Comparative verification of ciprofloxacin HCI by HPLC chromatogram, UV-Vis absorption spectra, and FT-IR spectra was tested using a variety of procedures to finds its efficacy towards antibiotics: A DFT study

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Abstract

Ciprofloxacin is a fluoroquinolone antibiotic that is widely used in anti-infective therapy nowadays because of its broad spectrum of activity and potential therapeutic applications. One of the reasons for its widespread use is the presence of multiresistant pathogens that are solely vulnerable to ciprofloxacin. This drug's potential improved efficacy in the treatment of different community-acquired and nosocomial infections, including as respiratory tract, urinary tract, and skin infections, as well as sexually transmitted diseases, is supported by the existing clinical evidence. Ciprofloxacin's pharmacokinetic profile, when compared to that of other medicines in its class, reveals similar or better bioavailability, higher plasma concentrations, and improved tissue penetration, all of which are reflected in the greater volume of distribution. Different molecular modifications of this medicine have been produced in order to improve its features even further. In this paper, several approaches for the analytical determination of ciprofloxacin and its metabolites in biological fluids have been described that make use of a variety of methodologies. In order to validate the experimental findings connected to the ciprofloxacin medicine, a theoretical inquiry is also carried out.

Keywords: Ciprofloxacin HCI, HPLC, UV, FT-IR, DFT, Verification

Introduction:

During the past 25 years, antimicrobial agents have been introduced at a rate exceeding our ability to integrate them into clinical practice[1]. Since their debut, fluoroqui nolones have become a cornerstone in the treatment of serious bacterial infections. These are synthetic antibacterial drugs structurally linked to nalidixic acid[2]. They display various positive qualities such as great bioavailability, good tissue penetrability, and a comparatively low incidence of unfavorable and toxic effects[3]. These medications are potentially utilized in the treatment of urinary tract infection and prostatitis. They are also employed against bacterial enteric infections, biliary tract infections, sexually transmitted diseases, and prophylaxis in the immune impaired neutropenia host[4]. In

1983, Bayer AG received a patent for ciprofloxacin, which was later licensed by the United States Food and Drug Administration (US FDA) for use in the United States in 1987. Ciprofloxacin is one of the most successful and commonly used compounds in the class. Ciprofloxacin is marketed worldwide under more than 300 different brand names, and since its inception, the value of fluoroquinolones for their particular uses has been recognized[5]. Ciprofloxacin is used to treat a variety of infections, including pneumonia.

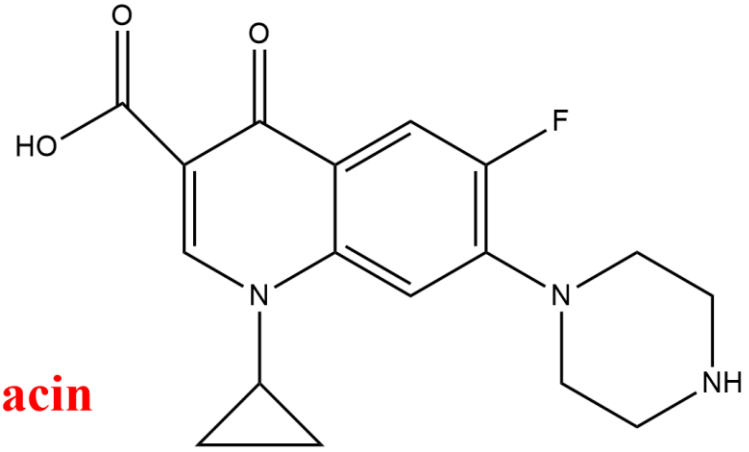
Ciprofloxacin has only a few approved medical uses in the United States, and it should only be used as a last resort if all other antibiotics have failed to treat the infection. As described in the package inserts, there are ten approved uses for this drug among adults and two approved uses for this drug among children. Additionally, there are numerous veterinary applications for this drug documented in the package inserts. Because its other applications have not been approved by the FDA, they can be considered off-label. It is possible that Ciprofloxacin will interact with a variety of other medications, including several herbal and natural supplements and certain thyroid medications[5]. A blockbuster antibiotic for Bayer A.G., Ciprofloxacin (Figure 1) has proven to be a moneymaker for the company, producing billions of dollars in additional income. In 1999, ciprofloxacin was the 11th most prescribed medicine in the United States, based on new prescriptions, and the 20th most popular drug overall in the United States, according to total sales figures. Bayer's gross sales of ciprofloxacin in the United States were around $1.04 billion in 1999, according to company records. A significant surge in the sale of ciprofloxacin occurred as a result of the anthrax threat in 2001.

Fluoroquinolones are categorized based on their spectrum of activity and pharmacokinetic profile, which are both important considerations. Ciprofloxacin is the strongest fluoroquinolones available, and it is effective against a wide range of bacteria, with the aerobic Gram-negative bacilli, particularly those of the enterobacteraceae and Neisseria, proving to be the most vulnerable. It is a fluoroquinolone of the second generation, and it has demonstrated a wide and diverse spectrum of activity against a wide range of infectious diseases in clinical trials. Ciprofloxacin is a highly promising and effective medication that possesses both substantial antibacterial action and well-established safety characteristics[6].

More than 250 million people have been treated effectively with ciprofloxacin since it was approved, and its safety profile has been carefully documented in a significant number of scientific publications since its approval. Pediatric populations, such as children with cystic fibrosis, may benefit from the use of ciprofloxacin as an antimicrobial therapy alternative. In a study of more than 1500 pediatric patients treated with ciprofloxacin for infection due to cystic fibrosis, researchers discovered that the safety profile in children and adolescents was equal to that in adults. After testing the minimum inhibitory concentration (MIC) of ciprofloxacin against several Gram-negative bacterial strains, it was found to be significantly higher than that of the other fluoroquinolones[7]. This is the first time that this has been demonstrated for any of the commonly used fluoroquinolones. The MIC90 for ciprofloxacin against Escherichia coli was found to be 0.015–0.25, but the MIC90s for ofloxacin, levofloxacin, and trovafloxacin were 0.12–0.39, 0.06–0.25, and 0.03–0.5, respectively, for the other antibiotics studied[8]. A similar finding was made with respect to Klebsiella pneumonia, with the MIC90 for Ciprofloxacin being found to be between 0.05 to 1.0, when compared to 0.1 to 0.5 and 0.12 to 1.0 for levofloxacin and ofloxacin, respectively. An additional experiment indicated that the fluoroquinolones ciprofloxacin and ofloxacin were more effective than some other fluoroquinolones, such as pefloxacin and ofloxacin, in avoiding infections caused by Gram-negative bacteria in a specific cohort of neutropenic patients[9]. Yamane and colleagues also discovered that the activity of levofloxacin against Gram-positive bacteria was either equivalent to or less than that of ciprofloxacin[10]. In another study, it was discovered that topical ciprofloxacin/dexamethasone therapy was superior to oral amoxicillin/clavulanic acid therapy in the treatment

of acute otitis media with otorrhea[11]. Additionally, studies from the literature suggest that ciprofloxacin, when administered orally, is superior to ampicillin and chloramphenicol in the treatment of typhoid in immune compromised animals.

Ciprofloxacin, a routinely used broad-spectrum antibiotic, has also piqued the scientific community's interest due to its antiproliferative and apoptotic activities in a number of cancer cell lines, which have been studied in depth. A number of carcinoma, osteosarcoma, and leukemia cell lines have been shown to exhibit growth inhibition and apoptosis in response to the treatment24. According to the findings of Aranha et al., ciprofloxacin may have a significant impact on the treatment of bladder cancer. Studies conducted in vitro on tumor cells originating from transitional cell carcinoma of the bladder demonstrated that ciprofloxacin inhibited cell development at concentrations that are readily obtainable in the urine of patients in a dose- and time-dependent manner.



Ciprofloxacin

1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid
Chemical Formula: $C_{17}H_{18}FN_3O_3$
Exact Mass: 331.13
Molecular Weight: 331.34
m/z: 331.13 (100.0%), 332.14 (18.7%), 333.14 (2.3%), 332.13 (1.1%)
Elemental Analysis: C, 61.62; H, 5.48; F, 5.73; N, 12.68; O, 14.49

Fig. 1 Chem draw chemical structure of ciprofloxacin with elemental analysis

It was discovered through these research that this fluoroquinolone drug has significant experimental evidence for its usage as a possible preventive and/or therapeutic agent for transitional cell carcinoma of the bladder (TCC) 25. They also demonstrated that the antibiotic ciprofloxacin inhibited the proliferation of human prostate cancer cells, which was related with cell cycle arrest and apoptosis. The antiproliferative and apoptosis-inducing effect of this fluoroquinolone on prostate cancer cells was demonstrated at levels typically used for the treatment of antibacterial infections. Furthermore, it was discovered that ciprofloxacin had no effect on non-tumorigenic prostate epithelial cells in this study. As a treatment for advanced hormone-resistant prostate cancer, the key advantage of this antibiotic is its relative non-toxicity when compared to existing chemotherapy, which is not particularly successful in most cases26. Pinto and colleagues investigated the effects of doxorubicin and docetaxel, two typical antineoplastic drugs in the treatment of hormone-refractory prostate cancer (HRPC), as well as ciprofloxacin, individually and in a variety of simultaneous and sequential medication combination strategies. Ciprofloxacin sensitized HRPC cell lines to doxorubicin and docetaxel therapy in a time-dependent manner, indicating that the drug was effective. Ciprofloxacin has been suggested to play a significant role in the

treatment of prostate cancer, according to a study published in the journal Cancer Research[12]. A unique antiproliferative and immune regulatory impact of ciprofloxacin on human intestinal epithelial cells was demonstrated by Bourikas et al. in a concentration and time-dependent manner on human intestinal epithelial cells[13].

Method Verification and Verification by using HPLC:

Quantitative Assay for determination of Active Constituent Ciprofloxacin (HCI) tablet USP by HPLC Method

To verify the test method according to protocol, for quantitative determination of Ciprofloxacin (HCI), an active ingredients of Cipro 250/500 mg tablet, finished product by HPLC. The verification protocol was executed to evaluate the linearity, precision, accuracy, detection limit, quantitation limit and robustness of the assay. The intended use of this test method is for quantitative determination of Ciprofloxacin (HCI), an active ingredient of Cipro 250/500 mg tablet. The scope of this study applies to quantitative determination of Ciprofloxacin (HCI), an active ingredient of Cipro 250/500 mg tablet.

The HPLC method is an effective method for quantitative determination of Active Pharmaceutical Ingredients (API). This HPLC method is based on the solubility of sample in the solvent. The solvent in general is a mixture of 0.025M phosphoric acid, pH adjusted by triethylamine 3.0 and acetonitrile solvent. The following validation parameters will be evaluated

- Precision, Accuracy, Linearity, Limit of Detection, Limit of Quantitation, Robustness

EQUIPMENT, METHOD & MATERIALS:

Equipment / Materials/ Solvents

- HPLC (Isocratic Shimadzu SPD-20AD or equivalent)
- Calibrated Balance
- Calibrated pH mater
- Purified RO Water
- Acetonitrile (Analytical grade)
- Filter Paper, Sartolon Polyamide, 0.45 µm

SOLVENT/MOBILE PHASE:

- Phosphoric acid (Analytical grade), Acetonitrile, Distilled water.
- Buffers / Solution preparations

Solution A:

Make 0.025M Phosphoric acid in water, and adjust pH 2.0 + 0.1 with triethylamine.

Solution B: Mix the following solvents in a given ratio,

Acetonitrile	:	Solution A
13%	:	87%

Solution C:

Make 0.025M Phosphoric acid in water, and adjust pH 3.0 + 0.1 with triethylamine.

Mobile phase: Mix the following solvents in a given ratio,

Acetonitrile	:	Solution C
13%	:	87%

Filter through 0.45µm filter paper and degas the mobile phase in an Ultra sonic bath for 5-10 minutes.

Diluents: Solution B

STANDARD PREPARATION

- Weigh accurately of RS Ciprofloxacin HCI (……...mg) or working standard equivalent to 100 mg Ciprofloxacin, and transfer to 100ml volumetric flask and dissolve it in 80 ml diluents and dilute with diluents to 100ml and mix well.

- Take 10 ml of above solution in a 50 ml volumetric flask and dilute up to the mark with diluents for the final concentration 0.2mg/ml.

SAMPLE PREPARATION:

Take NLT 20 tablets of sample of Cipro 500 mg tablet and grind to powder and take powder weight equivalent to 5 tablets and transfer to 500 ml volumetric flask and add about 400 ml diluents, sonicate for 20 minutes, cool and dilute to volume with diluents and mix for 5 minutes. Filter the above solution through filter and Take 2 ml of filtrate solution in a 25 ml volumetric flask and dilute up to the mark with diluents for the final concentration 0.2mg/ml.

CHROMATOGRAPHIC CONDITION

The following conditions have been found suitable

Dimensions	:	25cm x 4.6mm
Packing	:	Packing L1
Temperature	:	30 + 1°C
Flow rate	:	1.5ml/min
Detector	:	UV at 278 nm.
Injection volume	:	10 µl

Sample: Standard solution, Tailing factor: NMT 2.0, RSD: NMT 1.5%

Linearity of Ciprofloxacin (HCI):

Linearity experiments were conducted to identify the range over which Ciprofloxacin (HCI) exhibit linear response. The stock solution of Ciprofloxacin was prepared by dissolving 100 mg of finely powder homogeneous sample of Cipro 500 mg tablet into 100 ml of diluents for final concentration of 1.0 mg/ ml of Ciprofloxacin. The stock solution was gravimetrically diluted in diluents to concentrations of 50ppm (0.05 mg/ml) ,100 ppm (0.1 mg/ml) ,200 ppm (0.2 mg/ml) ,250 ppm (0.25mg/ml) ,300 ppm (0.3 mg/ml) and 400 ppm (0.4 mg/ml) respectively. The calibration graph is shown below, indicates linear relationship observed between the concentration and absorbance of the solutions. The R2 of calibration data point was calculated to 0.9999. This indicates that the test procedure obeys Beer's law.

Sr. No.	Concentration (mg/ml)	No.of injections	Retention time	Peak areas	Average peak areas of test solution
1	0.05	1	12.618	2470272	2470272
2	0.10	1	12.571	4956980	4956980
3	0.20	1	12.503	9903000	9903000
4	0.25	1	12.474	12347022	12347022
5	0.30	1	12.442	15195071	15195071
6	0.40	1	12.391	19765831	19765831

The calibration graph showing linear relationship between the absorbance and concentration of analyte in the solution is shown below.

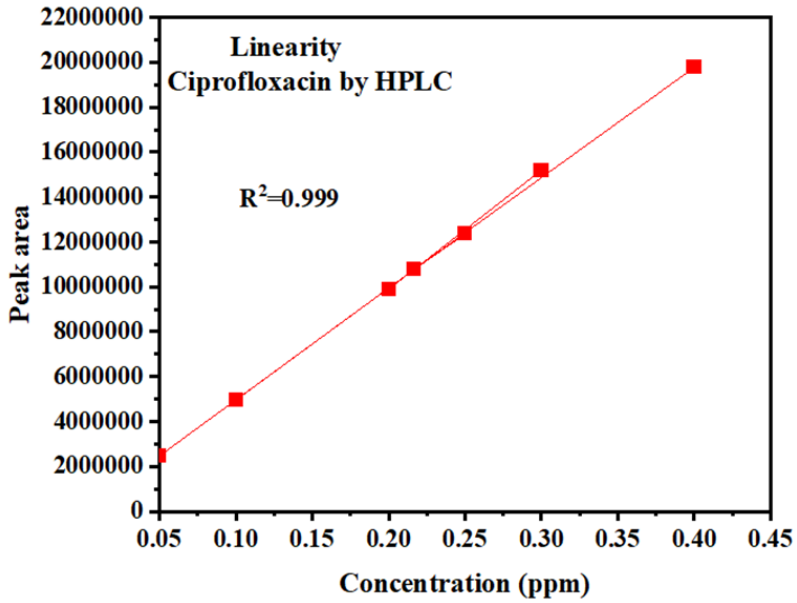


Fig. 2. Linearity graph of ciprofloxacin at different PPM solution with HPLC peak areas

Conclusion:

The calibration graph is showing linear relationship between the concentration and absorbance of the solutions. There by indicating that the test procedure follows Beer's law.

Precision:

Verification of tests for assay includes an investigation of precision. This is tested by repeatability and reproducibility if the test method evaluated as repeatability and reproducibility.

Repeatability (Ciprofloxacin):

It was calculated from the results of six consecutive determinations. To check repeatability, six samples were drawn and test solutions were prepared and tested according to the test procedure.

Weight of Reference Standard = 59.8 mg Purity 84.84%

Peak areas of Reference Standard = 1- 10268286 2- 10261654 3- 10268636

4- 10268656 5- 10268222

Average peak area of reference standard = 10267091

Sr. No.	Concentration (mg/ml)	Injections	Retention time	Peak areas	Average peak areas of test solution	% age Results of LC	Variation from theoretical Results
1	0.2	1	12.484	9973079	9977318	99.11%	-0.89%
		2	12.476	9970007			
		3	12.480	9988869			
2	0.2	1	12.482	9860487	9863310	98.49%	-1.51%
		2	12.490	9867688			
		3	12.499	9861755			
3	0.2	1	12.500	9926657	9917711	98.52%	-1.48%
		2	12.504	9900312			
		3	12.506	9926165			
4	0.2	1	12.508	9999633	10001463	99.09%	-0.91%
		2	12.510	9989845			
		3	12.512	10014913			
5	0.2	1	12.521	9810415	9809925	98.09%	-1.91%
		2	12.517	9820739			
		3	12.519	9798622			
6	0.2	1	12.521	9863634	9861411	98.47%	-1.53%
		2	12.523	9862536			
		3	12.526	9858065			

Range: (98.09 --- 99.11%), Mean : 98.62%, Standard Deviation = 0.397%, Relative Standard Deviation = 0.402% ± 2.00 %

Reproducibility of (Ciprofloxacin):

To check the repeatability; 2 sets of five samples equivalent to 100 % of label claim were prepared and assayed by two analysts individually.

Analyst 01

Weight of Reference Standard = 59.8 mg, Purity 84.84%

Peak areas of Reference Standard = 1- 10179503 2- 10213333 3- 10220246

4- 10228224 5- 10224867

Average peak area of reference standard = 10213234

Sr. No.	Concentration (mg/ml)	Injections	Retention time	Peak areas	Average peak areas of test solution	% age Results of LC	Variation from theoretical Results
1	0.2	1	14.088	10032982	10026708	99.61%	-0.39
		2	14.089	10025241			
		3	14.087	10021902			
2	0.2	1	14.084	10061157	10063761	99.98%	-0.02%
		2	14.082	10063550			
		3	14.080	10066576			
3	0.2	1	14.084	10082268	1005326	100.19%	0.19%
		2	14.084	10087489			
		3	14.085	10086221			
4	0.2	1	14.092	9932501	9933675	98.69%	-1.31%
		2	14.089	9936693			
		3	14.103	9931831			
5	0.2	1	14.129	9987566	9990370	99.25%	-0.75
		2	14.132	9991779			
		3	14.135	9991767			

Range: (98.69 – 100.19%), Mean: 99.54%, Standard Deviation = 0.597%, Relative Standard Deviation = 0.6001% ± 2.00 %

Analyst 02

Weight of Reference Standard = 59.8 mg, Purity 84.84%

Peak areas of Reference Standard = 1- 10239693 2- 10248565 3- 10250121

4- 10252431 5- 10252803 Average peak area of reference standard = 10249523

Sr. No.	Concentration (mg/ml)	injections	Retention time	Peak areas	Average peak areas of test solution	% age Results of LC	Variation from theoretical Results

1	0.2	1	14.153	9932722	9928187	98.28%	-1.72%
		2	14.156	9923872			
		3	14.160	9927968			
2	0.2	1	14.162	10048953	10045036	99.44%	-0.56%
		2	14.165	10039589			
		3	14.171	10046568			
3	0.2	1	14.176	10117107	10120693	100.06%	0.06%
		2	14.186	10121113			
		3	14.186	10123859			
4	0.2	1	14.192	10106700	10105454	99.19%	-0.81%
		2	14.195	10100199			
		3	14.202	10109463			
5	0.2	1	14.205	10016687	10016887	99.16%	-0.84%
		2	14.209	10017381			
		3	14.212	10016594			

Range: (98.28 – 100.06%), Mean: 99.22%, Standard Deviation = 0.6406%

Relative Standard Deviation = 0.6457% ± 2.00

Accuracy (Ciprofloxacin):

The accuracy of test method is determined by spiked Placebo method.

Spiked Placebo Method:

Three samples of 500 gm. each were prepared in the lab according the manufacturing procedure of the product and quantities equivalent to 80 %, 100 % and 120 % of the labeled amount of analyte were added to each Placebo. Test solutions were prepared of each concentration (i.e. 80%, 100% and 120%) assayed in duplicate and tested according to the test procedure of the product Results are tabulated below:

Weight of Reference Standard = 59.8 mg, Purity 84.84%

Peak areas of Reference Standard = 1- 10379740 2- 10366287 3- 10320816

4- 10327883 5- 10301461

Average peak area of reference standard = 10339238

Contents of Active Added in Placebo (% of Label Claim)	80 %		100 %		120 %	
Weights of Samples	795 mg	800 mg	766 mg	766 mg	733mg	735 mg

Peak area of test solution	9987672	10182795	10220444	10107747	10072974	10108027
% age of label claim	98.63%	99.93%	99.51%	98.41%	98.90%	98.97%
Variation from Theoretical Results or Difference	-1.37%	-0.07%	-0.49%	-1.59%	-1.1%	-1.03%
Average	99.28%		98.96%		98.93%	
Standard Deviation	-0.72%s		-1.04%		-1.07%	

The results of assay show contents of the analyst's equivalent to the theoretical contents in Placebo. The deviation observed is within the limits.

Robustness (Ciprofloxacin)

It is the measure how stable the test procedure is under slight variation in test procedure. The following changes were made deliberately in testing procedure. The test solution prepared according to the test procedure and kept at 15°C and 35°C for 24 hours and assayed according to the test procedure. The results are compound with initial results and tabulated below.

Weight of Reference Standard = 59.8 mg, Purity 84.84%

Peak areas of Reference Standard = 1- 10315010 2- 10358820 3- 10364915

4- 10374216 5- 10384705

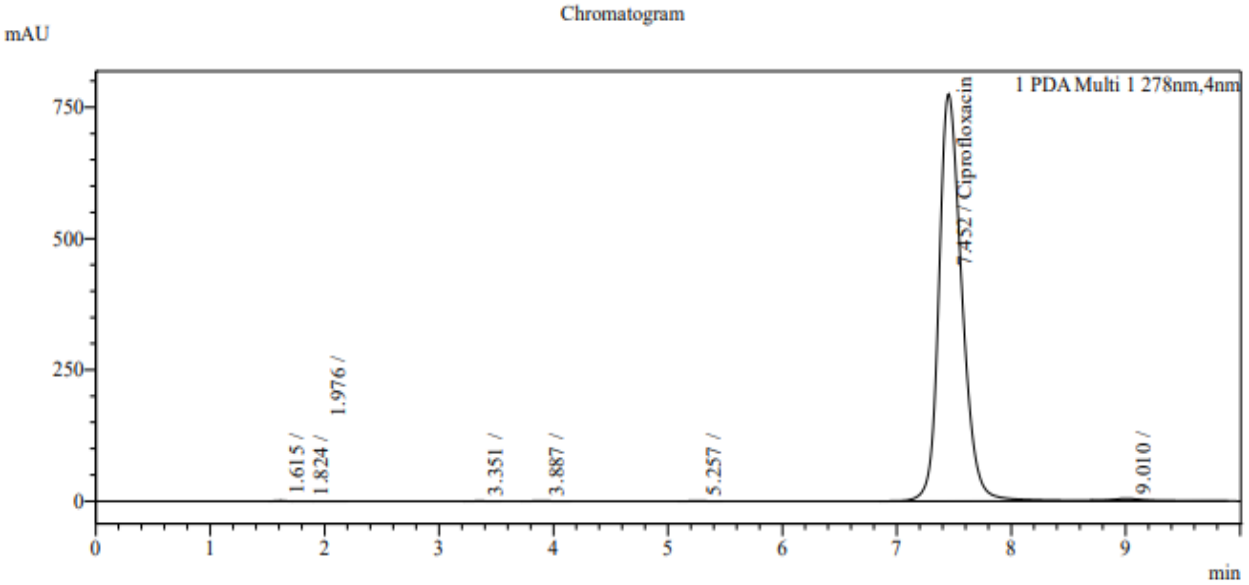
Average peak area of reference standard = 10359533

Average weight /tablet = 385 mg/tab (Cipro 250 mg tablet)

Storage Condition	**15°C**		**25°C**		**35°C**	
	Sample I	Sample II	Sample I	Sample II	Sample I	Sample II
Weight of Samples	385 mg	385 mg	385 mg	385 mg	385 mg	385 mg
Peak area of test solution	10112078	10165405	10249835	10052253	10153814	10363272
% of Label Claim	99.04%	99.56%	100.39%	98.45%	99.45%	101.50%
Average	99.3%		99.42%		100.47%	

Standard Deviation	-0.7%	-0.58%	0.47%

The test samples are stable for up to twenty four hours kept under the temperature as low as 15°C and as high as 35°C.



Peak Table

PDA Ch1 278nm

Peak#	ID#	Name	Ret. Time	Area	Height	Tailing Factor
1			1.615	3973	841	--
2			1.824	1059	154	--
3			1.976	1313	88	1.755
4			3.351	2039	304	1.096
5			3.887	4980	628	1.162
6			5.257	3196	365	1.059
7	1	Ciprofloxacin	7.452	10804519	775439	1.244
8			9.010	64689	4342	1.038
Total				10885768	782162	

Fig. 3. HPLC chromatogram of ciprofloxacin HCI with peak identification at RT 7.4

DFT study of Ciprofloxacin:

DFT and TD-DFT research help us locate and compare computationally the outcomes of our experiments in order to validate them. All calculations were carried out using the Gaussian 16 software package and the gauss view 06 version for visualizing the findings and drawing out the structures[14]. Four different hybrid functionals were used to find the wavelength of ciprofloxacin such as B3LYP [15], CAM-B3LYP[16], MPW1PW91[17], WB97XD[18], with basis set 6-31 G** level of theory. The experimental data were compared to theoretically computed UV/Visible absorption spectra at the 6-31G (d,p) level of theory, and it was found that the hybrid functional WB97XD well matched the theoretical results.

The absorption spectra were calculated using TD-DFT (Time dependent density functional theory) once the functional and basis sets had been chosen. . In order to obtain the wavelength at the excited state of ciprofloxacin, a solvent was required in addition to the absorption spectra. Alcohol was utilized as a solvent in the energy calculations of ciprofloxacin. As a result, our theoretically

computed spectra at 282nm for a particular functional and basis set were in excellent agreement with the experimental data available in the literature at 278nm.

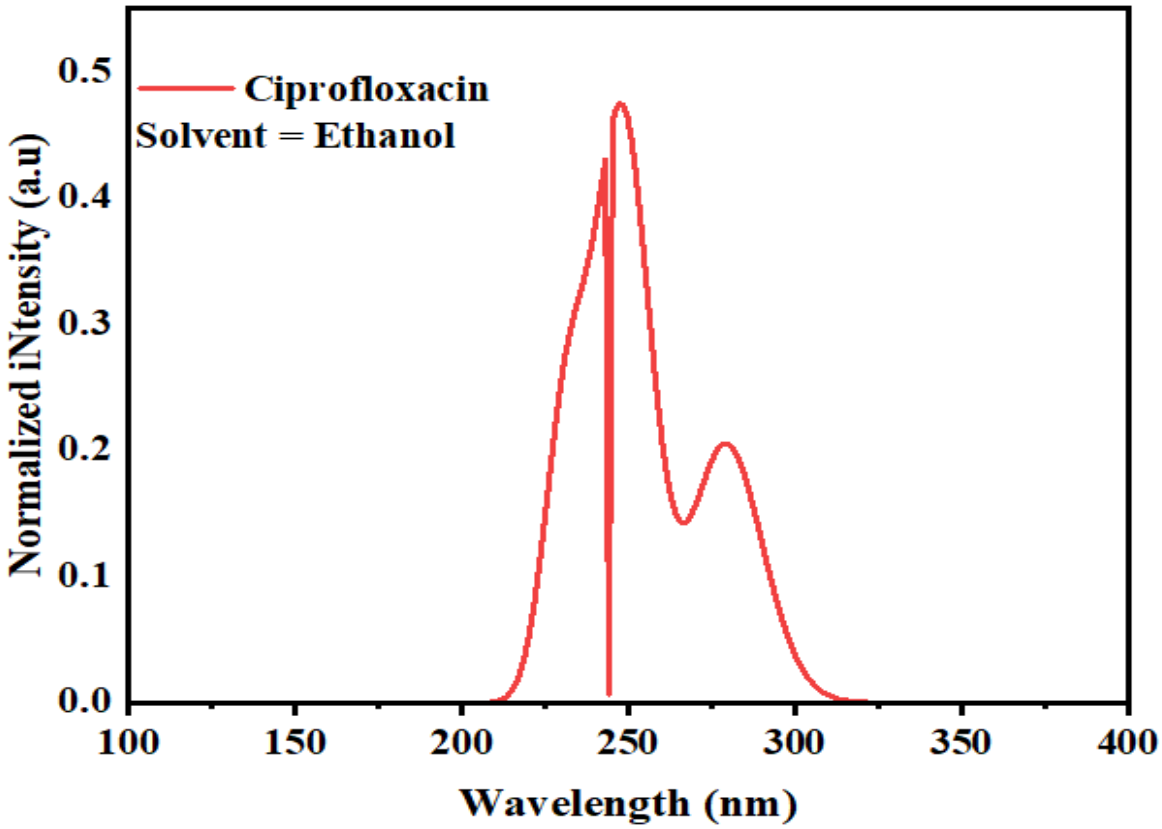


Fig.4 Theoretically Absorption spectra of ciprofloxacin at WB97XD/6-31G level of theory**

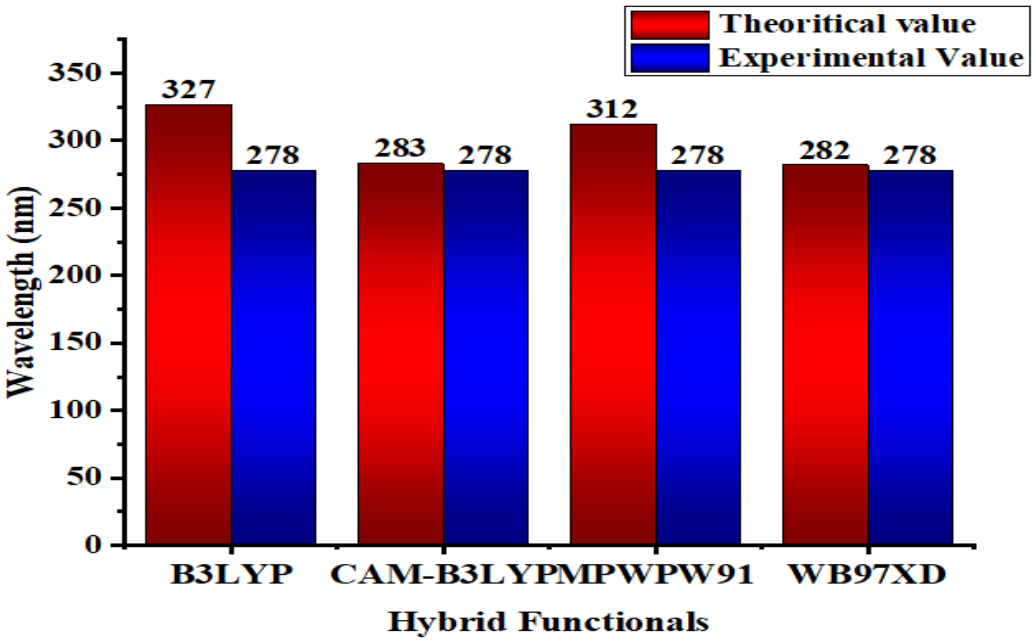


Fig. 5. Comparison diagram of λmax value for ciprofloxacin between experimental and theoretical with different hybrid functionals at 6-31G level of theory**

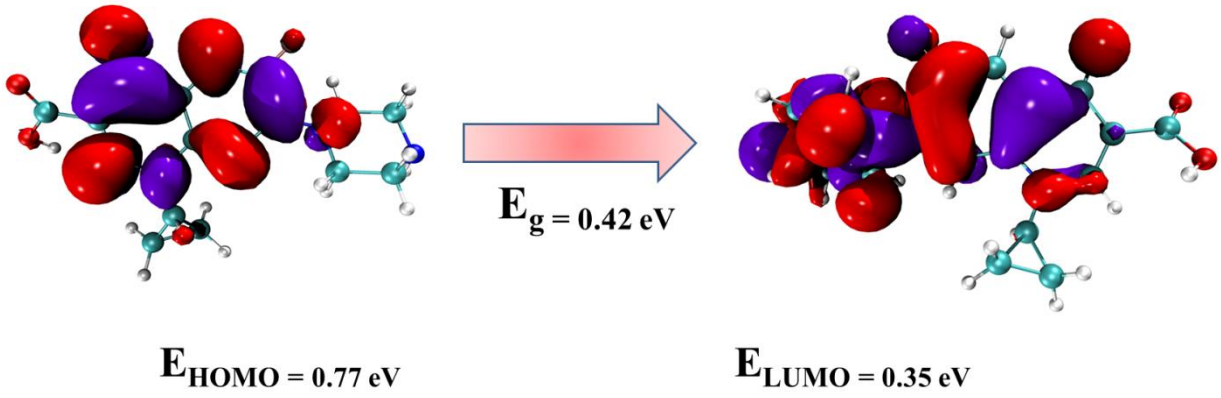


Fig. 6. FMOs distribution of ciprofloxacin at WB97XD/6-31G level of theory**

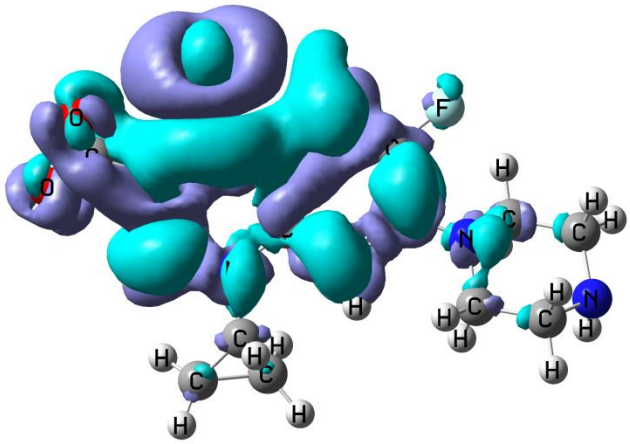


Fig. 7. Electron Density Differences maps (EDDM) of ciprofloxacin HCI at excited state

An electron density differences map (EDDM) provides us about the movement of electron density at excited state. The Purple and green color shows the where the electrons are coming and where they are going correspondingly.

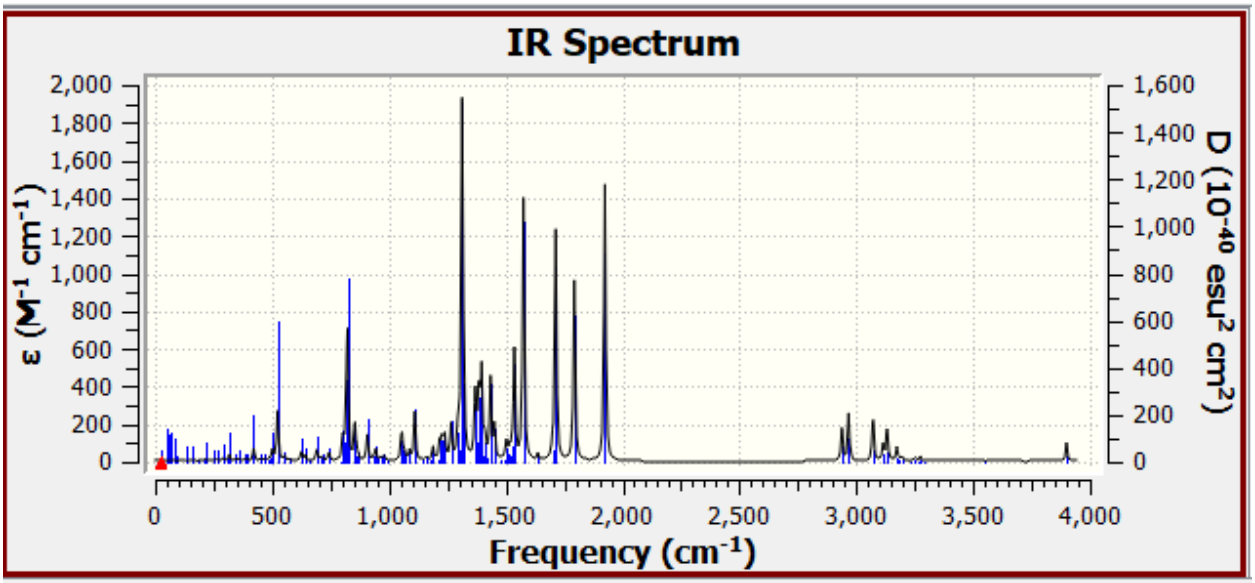


Fig. 8. IR spectra of ciprofloxacin at WB97XD/6-31G**

The compatibility study was performed by means of FTIR. The result was based on matching the main peak of the pure drug with the formulation, as the peak table shows there was no interaction between ciprofloxacin hydrochloride and polymer.

Drug interactions:

The addition of antacids containing magnesium, aluminum, and other agents such as sucralfate reduces ciprofloxacin absorption via the oral route of administration. Ciprofloxacin also interacts with goods containing multivalent cations. Exceptionally, ranitidine has no effect on ciprofloxacin's oral absorption. These interactions between ciprofloxacin and antacids may be dangerous when used to treat a serious infection[19]. Ciprofloxacin interacts more adversely with theophylline or other methylxanthines such as coffee.

Clinical indications:

Ciprofloxacin is effective against a wide variety of infections, including those that are very difficult to treat. Due to its broad spectrum bactericidal activity, oral efficacy, and tolerability, it is often used in blind therapy of infections. However, it should not be administered in mild cases or when Gram-positive organisms are the primary suspects.

Conclusion:

Current analytical techniques for ciprofloxacin determination (HPLC, UV, and FT-IR) or identification in diverse formulations and biological fluids have been examined, as well as significant pharmacological interventions. As a promising and effective medicine, Ciprofloxacin has a wide range of antibacterial action. This robust medicinal agent's therapeutic and quality profiles must be precisely controlled through more scientific and technological developments in pharmacology, medicinal chemistry, and analytical procedures, it is highlighted. With the use of density functional theory, we have obtained the best agreement in both practical and theoretical research (absorption spectra, Energy gap, electron density differences maps, excitation values), demonstrating the strongest coherence.

CONFLICT OF INTERESTS

There is no contradiction among the writers in this paper.

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