potassium dihydrogen orthophosphate and Methanol mixture was selected and analysis was carried out, but very high retention time of Cefdinir, 17 minutes was recorded. Then 82:18 ratio of Potassium dihydrogen orthophosphate and Methanol mixture was used for the experimental work, but no separation of cefdinir and Tinidazole peaks were obtained. Then 85:15 ratio of Potassium dihydrogen orthophosphate and Methanol mixture was used for the experimental work. The Retention time of Cefdinir was found to be 4.795 min. In order to achieve our aim to get the lowest possible Retention time mobile phase composition 80:20 ratio of Potassium dihydrogen orthophosphate

and Methanol mixture was used for the experimental work. The Retention time of Cefdinir was found to be at about 3 min with a very good resolution of 12.754. The respective chromatograms are shown in Fig. 3. Based on the above experiments, mobile phase composition of 80:20 ratio of Potassium dihydrogen orthophosphate and Methanol mixture was selected for the experimental work.

While optimizing the mobile phase pH, different pH values of mobile phase, 4.5, 3.5 and 2.5 were used. In case of pH values, 3.5 and 4.5 the Retention time of cefdinir was below 2 min but the resolution was not satisfactory. With pH 2.5 the Retention time was 2.6 min within a very good resolution of 12. Hence pH 2.5 of mobile phase was selected for the experimental work. The respective chromatograms are shown in Fig. 4.

While optimizing the flow rate, initially flow rate of 1.2 mL/min was used and the retention time of Cefdinir was 4.4 min. With an intention to reduce the Retention time of Cefdinir, the flow rate was

increased to 1.5 mL/min and the retention time of Cefdinir was recorded to be 3.5 min. To still decrease the retention time of Cefdinir, the flow rate was increased to 1.8 mL/min and it resulted low retention time of Cefdinir at 2.9 min with a good resolution of 12.754. The respective

chromatograms are shown in Fig. 5. Hence the flow rate of 1.8 mL/min was selected for the experimental work. The ultimate method developed is summarized in the section 2.8 below.

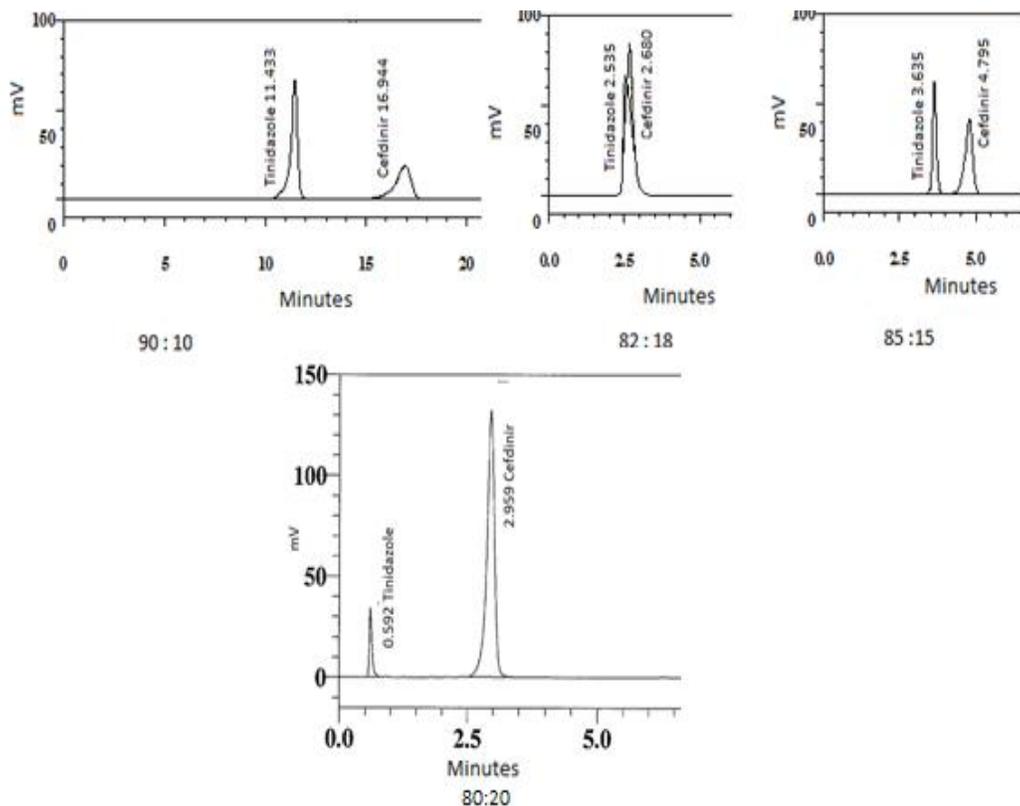


Fig. 3. Different mobile phase composition chromatograms

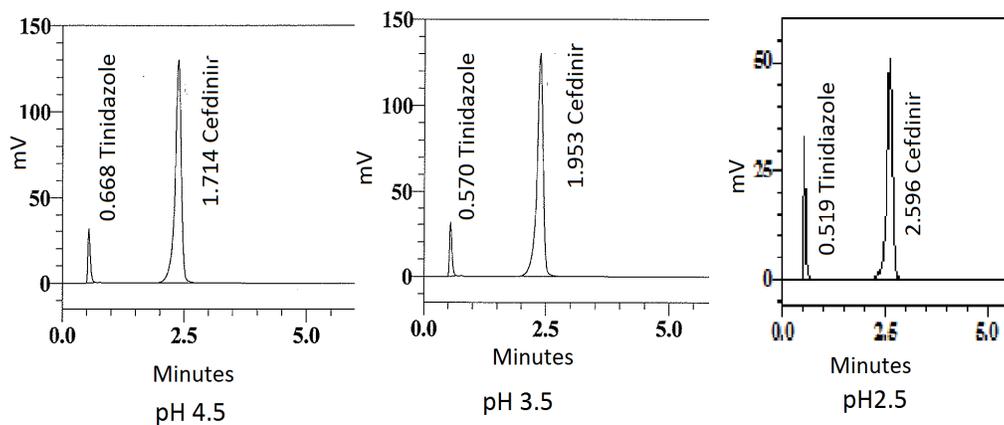


Fig. 4. Different pH chromatograms

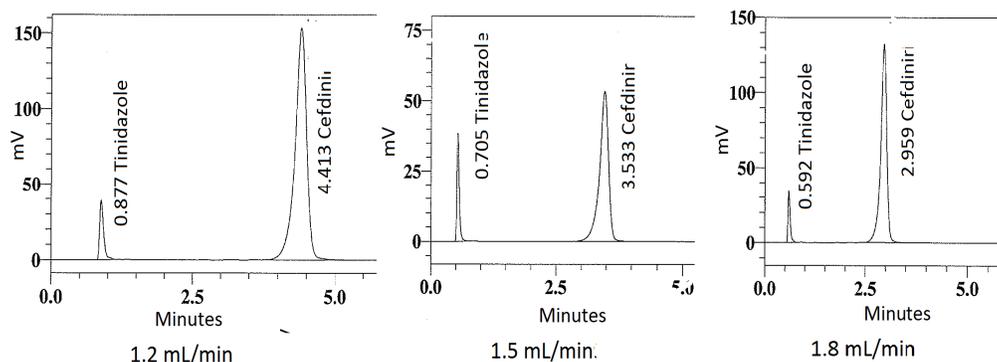


Fig. 5. Different flow rate chromatograms

2.8 Chromatographic Conditions

After systematic trials, we have been able to develop an isocratic method which can be adopted very easily and the details of the chromatographic conditions are as below:

- Column: C18, dimension 100 mm L x 4.6mm D, 5 μ m.
- Detection: 290 nm
- Flow rate: 1.8 mL/min
- Injection volume: 10 μ L
- Temperature: (~ 27°C)
- Run time: 10 min
- Mobile phase: Buffer and Methanol (80:20).
- Buffer was prepared by dissolving 0.025M of Potassium dihydrogen orthophosphate in 1000 ml of water. The pH was adjusted to 2.5 with Orthophosphoric acid.

2.9 Analytical Method Validation

2.9.1 Specificity of the method

This parameter was performed to know the Retention Time (RT) of Cefdinir in the presence of an internal standard Tinidazole, in standard and in the sample.

2.9.2 System Precision

System precision or system suitability test is used to demonstrate if the resolution and reproducibility of the chromatographic systems are adequate for the analysis to be done. The tests are based on the fact that the equipment, electronics, samples to be analyzed constitutes an integral system that can be evaluated as such. The limits for system suitability were set for Theoretical plates, Resolution and Asymmetry.

2.9.3 Linearity

To measure linearity of the method, concentrations of the standard mixture, 25%, 50%, 75%, 100%, 125% and 150% were prepared and injected. A graph was plotted for the concentration of the corresponding drug versus Area. The Correlation coefficient (r) for Cefdinir and internal standard, Tinidazole was calculated.

2.9.4 Accuracy

It is very important that the developed method is accurate, which is evaluated by the recovery of the drugs. The method of standard additions was used for this purpose. Three different solutions were prepared as mentioned above under section 2.5, preparation of Accuracy solution. The accuracy was expressed as the percentage of Cefdinir recovery.

2.9.5 Robustness

To check the robustness of the method, chromatograms were obtained with slight changes in the method. For this purpose, slight changes were made in the flow rate, temperature and mobile phase composition and the analysis was done. The flow rate as per the developed method was 1.8 mL/min. Changes to flow rate of ± 0.2 mL/min (1.6 mL/min and 2 mL/min) was done and the chromatograms were obtained. The temperature as per the developed method was 27°C. Changes to the temperature of $\pm 3^\circ\text{C}$ (24°C and 30°C) was done and the chromatogram were obtained. The mobile phase composition as per the developed method was 80:20. This has been purposely changed to 75:25 and 85:15 and the chromatogram were obtained.

2.9.6 Ruggedness

In order to check ruggedness, analysis was performed by different chemists on different days and the chromatograms were obtained. The result was compared with the previous results and checked for any variations. The percentage RSD for the retention time and area was calculated.

2.9.7 Performance of the method on Commercial Samples

As a final verification of the method, the method was applied to the analysis of drug in commercial tablets. Two market samples, Cefdiel, Batch No.2417457, manufactured by Ranbaxy Laboratories, Adcef DT, Batch No. Y6771001, manufactured by Torrent pharmaceuticals, were selected for the performance test of the method.

3. RESULTS AND DISCUSSION

The present work involves estimation of Cefdinir in bulk and dosage forms by HPLC using Tinidazole as an internal standard. The method was developed and optimized in such a way that the product can be analyzed rapidly by using a simple method, which results in saving the valuable time of the sophisticated instruments and the chemists. This is the reason that currently UFLC (Ultra-Fast Liquid Chromatography) technique [13,14] is gaining a lot of importance due to its high speed of analysis, though most of the Pharmacopeia still has the HPLC methods in their monographs.

This time, we have tried to use Tinidazole as an internal standard. The benefit of using internal standard in the analytical method is that it helps the analyst in attaining the consistency in the end result. The current analytical method is rapid and user friendly. The developed method has been validated as per the ICH guidelines. Findings of Validation parameters are expressed in following lines.

3.1 Specificity of the Method

The retention time of Cefdinir and Tinidazole, which was used as an internal standard was measured individually and it was found to be 2.975 min and 0.592 min respectively. Secondly, the drug Cefdinir was spiked with Tinidazole (internal standard) and the retention time was found to be 2.915 min and 0.592 min respectively for Cefdinir and Tinidazole. In the third case, the market sample of Cefdinir was taken and spiked with internal standard Tinidazole and the retention time was found to be 2.695 min and 0.592 min for Cefdinir and Tinidazole respectively. The analysis of the results indicates that the retention time values of Cefdinir were not changed even in the presence of Tinidazole, which was used as an internal standard. Also, in case of pharmaceutical dosage forms, there is no interference of excipient with the retention time values of Cefdinir. This indicates that this method can be successfully used for the estimation of Cefdinir in presence of an internal standard both in bulk and pharmaceutical dosage forms. The HPLC chromatograms of all the three instances are represented in Figs. 6, 7 & 8.

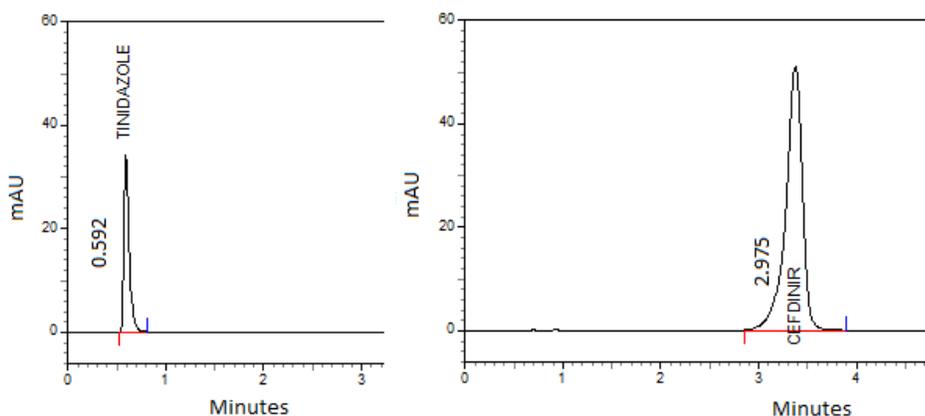


Fig. 6. Chromatograms of Cefdinir and Tinidazole individually

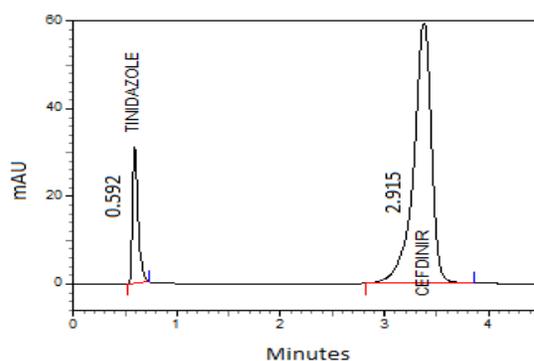


Fig. 7. Chromatogram of Standard Cefdinir solution containing Tinidazole as an internal standard

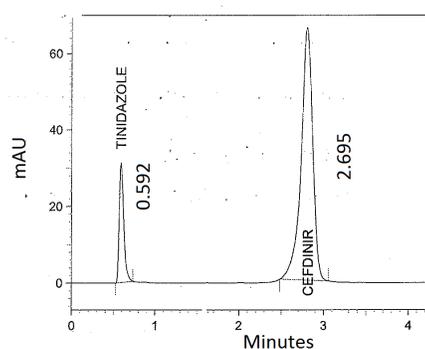


Fig. 8. Chromatogram of market Sample of Cefdinir spiked with Tinidazole as an internal standard

3.2 System Precision

To measure the system precision, five injections of the standard mix were done to get the respective chromatograms. The retention time, areas, resolution, theoretical plates and peak

asymmetry were calculated. Percentage RSD value was calculated. It was found that all the values were well within the acceptable range. The results obtained are given in following Table 1.

3.3 Linearity

Linearity of an analytical method is the ability of the method to elicit test results that are directly proportional to the concentration of the analyte. The concentration of both the analytes were found to be proportional to the area and the response of the detector. The acceptable correlation coefficient (r) is more than 0.99. The correlation coefficient (r) for both the drugs Cefdinir and Tinidazole was calculated and found to be more than 0.99, which is well within the acceptance range. The response was found to be linear over the range of 0.025 mg/mL to 0.15 mg/mL for Cefdinir and Tinidazole. The results are shown in Table 2. and respective linearity graphs are represented in Fig. 9.

3.4 Accuracy

As mentioned in the section 2.5, three spiked solutions were prepared and for all the three spiked solutions, chromatograms were obtained. Recoveries were calculated for all the three spiked solutions. The percentage recovery at 50%, 100% and 150% were found to be 104.61%, 99.02% and 104.77% respectively. The results were found to be within the acceptable range which is between 80-120% as per the ICH guidelines. As the method developed was found accurate, it can be used for the estimation of Cefdinir. The details of the results are shown in Table 3.

Table 1. System precision results

		Average	SD	%RSD
Cefdinir	Retention Time	3.3686	0.004	0.11
	Area	670419	3440.19	0.51
	Theoretical plates	2157.43	15.96	0.74
	Resolution	13.948	0.06	0.43
	Asymmetry	0.798	0.004	0.56
Tinidazole	Retention Time	0.59	0.004	0.76
	Area	120369	51.93	0.04
	Theoretical plates	1480.09	7.024	0.47
	Resolution	0	0	0
	Asymmetry	1.556	0.03	1.74

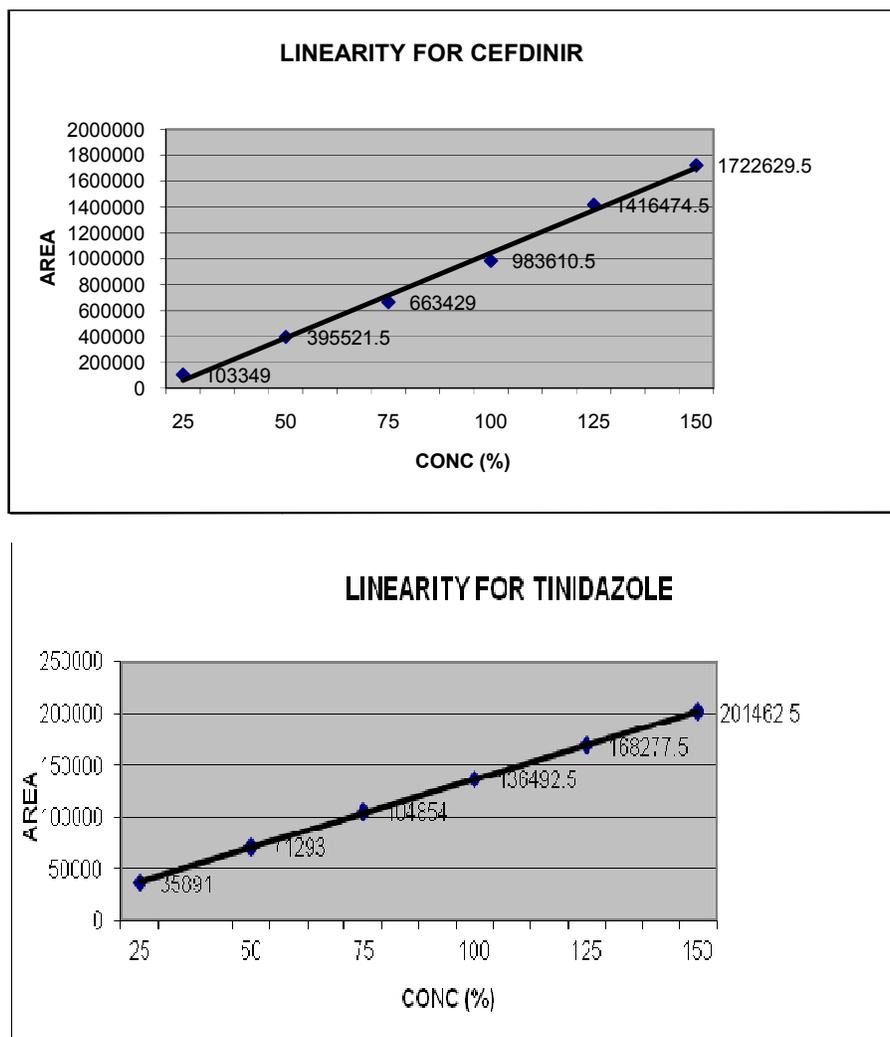


Fig. 9. Graphs showing linearity of Cefdinir and Tinidazole

Table 2. Linearity results

	Linearity Range	Correlation Coefficient
Cefdinir	0.025-0.15 mg/mL	0.9998
Tinidazole	0.025-0.15 mg/mL	0.9971

Table 3. Results for Accuracy of the method

Accuracy at--->	50%	100%	150%
Area (Known Concn + spiked)(a)	2056132	2530138	3522350
Area Cefdinir Known Concn (b)	1674528	1674528	1674528
Area Cefdinir (a-b)	381604	855610	1847822
Cefdinir Area (expected)	364792	864055	1763705
% Recovery (a-b)x100/c	104.61	99.02	104.77

3.5 Robustness

Due to deliberate change in the flow rate, temperature and mobile phase composition excellent performance of the method was observed. This indicates that the method is robust. The results obtained are shown in Table 4.

3.6 Ruggedness

Analysis has been performed on different days and by different analysts. Data have been evaluated and % RSD of Area and Retention time were calculated for various trials and data obtained are tabulated in Table 5. Based on the data it is very much evident that the method is Rugged.

3.7 Performance of the Method on Pharmaceutical Dosage Forms

To check the performance of the method on pharmaceutical dosage forms, two market samples were selected. The first one was cefdiel and as per the label claim, it constituted 300 mg of Cefdinir. The other market sample was Adcef DT and as per the label claim, it constituted 125 mg of Cefdinir. The experimental results show that Cefdiel constituted 309.43 mg of Cefdinir and Adcef DT constituted 124.29 mg of Cefdinir. The performance of the method was 103.14% for Cefdiel and 99.43% for Adcef DT. This shows that the method developed by us can be used for the estimation of cefdinir in any of the pharmaceutical dosage forms. The results are shown in Table 6.

Table 4. Robustness results

		Average retention time(min)		% RSD	
				Retention time	Area
Different flow rates	1. 6mL/min	3.774	Cefdinir	0.04	0.09
		0.66	Tinidazole	0.68	0.05
	2.0 mL/min	3.042	Cefdinir	0.03	0.34
		0.533	Tinidazole	0.08	0.21
Different temperatures	24°C	3.65	Cefdinir	0.15	0.1
		0.598	Tinidazole	0.6	0.9
	30°C	3.042	Cefdinir	0.01	0.34
		0.533	Tinidazole	0.08	0.21
Different mobile phase compositions	75:25	3.047	Cefdinir	0.07	0.99
		0.528	Tinidazole	0.88	0.2
	85:15	3.764	Cefdinir	0.05	0.24
		0.562	Tinidazole	0.29	0.14

Table 5. % RSD on different days and different analysts

		Average retention time (min)	% RSD	
			Retention time	Area
Day 1	Cefdinir	3.363	0.17	0.81
	Tinidazole	0.553	0.87	0.9
Day 2	Cefdinir	3.354	0.51	0.02
	Tinidazole	0.556	1.16	0.4
Analyst 1	Cefdinir	3.368	0.25	0.97
	Tinidazole	0.594	0.77	0.72
Analyst 2	Cefdinir	3.36	0.28	0.08
	Tinidazole	0.587	0.66	1.12

Table 6. Estimation of Cefdinir in commercial samples

	Label claim	Acquired data	% Recovery
Cefdiel	300 mg/cap	309.43 mg/cap	103.14%
Adcef DT	125 mg/tab	124.29 mg/tab	99.43%

4. CONCLUSION

The HPLC method developed in the present work is sensitive, accurate, unique, rapid, precise, user friendly and reproducible for the estimation of Cefdinir using Tinidazole as an internal standard in bulk mix and Pharmaceutical dosage forms. The method was partly validated as per ICH Guidelines. It is concluded that this method can be used by the industries and academic institutions for the estimation of Cefdinir.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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