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A VALIDATED RP-HPLC METHOD FOR THE DETERMINATION OF GEMIFLOXACIN IN BULK AND PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

A simple, accurate, precise, specific isocratic reversed phase-high performance liquid chromatography (RP-HPLC) method has been developed for the quantitative estimation of Gemifloxacin (GFX) in pharmaceutical formulations. RP-HPLC method was developed by using WELCHROM C_{18} Column (4.6 X 250mm, 5µm), SHIMADZU LC-20AT prominence liquid chromatography. The mobile phase used was phosphate buffer (pH-3.2): acetonitrile (60:40 v/v) with a flow rate of 1mL/min. The responses are measured at 280 nm using SHIMADZU SPD-20A prominence UV-Vis detector. The retention time of GFX found to be 5.663 min. The method possessed linearity in the range of 2-10 µg/mL and correlation coefficient was 0.999. The accuracy and reliability of the proposed method was ascertained by evaluating various validation parameters like linearity, precision and specificity according to ICH guidelines. The proposed method provides an accurate and precise quality control tool for routine analysis of GFX in tablet dosage forms.

KEY WORDS - Gemifloxacin, RP-HPLC, UV-Vis detector, Method Validation, Isocratic.

1. INTRODUCTION

Gemifloxacin (GFX) is a potent (Ann Allen, 2000) (De Souza, 2005), novel broad spectrum antibiotic belonging to fourth generation fluoroquinolones (http://en.wikipedia.org/wiki/Quinolone). IUPAC name of GFX is 7-[(4Z)-3-(aminomethyl) - 4 - (methoxyimino) pyrrolidin-1-yl] – 1 – cyclopropyl – 6 – fluoro – 4 – oxo - 1,4-dihydro-1,8- naphthyridine-3-carboxylic acid. Chemical structure of GFX is shown in Fig 1. GFX demonstrated improved activity against acute bacterial exacerbation of chronic bronchitis caused by Streptococcus pneumonia and respiratory pathogens like Haemophilus influenzae, Haemophilus parainfluenzae, or Moraxella catarrhalis (http://en.wikipedia.org/wiki/Gemifloxacin) (Bong, 2004) (Stephen Rittenhouse, 2000). GFX shows excellent against gram-negative aerobic organisms (Louis D, 2003). GFX shows considerable effect on atypical pathogens such as Chlamydia pneumonia, Legionella pneumophila, and Mycoplasma pneumonia (Bong K Yoo, 2004) (Stephen Rittenhouse, 2000) (Todd, 2000). GFX was proved to be effective against meningitis caused by Neisseria meningitides (Philippe, 2003). GFX was proved to be cost effective treatment (Halpern, 2002) for oral bronchitis compared to Clarithromycin. Comparative studies revealed that gemifloxacin was more potent on some microbes than other antibiotics (Stephen Rittenhouse, 2000) (Baltch, 2005). Few analytical methods have been developed for the estimation of GFX includes UV-spectroscopy (Danta Chhanda Charan and Sahu Satyabrata, 2011), simple HPLC and HPTLC method (Rote, 2009), HPLC-tandem mass spectroscopy (Doyle, 2000), microchip electrophoresis (Seung, 2004), capillary electrophoresis (Abdalla, 2008), simple LC method (Uday Shankar, 2009), ion-pair spectroscopic method (Marothu Vamsi Krishna, 2008), HPLC with fluorescence detection (Ann Allen, 2000) (Kaiser, 2011) (Al-Hadiya, 2010), RP-HPLC method (Yunoos Mohammad, 2010), HPLC method with UV detector (Ayan Das, 2011), LC-microdialysis method (Araujo, 2013) and fluorescence quenching method (Zhong, 2012). The goal of this study is to develop rapid HPLC methods for the analysis of GFX in bulk drug samples and tablet formulations using the most commonly employed C_{18} column with UV detection at appropriate wavelength.

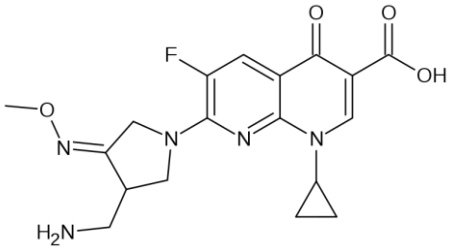

Fig 1: Chemical structure of Gemifloxacin

2. MATERIALS AND METHODS

Quantitative HPLC was performed on a high pressure gradient high performance liquid chromatography (SHIMADZU LC-20AT prominence liquid chromatography) with two LC-20AT VP pumps, manual injector with loop volume of 20 µL (Rheodyne), programmable variable wavelength SHIMADZU SPD-20A prominence UV-Vis detector and WELCHROM C_{18} Column (4.6 X 250mm, 5µm). The HPLC system was equipped with "Spincotech" software. In addition an electronic balance (Essae-Teraoka Ltd.,) digital pH meter (Systronics model 802), Ultra sonic bath sonicator (spectra lab, model UCB 40), Double beam spectrophotometer (Systronics model- 2203) were used in this study.

Standards and chemicals used: GFX was provided by Hetero Drugs Limited, Hyderabad, Andhra Pradesh, India. All the chemicals were analytical grade. Potassium dihydrogen orthophosphate and phosphoric acid from S.D Fine-Chem. Ltd., Mumbai, India, while acetonitrile (HPLC grade) and triethylamine (HPLC grade) from Merck Pharmaceuticals Private Limited (Mumbai, India). Commercial tablets of GFX were purchased from local market. G-CIN-320mg tablets manufactured by Lupin Ltd., GEMBAX-320mg tablets were manufactured by Ranbaxy Laboratories Ltd., India.

Preparation of mobile phase: A 10 mM phosphate buffer was prepared by dissolving 6.056 g of potassium dihydrogen orthophosphate in 445 mL of HPLC grade water. To this 55mL of 0.1M phosphoric acid was added and pH was adjusted to 3.2 with triethylamime. The above prepared buffer and acetonitrile were mixed in the proportion of 60: 40 v/v and was filtered through 0.22 µm nylon membrane filter and degassed by sonication.

Preparation of calibration standards: About 100 mg of pure GFX is accurately weighed and dissolved in 100 mL of mobile phase to get 1 mg/mL stock solution. Working standard solution of GFX was prepared with mobile phase. To a series of 10ml volumetric flasks, standard solutions of GFX in the concentration range of 2, 4, 6, 8, 10 µg/mL were transferred. The final volume was made with the mobile phase.

System suitability: The HPLC system was stabilized for forty minutes. One blank followed by six replicates of a single calibration standard solution of GFX was injected to check the system suitability. To ascertain the systems suitability for the proposed method, a number of parameters such as theoretical plates, peak asymmetry, retention time and parameters were taken and results were presented in Table 1.

Recommended procedure:

Construction of calibration curve: Replicates of each calibration standard solutions were (2, 4, 6, 8, 10 µg/mL) were injected into the chromatogram, the retention times and average peak areas were recorded. Calibration graph was plotted by taking concentration of GFX on X-axis and ratio of peak areas of standard GFX on Y-axis. Linearity and statistical analysis data for Gemifloxacin were represented in Table 2.

Assay of Gemifloxacin: Twenty tablets were transferred into a mortar and ground to fine powder. From this, tablet powder equivalent to 100 mg of GFX was taken and the drug was extracted in 100 mL of mobile phase. The resulting solution was filtered through 0.22 µm nylon membrane filter and degassed by sonication. This solution was further suitably diluted for chromatography. The test solutions were injected into the system by filling a 20 µL fixed volume loop manual injector. The chromatographic run time of 10 min. was maintained for the elution of the drug from the column. The elutes were monitored with UV detector at 280 nm. The amount of drug present in sample was computed from the calibration graph.

Validation study of Gemifloxacin: An integral part of analytical method development is validation. Once the method has been developed, it is necessary to evaluate under the conditions expected for real samples before being used for a specific purpose. The method validation was performed as per ICH guidelines for the determination of GFX in bulk and pharmaceutical dosage forms. The method was validated with respect to parameters including specificity, precision, accuracy, linearity, robustness, system suitability, limit of detection (LOD) and limit of quantification (LOQ).

Specificity: The effect of wide range of excipients and other additives usually present in the formulations of GFX in the determinations under optimum conditions is investigated. The specificity of the RP-HPLC method is established by injecting the mobile phase and placebo solution in triplicate and recording the chromatograms. The common excipients such as lactose anhydrous, microcrystalline cellulose, and magnesium stearate have been added to the sample solution and injected.

Precision: Precision of the method was performed as intraday precision and interday precision. To study the intraday precision, six-replicate standard solutions of GFX were injected. The percent relative standard deviation (% RSD) was calculated. The acceptable criteria are not more than 2.0. The percentage ranges of errors (0.05 and 0.01 confidence limits) were calculated and were presented in the Table 3.

Linearity: The linearity graphs for the proposed assay methods were obtained over the concentration range of 2-10 µg/mL GFX. Method of least square analysis was carried out for getting the slope, intercept and

correlation coefficient values and the results were presented in Table 2. Regression data of the proposed method was shown in table 3, regression statistics, anova data was represented in table 4. The linearity graph of GFX was shown in Fig. 9.

Accuracy (Recovery studies): The accuracy of the method was determined by calculating recovery of GFX by the method of addition. Known amount of GFX at 25%, 50%, 100%, and 150% was added to a pre quantified sample solution. The recovery studies were carried out in the tablet in triplicate each in the presence of placebo. The mean percentage recovery of GFX at each level was not less than 99% and not more than 101.

Robustness: Robustness of the proposed methods was evaluated by making small changes in flow rate (± 0.2 mL/min), temperature (± 5^{o}C), Mobile phase composition (±5%), and pH of the buffer solution.

Ruggedness: Ruggedness of the method was evaluated by comparing the results of assay of GFX obtained from two analysts, systems and two columns. RSD was always found to be < 2%, which indicates the method was rugged.

Limit of Detection (LOD): The limit of detection (LOD) is defined as the lowest concentration of the analyte that can be detected but not necessarily quantified. LOD is calculated using formula (3.3*S.D)/slope.

Limit of quantitation (LOQ): The limit of quantitation (LOQ) is defined as the lowest concentration of the analyte that can be quantified with acceptable precision and accuracy. LOQ is calculated using formula (10*S.D)/slope.

3. RESULTS AND DISCUSSION

The mobile phase consisting of phosphate buffer (PH-3.2): acetonitrile (60:40 v/v at 1mL/min flow rate was optimized which gave symmetric peak, minimum tailing factor with short runtime for GFX. The retention time for GFX was 5.663 min. A UV spectrum of GFX showed that the drug absorbed maximum at 280 nm, so this wavelength was selected as the detection wavelength. System suitability parameters and optimized chromatographic conditions were shown in Table 1. The calibration curve for GFX was found to be linear over the range of 2-10 µg/mL. Linearity and statistical analysis data for Gemifloxacin was shown in Table 2. Linear regression data of proposed method of Gemifloxacin was shown in Table 3 and the regression statistics, anova data was shown in Table 4. The developed method was applied to the assay of GFX tablets. The experimental results were given in Table 5. The results were very close to labeled value of commercial tablets. The representative standard and sample chromatograms of GFX were shown in Fig. 2 and 3 respectively. The regression equation was found to be Y=58.24x + 0.439 with correlation coefficient is r^2 =0.999 which indicates this method has good linearity. The representative chromatograms indicating the GFX were shown in Fig. 4 to 8. The calibration of the plot of GFX was shown in Fig. 9. The specificity was studied for the examination of the presence of interfering components, while the comparison of chromatograms there was no interference from placebo with sample peak. They did not disturb the elution or quantification of GFX, furthermore the well-shaped peaks also indicate the specificity of the method. Therefore, it was concluded that the method was specific. The specificity results were summarized in Table 6. Precision was studied to find out intra and inter day variations in the test methods of GFX for the three times on the same day and different days. The intra-day and inter-day precision obtained was with in the limits i.e., % RSD (< 2) which would indicates that the proposed method was quite precise and reproducible and results were shown in Table 7. The regression equation was found to be Y=58.24x + 0.439 with correlation coefficient was r^2 =0.999 which indicates this method had good linearity. The representative chromatograms indicating the GFX were shown in Fig. 4 to 8. The linearity of the graph was shown in Fig. 9. Recovery studies of the drug were carried out for the accuracy parameter at three different concentrations levels i.e. multiple level recovery studies. A known amount of GFX standard was added into pre-analyzed sample and subjected them to the proposed HPLC method. The % recovery was found to be within the limits as listed in Table 8. Generally the mean percentage recovery of GFX at each level was not less than 99% and not more than 101%. The percent recovery of GFX was found to be between 99.027% and 100.089%. Robustness was done by small changes in the chromatographic conditions like mobile phase flow rate, temperature, detection wavelength, mobile phase composition etc. It was observed that there were no marked changes in the chromatograms. Infact the parameters are within the limit and results are found to be not affected by these small alterations, which indicates that the method had highly robustness and suitable for routine use. The Robustness results were presented in Table 9 indicates that the selected factors remain unaffected by small variations of the parameters. The limit of detection (LOD) and limit of quantitation (LOQ) were calculated based on the standard deviation (SD) of the response and the slope (S) of the calibration curve at levels approximating the LOD and LOQ. The limit of detection (LOD) was 0.163 µg/mL

and the limit of quantitation (LOQ) was 0.494 µg/mL which showed that this method was very sensitive and the results were presented in Table 10.

Table1: Optimized chromatographic conditions and system suitability parameters for proposed method Gemifloxacin

Parameter	Chromatographic conditions
Instrument	SHIMADZU LC-20AT prominence liquid chromatograph
Column	WELCHROM C_{18} Column, (4.6 X 250mm, 5µm)
Detector	SHIMADZU SPD-20A prominence UV-Vis detector
Diluents	Buffer: Acetonitrile (60:40 v/v)
Mobile phase	Buffer: ACN (60:40 v/v)
Flow rate	1mL/min.
Detection wave length	By UV at 280 nm.
Run time	15 minutes
Column back pressure	110-120(kg/cm^2)
Temperature	Ambient temperature (25^oC)
Volume of injection loop	20(µL)
Retention time	5.663 min
Theoretical plates[th.pl] (Efficiency)	13055
Theoretical plates per meter[t.p/m]	261090
Peak asymmetry	1.103

Table 2: Linearity and statistical analysis data for Gemifloxacin

S.No	Linearity level (µg/mL)	Peak area	Slope	Y-intercept	Correlation Coefficient(r^2)
1	2 µg/mL	117.211	58.24	0.439	0.999
2	4 µg/mL	232.936			
3	6 µg/mL	352.851			
4	8 µg/mL	462.841			
5	10 µg/mL	584.002			

Table 3: Linear regression data of the proposed method of Gemifloxacin

Parameter	Method
Detection wavelength(λ max)	By UV at 280nm
Linearity range (µg/mL)	2-10µg/mL
Regression equation (Y=a+bc)	58.24x+0.439
Slope(b)	58.24
Intercept(a)	0.439
Standard deviation of slope (S_b)	2.881859
Standard deviation of intercept (S_a)	0.434456
Correlation coefficient (r^2)	0.999
% Relative standard deviation* i.e., Coefficient of variation(CV)	0.3918
Percentage range of errors* (Confidence limits) 0.005significance level 0.001 significance level	 0.082818443 0.00142202

*Average of six determinations

Table 4: Regression statistics of Gemifloxacin

Regression Statistics	0.99991635					
R Square	0.999832706					
Adjusted R Square	0.999776942					
Standard Error	2.747745573					
Observations	5					
ANOVA						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.922	2.881859869	0.31993228	0.770006494	-8.249364294	10.09336429
x variable	58.1743	0.434456722	133.9012543	9.18395E-07	56.79166481	59.55693519

Table 5: Assay results of Gemifloxacin formulations

S.No	Formulations	Labeled amount	Amount found	% Assay ±RSD*
1	G-CIN (Lupin)	320mg	319.489mg	99.84±0.034
2	GEMBAX (Ranbaxy)	320mg	319.709mg	99.91±0.026

***Average of six determinations.**

Table 6: Specificity study

Name of the solution	Retention time in min.
Blank	No peaks
Gemifloxacin	5.663

Table 7: Results of Intraday and interday precision study

Sample	Injection number	Interday precision	Intraday precision
		Peak area	Peak area
Gemifloxacin	1	584.002	584.002
	2	584.189	584.104
	3	584.234	583.891
	4	583.721	583.821
	5	583.961	583.951
	6	584.235	584.203
	Mean	584.056833	583.9948
	Standard deviation	0.20286292	0.140619
	% RSD acceptance criteria 2.0)	0.81145170	0.562477

Table 8: Recovery data of the proposed Gemifloxacin RP-HPLC method

S. No	Concentration level	Amount added (µg/mL)	Amount found (µg/mL)	Area obtained	Mean % Recovery ± SD*	% RSD #
		5	4.92	291.61		
1	50%	5	4.95	293.367	99.027±0.604	0.60
		5	4.98	295.127		
		10	9.99	592.302		
2	100%	10	9.85	584.002	99.533±0.907	0.90
		10	10.02	594.081		
		15	15.10	890.386		
3	150%	15	15.02	885.669	100.089±0.601	0.60
		15	14.92	879.772		

*** SD Standard deviation.**
 # %RSD is percentage of relative standard deviation.

Table 9: Robustness results of Gemifloxacin

S. No	Parameters	Optimized	Used	Peak area	Retention time (Rt)	Plate count	Peak asymmetry
1.	Flow rate (±0.2)	1 ml/min	0.8	604.432	7.122	12630	1.160
			1	584.002	5.663	13055	1.133
			1.2	472.941	4.782	11932	1.181
2.	Temperature (±5^{0}c)	25^{0}C	20	521.897	5.823	12989	1.231
			25	584.002	5.663	13055	1.133
			30	534.612	4.882	12900	1.142
3.	Mobile phase Composition (±5)	60:40	55:45	422.791	4.763	12654	1.143
			60:40	584.002	5.663	13055	1.133
			65:35	548.321	7.220	11322	1.026

Table 10: Limit of Detection (LOD) and Limit of Quantitation (LOQ)

Limit of Detection(LOD)	0.163 µg/mL
Limit of Quantitation(LOQ)	0.494 µg/mL

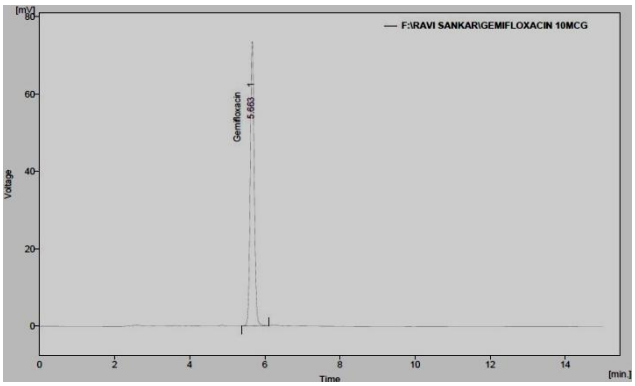

Fig. 2: Standard chromatogram of Gemifloxacin (10µg/mL)

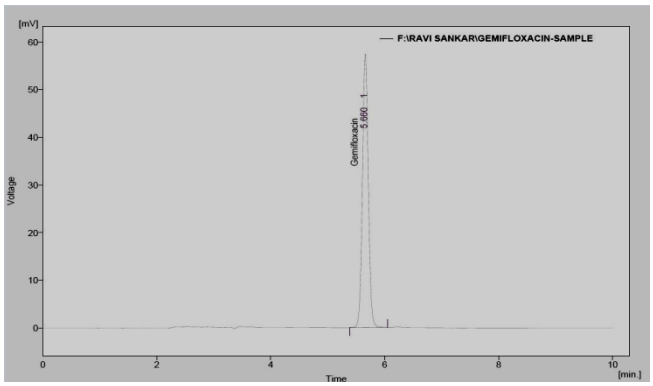

Fig. 3: Sample Chromatogram of Gemifloxacin.

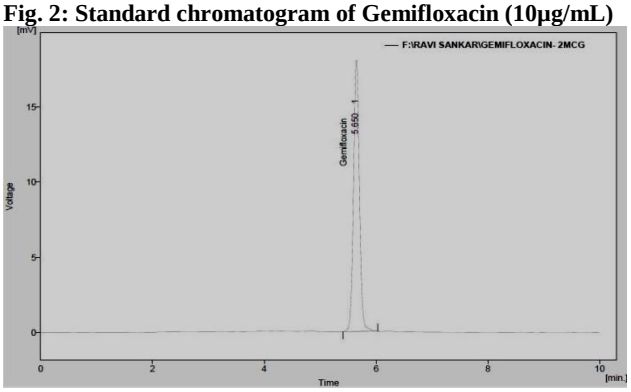

Fig. 4: Standard chromatogram of Gemifloxacin (2 µg/mL)

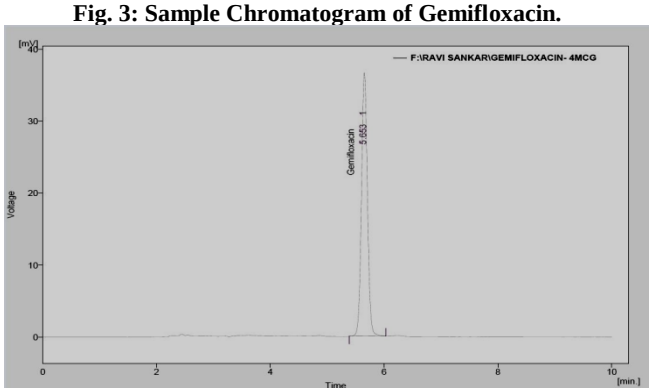

Fig. 5: Standard chromatogram of Gemifloxacin (4µg/mL)

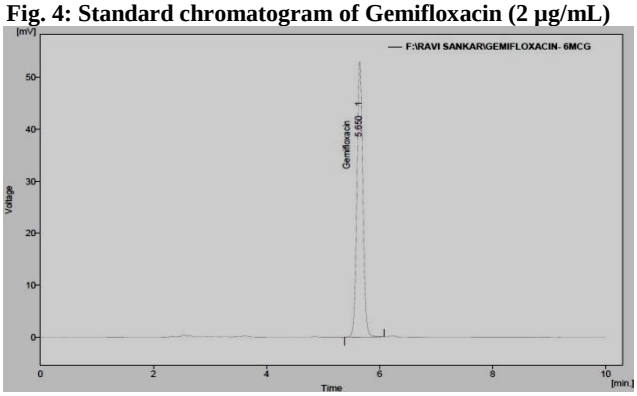

Fig. 6: Standard chromatogram of Gemifloxacin (6 µg/mL)

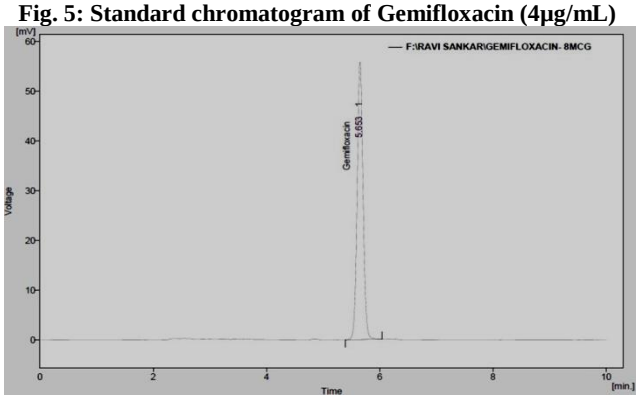

Fig. 7:Standard chromatogram of Gemifloxacin (8 µg/mL)

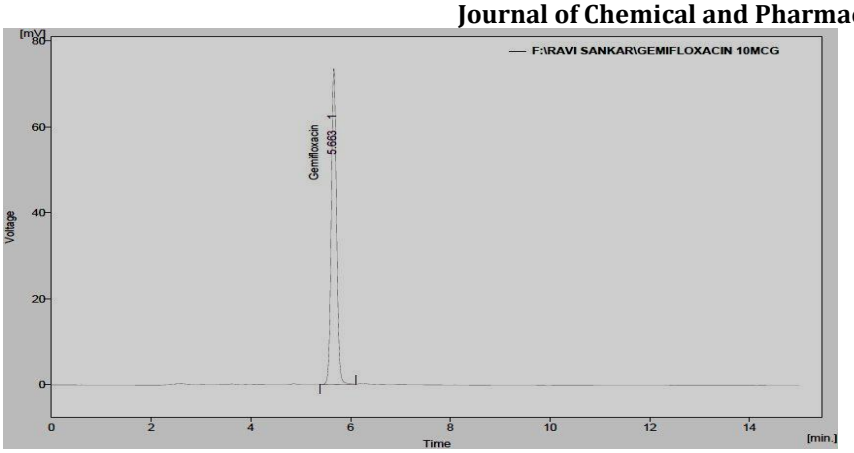

Fig. 8: Standard chromatogram of Gemifloxacin (10 µg/mL)

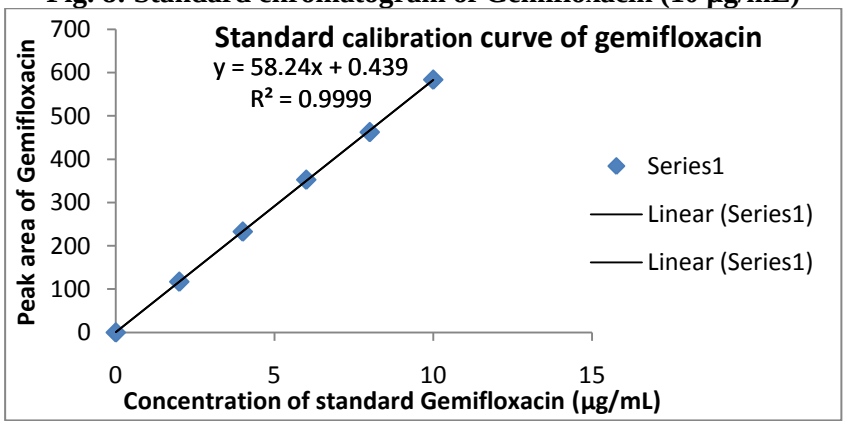

Fig. 9: Calibration plot of Gemifloxacin

4. CONCLUSION

The developed HPLC technique is precise, specific, robust and accurate. Results of analysis of pharmaceutical formulations reveal that the proposed methods are suitable for their analysis with virtually no interference of the usual additives presented in pharmaceutical formulations. This method is simple, reliable, accurate, linear, sensitive, economical and reproducible. Statistical analysis also proves that the method is suitable for routine quality control analysis of gemifloxacin in active pharmaceutical ingredient (API) and pharmaceutical preparations.

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