

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

ABSTRACT

The present work includes development of a rapid and reproducible HPLC method and its validation for the estimation of the drug Cefdinir using Tinidazole as an internal standard in bulk drug and pharmaceutical dosage forms. The estimation was carried out by using C18 column (100mm x 4.6mm, 5µm); mobile phase consisting of buffer at pH 2.5 and Methanol; the flow rate of 1.8 mL/min and ultraviolet detection at 290 nm. The retention time of Cefdinir was found to be 2.9 min. The method was validated with respect to Precision, Linearity, Accuracy, Ruggedness and Robustness as per ICH guideline. 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 in 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 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 the error free analytical results.

Cefdinir is a semi-synthetic oral antibiotic in the cephalosporin family of antibiotics. Cefdinir prevents the bacteria from forming the walls that surround them. These walls are necessary as they protect the bacteria from their environment and they also keep the contents of the bacterial cell together. The bacteria cannot survive without a cell wall. 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.

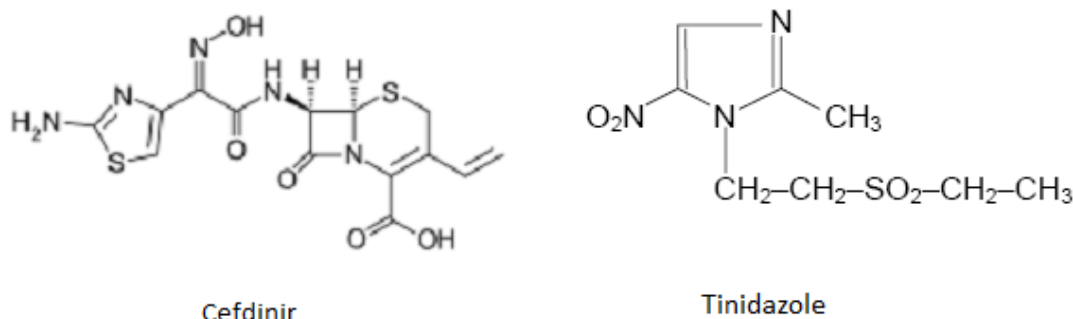


Fig. 1. Chemical structures of Cefdinir and Tinidazole

For the estimation of the drug Cefdinir, several methods are available in the literature [7-12]. But our aim is 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. MATERIAL AND METHODS

2.1. Materials, Reagents and Chemicals:

Cefdinir and Tinidazole Standards were obtained from Startech Labs. Tablets 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.

2.2. Equipments:

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

2.3. Preparation of Standard solution:

Stock solution of Cefdinir was prepared by taking 25 mg of Cefdinir in 25 mL volumetric flask and diluted upto the mark with mobile phase. Standard solution of 0.1 mg/mL of Cefdinir (treat this as 100% for various experimental purpose) was prepared by taking 1 mL of Cefdinir stock solution in 10 mL volumetric flask and diluted up to the mark with mobile phase. Stock solution of Tinidazole was prepared by taking 25 mg of Tinidazole in 25 mL volumetric flask and diluted upto the mark with mobile phase. Standard solution of 0.1 mg/mL of Tinidazole (treat this as 100 % for various experimental purpose) was prepared by taking 1mL of Tinidazole stock solution in 10mL volumetric flask and diluted upto the mark with mobile phase.

2.4. Preparation of Linearity solutions:

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

2.5. Preparation of Accuracy Solution:

25 mg of Cefdinir standard was taken in a 25 mL volumetric flask and diluted up to the mark with mobile phase. Further 1 mL of the above prepared solution and 1 mL Tinidazole standard stock solution was taken in 25 mL volumetric flask and diluted up to the mark with 50%, 100% & 150 % linearity solutions for getting the respective spiked 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 subjected to sonication for 5 minutes and then followed by cyclomixing for 5 minutes to extract the drug in solution. The solutions obtained were filtered by using Millipore syringe filter (0.42μ). The clear solutions obtained were injected in HPLC in duplicate as per the method.

2.7. Method Development

Both the drugs, Cefdinir and Tinidazole were scanned by UV, individually, in a wavelength range of 200-400 nm and maxima for each drug was measured. 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.

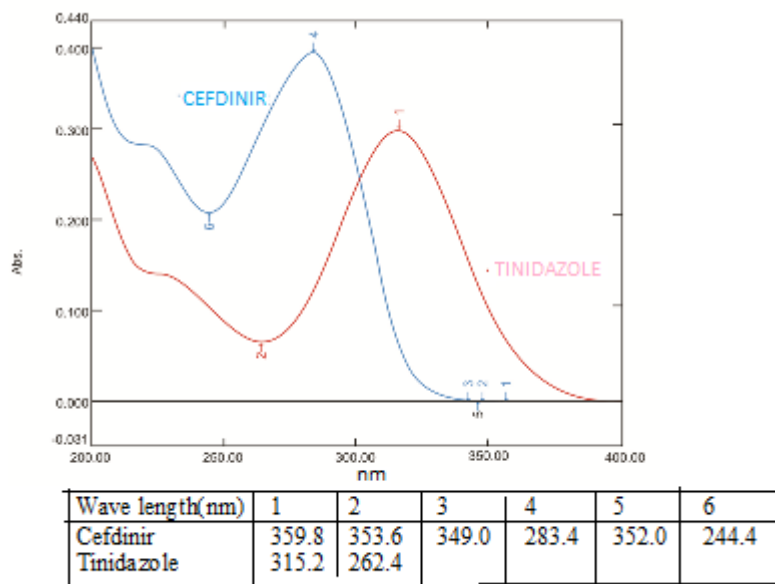


Fig. 2. UV spectrum of Cefdinir and Tinidazole

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 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.

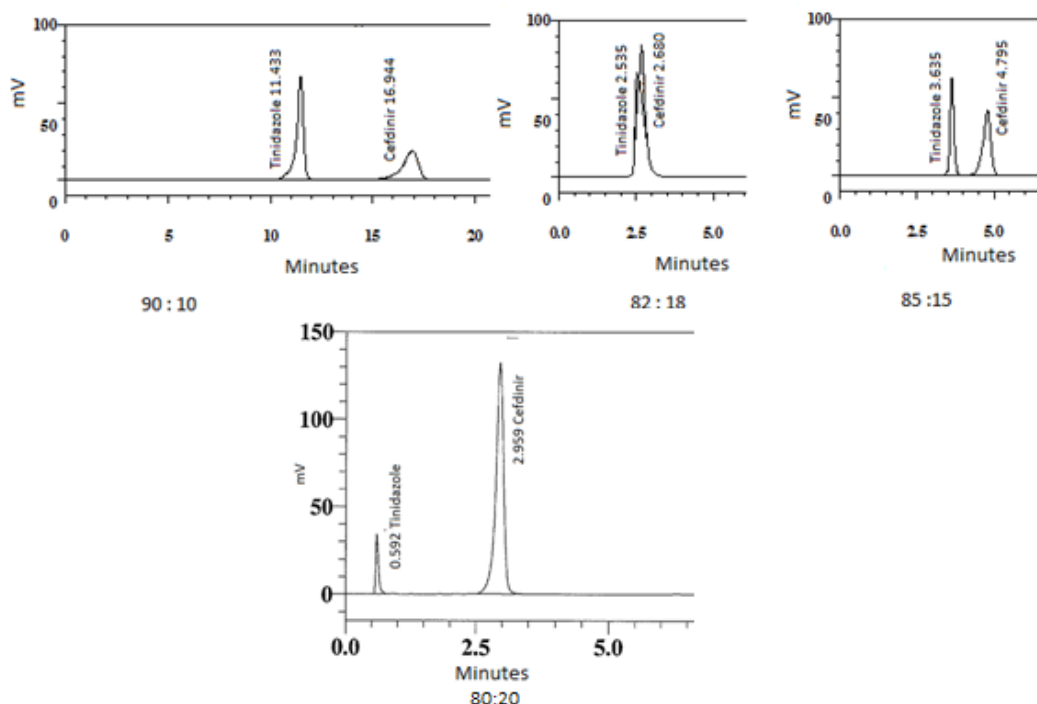


Fig.3. Different mobile phase composition chromatograms

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.

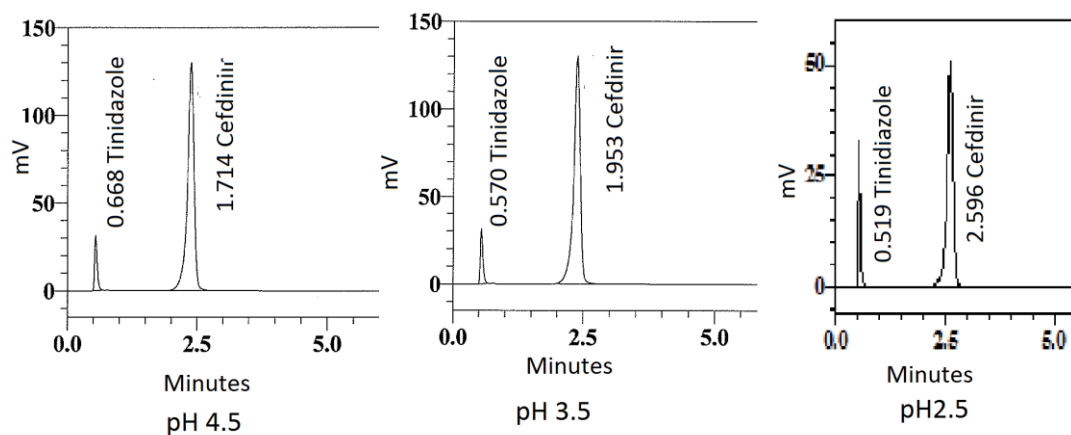
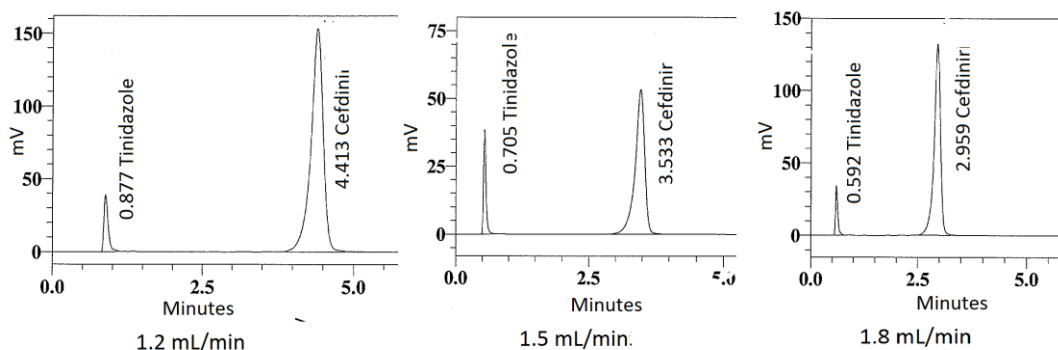


Fig.4. Different pH chromatograms

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

149 12.754. The respective chromatograms are shown in Fig.5. Hence the Flow rate of 1.8
150 mL/min was selected for the experimental work. The ultimate method developed is
151 summarised in the section 2.8 below.



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153 **Fig.5. Different Flow rate chromatograms**
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155 2.8. Chromatographic conditions:

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

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

167 2.9. Analytical Method Validation

168 2.9.1. Specificity of the method:

169 The parameter, specificity of the method was performed to know the Retention Time (RT) of
170 Cefdinir in the presence of an internal standard Tinidazole, in standard and in the sample.
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172 2.9.2. System Precision:

173 System precision or system suitability test is used to demonstrate if the resolution and
174 reproducibility of the chromatographic systems are adequate for the analysis to be done.
175 The tests are based on the fact that the equipment, electronics, samples to be analyzed
176 constitutes an integral system that can be evaluated as such. The limits for system suitability
177 were set for Theoretical plates, Resolution and Asymmetry.
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179 2.9.3. Linearity:

180 To measure linearity of the method, concentrations of the standard mixture, 25%, 50%, 75%,
181 100%, 125% and 150% were prepared and injected. A graph was plotted for the
182 concentration of the corresponding drug versus Area. The Correlation coefficient (r) for
183 Cefdinir and internal standard, Tinidazole was calculated.
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185 2.9.4. Accuracy:

186 It is very important that the developed method is accurate, which is evaluated by the
187 recovery of the drugs. The method of standard additions was made for measuring the
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recovery of the drugs to determine the recovery in sample preparation. To the known standard concentrations (0.04 mg/ml) of the drug, 50%, 100% and 150% of Cefdinir was added. Three different solutions were prepared as mentioned above under sample preparation for Accuracy. 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. Analysis was done by making slight changes in the Flow rate, Temperature and mobile phase composition. The flow rate as per the developed method is 1.8 mL/min. This has been purposely changed to 1.6 mL/min and 2 mL/min and the chromatograms were obtained. The temperature as per the developed method is 27°C. This was changed deliberately to 24°C and 30°C and the chromatogram were obtained. The mobile phase composition as per the developed method is 80:20. This has been purposely changed to 75:25 and 85:15 and the chromatogram were recorded.

2.9.6. Ruggedness:

Analysis was performed on different days and different chemists and the chromatograms were obtained and checked for any variation in the results in order to demonstrate the ruggedness. 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. For this purpose, performance test of the method has been conducted on two market samples, Cefdiel, Batch No.2417457, manufactured by Ranbaxy Laboratories, Adcef DT, Batch No.Y6771001, manufactured by Torrent pharmaceuticals.

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 rapid by using a simple method, which results in saving sophisticated instruments and chemist's valuable time. 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 have 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 times of the drug Cefdinir and the internal standard Tinidazole were measured individually and found to be 2.975 min and 0.592 min, respectively. The retention time of a mix solution of Cefdinir and internal standard Tinidazole was measured and found to be 2.915 min and 0.592 min, respectively. The retention time of Cefdinir and Tinidazole was found to be 2.695 min and 0.592 min, respectively for the sample solution (market sample in the form of Tablet spiked with the internal standard). This shows that there is no specific change in the retention time of the drug individually or in the presence of an internal standard in bulk and dosage forms. This indicates that there is no any interference of the internal standard or the excepiant and hence the method can be used for the determination of Cefdinir in the presence of an internal standard; both in bulk and pharmaceutical dosage forms. Respective HPLC chromatograms are represented in the Fig. 6, 7 and 8.

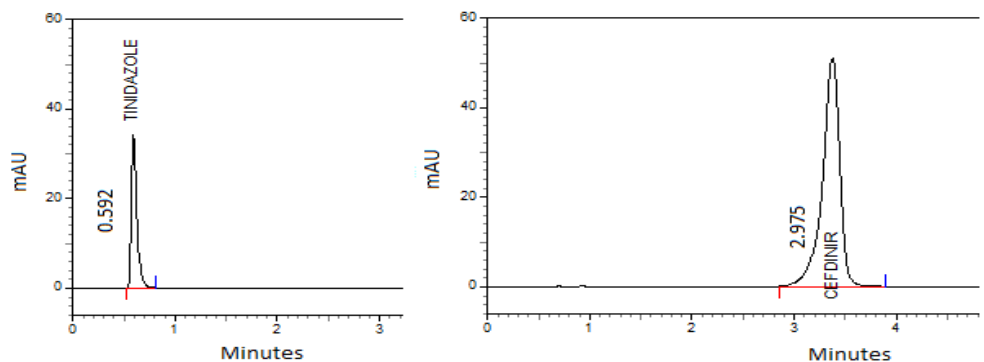


Fig.6. Chromatograms of Cefdinir and Tinidazole individually

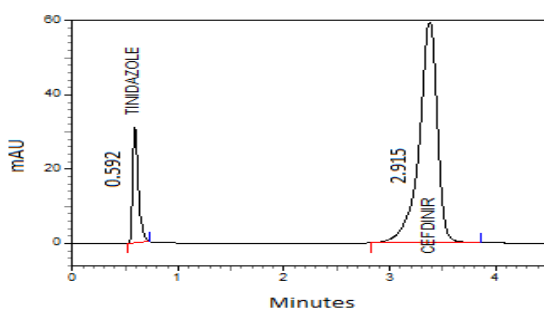


Fig.7. Chromatogram of Standard Cefdinir solution containing Tinidazole as an internal standard

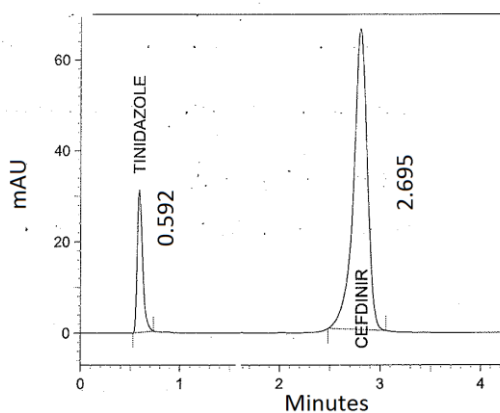


Fig.8. Chromatogram of market Sample of Cefdinir spiked with Tinidazole as an internal standard

3.2. System Precision:

For measuring system precision, five injections of the standard mix were injected and the respective chromatograms were obtained. The Retention time, Areas, Resolution, Theoretical plates and peak Asymmetry were calculated. Percentage RSD value was calculated. All the values have been found to be well within the acceptable range. The results obtained are given in following Table 1.

260 **Table 1. System Precision Results**
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		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

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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 correlation coefficient (r) obtained was calculated and it was found to be more than 0.99 for Cefdinir and Tinidazole, 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.

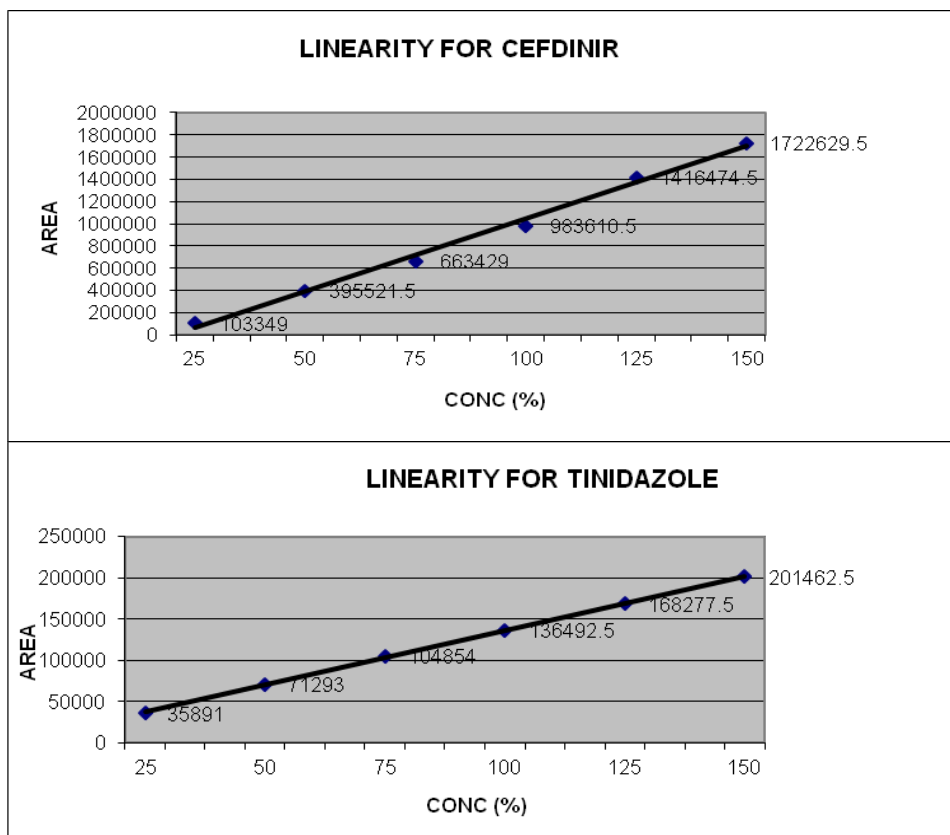


Fig. 9. Graphs Showing Linearity of Cefdinir and Tinidazole

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

3.4. Accuracy:

For measuring the accuracy of the method, 3 spiked solutions have been prepared as mentioned in Materials and method section under the heading Preparation for accuracy solution. Chromatograms were obtained for all the three spiked solutions and recoveries have been calculated. As per the ICH guidelines, the acceptable range of recovery should be between 80-120%. The results obtained were in the range of 99.02 and 104.77, which indicates that the recoveries are well within the acceptance range. Therefore, the method is accurate and it can be used for the estimation of Cefdinir. Details are presented in Table 3.

306 **Table 3. Results for Accuracy of the method**
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Accuracy at---→	50 %	100 %	150 %
Area (Known Concn + spiked)(a)	2056132	2530138	3522350
Area Cefdinir Known Conc (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

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309 **3.5. Robustness:**

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

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314 **Table 4. Robustness results**
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		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
	2.0mL/min	3.042	Cefdinir	0.03	0.34
		0.533	Tinidazole	0.08	0.21
Different Temperatures	24 ⁰ C	3.65	Cefdinir	0.15	0.1
		0.598	Tinidazole	0.6	0.9
	30 ⁰ 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

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318 **3.6. Ruggedness:**

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

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332 **Table 5. % RSD on different days and different Analysts**
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		Average Retention	% RSD	
		Time (min)	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

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3.7. Performance of the Method on Commercial Formulations:

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For evaluating the performance of the method, two market samples have been taken namely Cefdiel, Adcef DT. As per the label claim, Cefdiel capsules contain 300mg of Cefdinir and Adcef DT tablet contain 125 mg of Cefdinir. The quantification of the drug was done in both the formulations and the results have been found to be in the range of 99.8 to 100.3 %. This indicates that the method developed by us can be used for the estimation of Cefdinir in any of the pharmaceutical dosage forms. The results obtained are shown in Table 6.

Table 6. Estimation of Cefdinir in commercial samples

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

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4. CONCLUSION

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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 validated as per ICH Guidelines. Hence, it is conclude that, this method can be used by the industries and academic institutions for the estimation of Cefdinir.

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