

Gatifloxacin: A Comprehensive Review on Analytical Method

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***Corresponding Author:** Pritam S Jain, R.C. Patel Institute of Pharmaceutical Education and Research, India.**Received:** April 08, 2019; **Published:** May 03, 2019**DOI:** 10.31080/ASPS.2019.03.0272**Abstract**

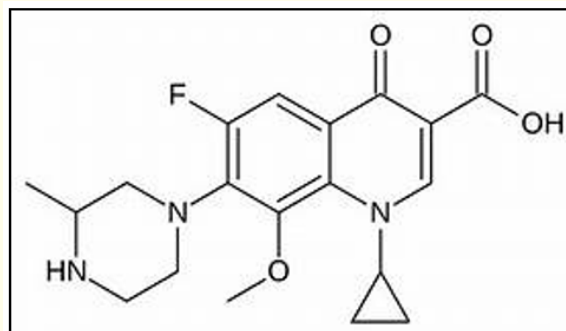
This review focuses on the recent advances in analytical techniques for assessment of Gatifloxacin only or in combinations with other drugs in various biological media. Gatifloxacin is an 8-methoxyfluoroquinolone with improved activity beside Gram-positive, anaerobes, and broad-spectrum activity against Gram-negative bacteria. This article investigate that published analytical methods mentioned so far in the literature for the quantification of GA in pharmaceutical preparations and biological fluids. GA accessible single or in combination with added drugs in pharmaceutical matrices with many drugs like Levofloxacin, Moxifloxacin, Dexamethasone, Satranidazole, Difluprednate. They include different techniques similar to High-performance liquid chromatography, Spectrophotometry, electrochemical methods, Spectrofluorometric and High-performance thin layer chromatography. The concise reviews demonstrate the percentage utilization of the different approaches for analysis of GA.

Keywords: Gatifloxacin; Review; Analytical Method; Chromatography**Abbreviations**

GA: Gatifloxacin; SAR: Structural Activity Relationship; OZ: Ornidazole; LOM: Lomefloxacin; LEV: Levofloxacin; AM: Ambroxol Hydrochloride; DFP: Difluprednate; SAT: Satranidazole; DNA: Deoxyribonucleic Acids; HPLC: High Performance Liquid Chromatography; RP-HPLC: Reverse Phase High Performance Liquid Chromatography; PRED: Prednisolone Acetate; MOX: Moxifloxacin; TRO: Trovafloxacin; RSD: Relative Standard Deviation; LOD: Limit of Detection; LOQ: Limit of Quantitation.

Introduction

Gatifloxacin is chemically known as 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl piperazin-1yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid. GA is a well know fourth-generation fluoroquinolone. GA has a broad spectrum of activity, with dynamic outstanding activity against atypical organisms and Gram-negative bacteria, as well as activity against Gram-positive bacteria [1]. Gatifloxacin is well absorbed from the gastrointestinal (GI) tract (oral availability approximately 100%), and concomitant administration of a continental breakfast, 1050 kcal, had no effect on its availability [2]. The standard dose for GA is 400 mg once a day and both oral and IV formulations are available [3,4].

**Figure 1:** Structure of Gatifloxacin.**Chemistry of gatifloxacin**

SAR studies of Gatifloxacin fluoroquinolone (GA) antibacterial entities demonstrated that the basic group at the C-7 position is the most accommodable site for chemical change and an area that considerably affects their potency, spectrum and safety [5]. Pyrrolidinyl and Piperazinyl type side chains have been proven to be the optimal substituent. For example, several of the early fluoroquinolone (ciprofloxacin and ofloxacin), have a Piperazinyl group at the C-7 position, and introduction of the noted pyrrolidine derivatives to

the fluoroquinolones (moxifloxacin and trovafloxacin) resulted in a dramatic advancement of Gram-positive activity [6,7]. Fluoroquinolones act by obstructing two enzymes involved in bacterial DNA synthesis, both of which are DNA topoisomerases that human cells lack and that are essential for DNA replication of bacteria, thereby allowing these agents to be both bactericidal and specific.

Figure 2: Structure activity relationships in the fluoroquinolone nucleus.

Pharmacokinetic properties

The Gatifloxacin drug has high oral bioavailability about 96%, and hence, intravenous and oral formulations are interchangeable and bioequivalent. GA has a low protein binding (~20%), large volume of distribution (~1.8 L kg⁻¹) and broad tissue distribution and is primarily excreted unchanged in the urine (180%). The drug has high oral bioavailability near about 96% and therefore, intravenous and oral formulations are interchangeable and bioequivalent. Gatifloxacin has a low protein binding (~20%), large volume of distribution (~1.8 L/kg), and broad tissue distribution and is primarily excreted unchanged in the urine (180%) [8].

Pharmacodynamic properties

GA be able to administered externally dose modification in patients with hepatic impairment, in women and in the elderly. Clinical studies and in-vitro experiments designate that GA does not associate with drugs metabolized by the cytochrome P450 enzyme family. At therapeutically valid doses, Gatifloxacin is pharmacodynamically linked parameters (the ratio of the AUC to minimum inhibitory concentration and the ratio of Max. serum concentration to Mini. inhibitory concentration) are near to each other or better than those of other fluoroquinolones. Clinical studies indicate that

Gatifloxacin has insufficient potential to prolong the QT interval on the electrocardiogram and lacks the potential to cause crystaluria as well as produce photosensitivity reactions, make alteration to oral glucose tolerance [8].

Analytical method

The substantial literature survey exposed that, many analytical methods have been discover for validation and development of analytical methods for identification and quantification of drugs and other molecules of interest in Pharmaceutical Matrices. More analytical methods were ornamented for the determination of Gatifloxacin in biological fluids and in pharmaceutical formulations. Such as HPLC, RP-HPLC, UV Visible spectroscopy, Spectrofluorometry, absorption ratio method and electrochemical method, has been developed. Methods such as HPLC, electrochemical analysis and simultaneous UV spectroscopic methods of Gatifloxacin are reported for estimation of Gatifloxacin alone or in combination with others Levofloxacin, Moxifloxacin, Dexamethasone, Satranidazole, Difluprednate, and Difluprednate.

Bioanalytical method

The development of a reliable bioanalytical methods are of predominant importance throughout the duration of drug discovery and development, culminating in a marketing approval. Bioanalysis, employed for the quantitative estimation of drugs entities as well as their metabolites into biological fluids, plays a important role in the interpretation and evaluation of PK, toxic kinetic studies and bioequivalence [9].

HPLC

High performance liquid chromatography was developed early in the year 1960. HPLC is a type of liquid chromatography method, where separation occurs between a stationary phase and a mobile phase. Separation is depends upon the nature of the stationary phase, the separation process can be of four different modes: partition chromatography, ion-exchange chromatography, adsorption chromatography, and size exclusion chromatography. It is an instrumental analytical method that gained increased acceptance mainly because it met two basic factors: (a) the need for methods that can be simply mechanical, and (b) the need for a wide range of accelerated analysis for nutrients. HPLC method is administered to several categories of substances such as lipids, carbohydrates, vitamins, synthetic colorings, additives, natural pigments, and amino acids contaminants [10]. Estimation of Gatifloxacin in single or in combination with added drugs in biological fluid and pharmaceutical matrices by HPLC are note down in Table 1.

Sr. No	Drugs	Matrix	Column	Mobile phase	Detector	Lambda Max	Linearity	LOD and LOQ	System suitability	Ref
1	GA	Bulk drug and pceutical preparations	RP SUPE-LCO® 516 C ₁₈ DB, 50306-U, column	disodium hydrogen phosphate buffer: acetonitrile (75:25, v/v)	UV-visible detector model SPP-6A	293 nm	4.0–40 µg/mL	LOD -6.507 µg/mL LOQ- 1.538 µg/mL	RT- 2.767 min	[11]
2	GAT SAT	Bulk and Tablet	RP Lichrospher 100 C ₁₈	Water: Acetonitrile: Triethylamine (75:25:0.35, v/v/v)	Hitachi L - 7420 UV - Visible detector	320 nm	1-70 µg/mL	LOD- 0.5µg/mL 0.803ug/ml LOQ- 1.0 µg/mL 2.411ug/ml	RT- 6 min TP- 3725.8 TF - 1.66	[12]
3	GA	Pure form	RP Stainless steel C ₁₈ column	Buffer: acetonitrile (80:20)	UV/VIS detector model 1575	210 nm	10-50µg/mL	LOD- 6.5 µg/mL LOQ- 21.33 µg/mL	RT- 1085 min TP - 7271	[13]
4	GA DFP	Bulk and Tablet	C ₁₈ column (250 mm x 4.6 mm,5µ)	Methanol: 0.01M Disodium hydrogen phosphate (60 :40 v/v)	PDA detector	242 nm	60-360 µg/mL	LOD -6.5 µg/mL- LOQ- 21.33 µg/mL	RT- 3.01	[14]
5	GA	Pure form and Ophthalmic Solution	RP HPLC Inertsil C ₁₈ column	0.1 M sodium dihydrogen phosphate Buffer: acetonitrile (70:30 v/v)	PDA detector	254 nm	25-150 µg/mL	LOD -1.2 µg/mL LOQ- 2.8 µg/mL	TF- 1.23 TP-2605.79	[15]
6	GA and AM Tablet	Tablet dosage forms	RP HiQ Sil C ₁₈ column	Potassium dihydrogen orthophosphate buffer and acetonitrile (70:30, v/v)	UV-2075 variable wavelength detector	247 nm	GA- 10–60 µg/mL AM- 5–30 µg/mL	GA- LOD- 0.3 µg/mL LOQ- 0.5 µg/mL	-	[16]

7	GA, LEV, LOM	Bulk drug	LiChrospher® 100 RP-C ₁₈ column	Water: Acetonitrile (80:20, v/v)	UV detector	179-295 nm	4.0 to 24.0 µg/mL	GA- LOD- 0.13 µg/mL LOQ- 0.39µg/mL	GA- RT- 4.14 LEV- RT- 2.37 LOM- RT- 2.81	[17]
8	GA	Tablet	RP X terra C ₁₈ column (4.6 mm 150 mm)	Buffer: acetonitrile (60:40 v/v)	Dual lambda absorbance uv-visible detector	298 nm	0.01 to 0.50 µg/ml	LOD- 0.13µg/mL LOQ- 0.39 µg/mL	RT- 2.34 TF- 0.5123 TP- 10012	[18]
9	GA, OZ	Tablet	C ₁₈ column	Acetonitrile: 0.025M Potassium dihydrogen-phosphate buffer (50:50 v/v)	UV Detector	300 nm	2-24 µg/mL	LOD -0.0004 µg/mL LOQ- 0.0012 µg/mL	RT- 2.89 min TF- 1.25 TP- 37108.8	[19]
10	GA Keto-lac Trometham-ine	Pure form	RP BDS Hypersil C8 column (250×4.6 mm)	Methanol: Phosphate buffer (pH 3.0) (55:45 v/v)	UV detector.	270 nm	GA- 30-90 µg/mL Ketorolac Trometham-ine- 50-110 µg/mL	-	-	[20]
11	GA and Dexamet-hason	Pure form	Hypersil C ₈ column (0.250 m X 4.6 mm)	0.02 M phosphate buffer: Methanol (42:58 v/v)	DAD Detector.	270 nm	GA- 0.000040-0.000280 mol/L	-	RT- 3.38 min TF- 1.41 TP- 4588	[21]

Table 1: HPLC analytical determination of GA.

Analytical determination of Gatifloxacin

Ibrahim A. Aljuffali, *et al.* (2014) proposed a quantitative determination of Gatifloxacin into solid lipid nanoparticles (SLNs), eye-drops and tablets employing a very rapid and easy chromatographic technique was developed and validated. Formulations

were analyzed using a reverse phase SUPELCO® 516 C₁₈-DB, 50306-U, HPLC column (250 mm × 4.6 mm, 5 µm) and a mobile phase consisting of acetonitrile: disodium hydrogen phosphate buffer (25:75, v/v) and with orthophosphoric acid pH was make up to 3.3. The analyte flow rate was adjusted to 1 mL min⁻¹ and analyte concentra-

tions were estimated with the help of UV- visible detector at 293 nm wavelength. The analysis was carried out at room temperature (RT- $25 \pm 2^\circ\text{C}$). Gatifloxacin was parted from all the formulations within 2.767 min. There were linear calibration curves over a concentration range of $4\text{--}40 \mu\text{g mL}^{-1}$ as well as correlation coefficients i.e. R_2 was found to be 0.9998 with an average recovery more than 99.91%. Detection of analyte from different formulations at the similar R_t indicates the specificity and stability of the developed method [11].

N. J. Shah, *et al.* (2009) proposed a easy, accurate, precise as well as precise reverse phase high performance liquid chromatographic method has been developed and validated for the determination of Gatifloxacin and Satranidazole simultaneously into combined dosage forms. A Lichrospher 100 C18 and having mobile phase of Triethylamine: Acetonitrile: Water (0.35: 25: 75, v/v/v) were utilised for separation. pH was accustomed up to 3.2 ± 0.02 with 10% v/v o-phosphoric acid. Measurements were made at the effluent flow rate of 1.0 mL min⁻¹ through injection quantity up to 20 μl and ultraviolet (UV) detection was carried out at 320 nm, as in cooperation components shows logical good response at this wavelength. The retention times (R_t) of Gatifloxacin and Satranidazole were 3.44 min and 6.0 min, respectively. The planned method was validated in appearance of linearity, precision, accuracy, specificity and robustness. Linearity of Gatifloxacin as well as Satranidazole was established to be in the range of $1\text{--}70 \mu\text{g/mL}$ and $1\text{--}70 \mu\text{g/mL}$, correspondingly. Average proportion recoveries obtained for Satranidazole and Gatifloxacin were 99.80 % and 100.20 %, correspondingly. The limit of detection and limit of quantification were originate to be 0.3 and 1.0 mg/mL for Satranidazole, correspondingly and for Gatifloxacin were 0.5 and 1.0 mg/mL, correspondingly. The process is helpful in the quality control of bulk manufacturing as well as pharmaceutical dosage forms [12].

Ankit Agarwal, *et al.* (2013) initiated an easy, hasty accurate HPLC process for instantaneous quantitative assessment of Dexamethasone and Gatifloxacin in ophthalmic solution. Chromatographic separation was implemented with PDA detector utilizing Inertsil C₁₈, (250 x 4.6mm, 5 μ) reverse phase analytical column. The mobile phase consists of Acetonitrile: Buffer (30: 70 v/v), was introduced through the column at flow rate (R_t) of 1.0 mL/min. The method was executed at wavelength 254 nm. The testing was carried out at 30°C. The calibration curve was linear across the concentration series of 25%- 150% of the functioning concentration. The lower limit of quantification (LOQ) was found to be $2.8 \mu\text{g/mL}$ for Gatifloxacin and $1.6 \mu\text{g/mL}$ for Dexamethasone. The accuracy

was found to be in the range (i.e. 98% - 102%) for both Gatifloxacin as well as Dexamethasone. Developed method was utilized for simultaneous quantitative determination of Dexamethasone and Gatifloxacin in ophthalmic formulations and method was validated as per ICH guidelines and most valuable for industrial scale as well as academic [15].

Shahed Mirza, *et al.* (2008) initiated a reversed-phase high performance liquid chromatography (RP-HPLC) analytical technique was developed as well as validated intended for quantification of GA and AM, starting its tablet formulations. The chromatographic separation was achieved through utilizing a HiQ Sil C₁₈ column (250 mm x 4.6 mm, 5 μm), through a mobile phase having a blend of 0.01 mol L^{-1} Potassium dihydrogen ortho phosphate buffer (PDP) and Acetonitrile (70:30, v/v), and pH accustomed to 3 with ortho-phosphoric acid, at a flow rate of 1 mL/min. The technique was performed at wavelength 247 nm. Separation was concluded in a lesser amount of 10 min. As for every International Conference on Harmonisation (ICH) guidelines the process was validated for linearity, accuracy, precision, limit of quantitation, limit of detection, and robustness. The linearity of Gatifloxacin was obtained in excess of the series of $10\text{--}60 \mu\text{g/mL}$ and so as to Ambroxol hydrochloride was found to be $5\text{--}30 \mu\text{g/mL}$. The correlation coefficients (r_2) were establish to 0.9996 for Gatifloxacin (GA) along with 0.9992 for Ambroxol hydrochloride (AM). The tablet analysis ($n = 5$) were originate to be 99.94% with $\pm 0.25\%$ standard deviation (SD) in totalling to 99.98% with $\pm 0.36\%$ SD on behalf of GA and AM correspondingly. Percent recovery of GA was found to be 99.92%-100.02% and that of AM was 99.86% -100.16%. The assay experimentation shows that the technique is free from intervention of recipients. This demonstrates with the purpose of the residential HPLC technique is trouble-free, linear, precise and accurate, as well as can be conveniently adopted for the schedule quality control analysis of the tablet [16].

Bioanalytical determination of Gatifloxacin

Leandro Tasso, *et al.* 2007 instigate involuntary coordination utilizing an on-line solid phase withdrawal and HPLC through fluorimetric detection was developed as well as validated for quantification of Gatifloxacin within rat plasma. The extraction was conceded out by means of C₁₈ cartridges (Bond Elute), through a high extraction yield. Following washing, GA was eluted commencing the cartridge through mobile phase by using C₁₈ HPLC analytical column. The mobile phase having a blend of Phosphoric acid (2.5 mM), Acetonitrile, Methanol and Triethylamine (64.8:20:15:0.2,

v/v/v/v) as well as pH accustomed to 2.8. Every one standard as well as samples solutions were chromatographed at 28°C. The technique fashioned was selective and linear for drug over the concentrations series between 20 and 600 ngmL⁻¹. The recovery series intended for Gatifloxacin was establishing to 95.6 to 99.7%, as well as the limit of quantification (LOQ) was originate as 20ng/mL. The inter and intraday-assay accurateness were awake to 94.3%. The precision approximately not more than 5.8% in favour of coefficient of variation. High yield obtained up to 95%. Drug stability within plasma was exposed in freezer at -20°C up to 1 month, following three freeze-thaw cycles and in favour of 24 hrs in the auto-sampler after processing. The assay method has effectively functional to evaluate gatifloxacin plasma concentrations in pharmacokinetic study with rat [23].

Angelo Spadaro, *et al.* 2015 initiate in order to improve the frequent dosing regimen reported for the commercial aqueous gatifloxacin eye drops, two new ophthalmic mucoadhesive formulations based on high molecular weight sodium hyaluronate were prepared. The pharmacokinetic profiles outlined showed a strong bioavailability increase for Gatifloxacin hyaluronate formulations with respect to aqueous conventional eye drop. Gatifloxacin quantification in aqueous humour of albino rabbits was performed by an extremely simple, rapid, direct, sensitive and specific HPLC-UV method. Separations were obtained on an Adsorbosphere HS C₁₈ column using CH₃CN and an aqueous solution of 10 mM SDS, 10 mM TBAA and 25 mM citric acid (pH 2.5) (50:50 v/v). Detection was performed at 293 nm using a flow rate of 1.0 mL/min. The developed method fulfils the validation requirements of FDA and EMEA and it is suitable for the pharmacokinetic study in rabbit eye [24].

Sr. No	Drug	Matrix	Column	Mobile phase	Detector	Linearity	ACC and Preci	LOD & LOD	Ref
1	GA	Pure form	Nucleosil-100 5C ₁₈ column	Acetonitrile: 0.1 M phosphoric acid (90: 10 V/V)	Fluorescence detector	0.025- 5.00 mg L ⁻¹	Acc- 102.2.3 %	LOD-Serum- 0.03 mg/L Urine- 1.7 mg/L LOQ- Serum- 0.06 mg/L Urine- 3.5 mg/L	[22]
2	GA	Pure form	Bond Elut C ₁₈ , (10 mm × 2 mm) column	2.5 mM phosphoric acid methanol: acetonitrile: triethylamine (64.8:15:20:0.2, v/v/v/v)	RF-10AXL detector	20 - 600 ng/ml	Accu- 95.6 -99.7% Price- Intraday- 5.2-5.7% Intraday- 4.8-5.8%	LOQ- 20 ng/ml	[23]
3	GA	Mucoadhesive Formulations	Adsorbosphere HS C ₁₈ column	CH ₃ CN:10 mM sodium dodecyl sulfate (50:50) 10 mM tetrabutylammonium acetate: 25 mM citric acid (pH 2.5) (50:50 v/v).	PDA Detector	50-3000 ng/m	Acc- 1.4-4.94% Price- Interday- 98.42 to 99.71% Intra- day- 98.67 to 99.64%	LOD- 18 ng/mL LOQ- 50 ng/ml	[24]

4	GA LEV MOX TRO	Pure form	RP LiChroC-ART® Purosphere Star C ₁₈ column (55 mm × 4 mm)	Methanol: 37% hydrochloric acid (99.5:0.5, v/v)	UV Detector	GAT -0.005–5 µg/mL LEV - 0.02–5 µg/mL MOX- 0.04–5 g/mL	Acc- GA- 6.80% LEV-10.49 % MOX-10.83% Prici-Inter-day- 98.42 to 99.71% Intra-day- 98.67 to 99.64%	LOD- GA-0.0025 LEV-0.01 MOX-0.02 µg/mL LOQ- GA-0.005 LEV-0.02 MOX-0.04 µg/mL	[25]
5	GA	Pure form and Tablet	X-Terra RP C ₁₈ column	Water:acetonitrile (90:10)	DAD and fluorescence detector	DAD- 0.02 -2.00 µg/mL Fluorescence 2 to 20 µg/mL	Acc- DAD- 95% Fluorescence - 95% Prici- DAD- 3.4% µg/mL Fluorescence- 2.8% µg/mL	DAD- LOD- 0.7 µg/mL LOQ- 0.01 µg/mL Fluorescence- LOD- 2.3 µg/mL LOQ- 0.03 µg/mL	[26]
6	GA	Pure form	VP-ODS C ₁₈ (250 mm×4.6 mm) analytical column	Triethylamine phosphate (1%, pH4.30): Acetonitrile (13:87, v/v)	Diode array detector	5–200 ng/mL	Accu- 102.0 Prici- 2.3%	LOD- 30 ng/mL	[27]
7	GA	Pure form	RP X Terra MS C18 (3mm×50 mm) column	0.025M disodium hydrogen phosphate: Acetonitrile (80:20 v/v)	Diode array detector	0.10–6.0 µg/ml	Accu- 99–107% Prici-Intra-≤2.77% Inter- ≤4.59%	LOQ- 0.10.µg/ml	[28]

Table 2: HPLC bioanalytical methods for Gatifloxacin.

Spectrophotometric method

A compilation of the new developments in terms of detection, detections systems and detection strategies in Ultraviolet-Visible (UV-Vis) spectrophotometry is presented and discussed. It is shown that this evolution has promoted the use of UV-Vis spectrophotometry as a simple, sensitive, reliable, and low cost technique, that allows the determination of very low concentrations of compounds, and the use of very small amounts of samples [29]. Ultraviolet and Visible absorption spectrophotometry is the technique based on attenuation of electromagnetic radiation measurement by an absorbing substance. The function of a UV-Vis detector is to convert a light signal into an electric signal [30].

In the literature survey total 11 methods were reported for the estimation of GA using spectrophotometry, of which 6 methods are for estimation GA alone, while the others GA in combination with other drug substances. In the literature also, 2 spectrofluorometric methods have been established of GA. Spectrophotometric and spectrofluorometric methods have been presented for the determination of GA alone and in Combinations are note down in Table 3.

Estimation of GA as single entity

K.Venugopal., *et al.* (2005) Novel, easy and price effective UV-spectrophotometric methods were developed for the evaluation of Gatifloxacin in bulk and pharmaceutical formulations. Gatifloxacin

was analysed at 286nm having 100 mM phosphate buffer (pH 7.4) as well as at 292 nm having 100 mM hydrochloric acid (pH 1.2). Linearity range was found to be 1–18 µg/mL (regression equation: absorbance = 0.0684 × Concentration in µg/mL + 0.0050; r² = 0.9998) in the phosphate buffer (pH 7.4) and 1–14 µg/mL (regression equation: absorbance = 0.0864 × Concentration in µg mL⁻¹ + 0.0027; r² = 0.9999) in hydrochloric acid medium (pH 1.2). The apparent molar absorptivity was found to be 2.62 × 10⁴ l mol⁻¹ cm⁻¹ in the phosphate buffer and 3.25 × 10⁴ l mol⁻¹ cm⁻¹ in hydrochloric acid media. In cooperation the projected techniques sandell's sensitivity was found to be regarding 0.01 µg cm⁻²/0.001A. These

methods were experienced and validated for different constraints with regards to ICH guiding principle and USP. The quantitation limits were found to be 0.312 and 0.3 µg ml⁻¹ in the phosphate buffer and hydrochloric acid medium, respectively. The projected systems were effectively applied for the determination of Gatifloxacin into pharmaceutical formulations (tablets, ophthalmic solution as well as injection). The results recognized that the modus operandi is accurate, precise as well as reproducible (relative standard deviation < 2%), while being easy, inexpensive and not as much of time consuming and can be rightfully useful for the assessment of Gatifloxacin in unlike dosage forms and dissolution studies [31].

Sr. No	Drug	Method	Lambda Max	Linearity	LOD/LOQ	Correlation coefficient (R ²) Value	Ref
1	GA	UV-Vis NIR spectrophotometric Method	Phosphate buffer (pH 7.4) -286nm Hydrochloric acid (pH1.2)- 292 nm	Phosphate buffer (pH 7.4) - 1-14 µg/mL Hydrochloric acid (pH1.2) - 1-18 µg/mL	LOD-PDP (pH 7.4) -0.103µg/mL Hydrochloric acid (pH1.2)- 0.099 µg/mL LOQ- PDP (pH 7.4) -0.312µg/mL Hydrochloric acid (pH1.2)- 0.300 µg/mL	Phosphate buffer (pH 7.4) -0.999 Hydrochloric acid (pH1.2)- 0.999	[31]
2	GA + PRED	First-order UV derivative Spectrophotometric method	GA - 348 nm PRED -263 nm	GA - 3-21 µg/mL PRED - 6-42 µg/mL	GA - LOD- 0.33 µg/mL LOQ- 0.10 µg/mL PRED -LOD- 0.16 µg/mL LOQ- 0.55 µg/mL	GA- 0.999 PRED- 0.999	[32]
3	GA + DFBA	UV-SpectrophotometricQ-Absorption Ratio Method	GA - 241 nm DFBA- 236 nm	GA - 1-30 µg/mL DFBA - 1-30 µg/mL	GA - LOD- 0.06 µg/mL LOQ- 0.20µg/mL DFBA - LOD- 0.05 µg/mL LOQ- 0.173 µg/mL	GA- 0.998 DFBA - 0.999	[33]
4	GA	Area under curve spectrophotometric method	316-346 nm	5-25 µg/mL	-	GA- 0.999	[34]
5	GA	Spectrophotometric method	BCG- 415 BCP- 412 BPB- 417 BTB- 414	BCG- 2-20 µg/mL BCP- 2-14 µg/mL BPB- 2-16 µg/mL BTB- - 2-16 µg/mL	BCG- LOD- 0.218 µg/mL LOQ- 0.950 µg/mL BCP- LOD- 0.252 µg/mL LOQ- 0.840 µg/mL BPB- LOD- 0.312 µg/mL LOQ-1.03µg/mL BTB- LOD- 0.232 µg/mL LOQ- 0.773 µg/mL		[35]

6	GA + AMB	Spectrophotometric method	GA- 286 nm AMB- 242 nm	GA- 4-16 µg/mL AMB- 10 - 50 µg/mL	LOD-1.4 and 1.9 µg/mL	GA- 0.9994 AMB- 0.9952	[36]
7	GA + AM	Spectrophotometric methods	GA- 289 nm AM- 246 nm	GA- 2-10 µg/mL AM- 5 - 15 µg/mL	-	GA- 0.9907 AM- 0.9896	[37]
8	GA + PRED	Spectrophotometric methods	GA - 292 nm PRED -242 nm	GA - 0.6-3 µg/mL PRED - 2-10 µg/mL	GA - LOD- 0.01388 µg/ml LOQ- 0.04208 µg/ml PRED - LOD- 0.02782 µg/ml LOQ- 0.08432 µg/ml	GA- 0.999 PRED- 0.999	[38]
9	GA	spectrophotometric method	GA - 287 nm	4 to 14 µg/mL	GA - LOD- 0.21 µg/ml LOQ- 0.64 µg/ml	GA- 0.999	[39]
10	GA	spectrofluorometric method	487 nm after excitation at 290 nm	10 to 100 ng/ml	GA - LOD- 0.2305 ng/ml LOQ- 0.6986 ng/ml	GA- 0.9996	[40]
11	GA	spectrofluorometric method	470 nm after excitation at 292 nm	ASM- 0.040-0.700 µg/mL MEM- 0.020-0.450 µg/mL	ASM- LOD- 10 µg/ml LOQ- 30 µg/ml 0.6986 ng/ml MEM- LOD- 2 µg/ml 0.2305 ng/ml LOQ- 6 µg/ml	ASM- 0.9997 MEM- 0.9998	[41]

Table 3: Spectrophotometric and Spectrofluorimetric methods for estimation of GA alone and in combined dosage form.

Mangal Gahandule., *et al.* (2017) the aim of present work was to develop an accurate, simple and cost effective UV spectrophotometric method for estimation of gatifloxacin. This method was based on area under curve of UV spectrum between 316 – 346 nm and validation as per ICH guideline Q2 (R1). The method has followed linearity in the range of 5-25 µg/ml. The value of correlation coefficient was 0.999. Satisfactory value of percent relative standard deviation for the intraday and inter-day precision indicates that method was precise. Result of the recovery studies (102%) shows accuracy of method. The developed technique can be used for schedule assessment of Gatifloxacin into bulk as well as dosage form. The developed method can be concluded as accurate, sensitive and precise and can be easily applied to the pharmaceutical formulation [34].

Alaa S. Amin., *et al.* (2017) Straightforward, rapid, and extractive spectrophotometric method were developed for the determination of Gatifloxacin (GA) into bulk as well as in to pharmaceutical dosage

form. These methods are based on the formation of yellow ion-pair complexes between the basic nitrogen of the drug and three sulphophthalein acid dyes, namely; bromocresol green (BCG), bromocresol purple (BCP), bromophenol blue (BPB) and bromothymol blue (BTB) in phthalate buffer pH 3.0, 3.4 and 3.2, using BCG, BCP and (BPB or BTB), respectively. The formed complexes were extracted with chloroform and measured at 415, 417, 412 and 414 nm for BCG, BPB, BCP and BTB, respectively. The analytical parameters and their effects on the reported systems are investigated. The reactions were extremely rapid at room temperature and the absorbance values remains unchanged at 48 h for all reactions. Beer's law was obeyed in the ranges 2.0–20, 2.0–14 and 2.0–16 µg mL⁻¹ for BCG, BCP and (BPB or BTB), respectively. The composition of the ion pairs was found 1:1 by Job's method. Beer's law substantiation accuracy, precision, limits of detection, limits of quantification. The projected processes have been applied effectively for the investigation of the drug bulk form as well as its dosage form. The results

were in good quality concurrence with those obtained by the administrators as well as reported methods [35].

Estimation of GA in Combinations

Sversut, R.A., *et al.* (2014) an uncomplicated technique used for instantaneous determination of Gatifloxacin as well as Prednisolone acetate into ophthalmic formulation was developed and validated by means of UV spectrophotometry. Gatifloxacin and Prednisolone acetate were enumerated by means of the first-order derivative of the UV spectra. The projected technique was validated according to the guiding principle of the International Conference on Harmonization as well as the Association of Official Analytical Chemists International. The measurements were completed having acetonitrile: water (70:30 v/v) at 348 nm used for Gatifloxacin as well as having Prednisolone acetate at 263 nm. The calibration curves were linear having concentration assortment of 3–21 $\mu\text{g mL}^{-1}$ used for Gatifloxacin as well as 6–42 $\mu\text{g mL}^{-1}$ for Prednisolone acetate by means of Sandell's sensitivities of 0.349 $\mu\text{g cm}^{-2}$ and 0.402 $\mu\text{g cm}^{-2}$, correspondingly. The represent recovery and the limit of quantification for Gatifloxacin having 99.76 \pm 0.41% as well as 1.11 $\mu\text{g mL}^{-1}$ and for Prednisolone acetate were 99.52 \pm 0.87% as well as 0.55 $\mu\text{g mL}^{-1}$, correspondingly. The technique was precise, among a relative standard deviation of fewer than 2.50% for both drugs. For robustness, the feature analyzed did not extensively influence the quantification of Gatifloxacin and Prednisolone acetate. The results of the validated process did not be at variance notably from high-performance liquid chromatography (HPLC), which was up to that time developed and validated for the identical drugs. In this type, the technique was appropriate for regular analysis of Gatifloxacin and Prednisolone acetate within their combined dosage form in ophthalmic formulations [32].

Parth Patel., *et al.* (2001) two uncomplicated, susceptible, precise, accurate and inexpensive UV-Spectrophotometric technique developed for the quantitative evaluation of Difluprednate and Gatifloxacin into bulk and combined ophthalmic emulsion. The first technique concerned for determination of Difluprednate and Gatifloxacin by means of the Q-absorption ratio method, which involves the formation having Q-absorbance equation found at 236 nm (iso-absorptive point) as well as at 241 nm, it is λ -max of Difluprednate. The linearity was achieved in the concentration assortment of 1–30 $\mu\text{g/mL}$ for both the drugs. The second technique involved determinations of these two drugs by means of the first-derivative spectrophotometric techniques were completed at 322.60 nm (ZCP of Difluprednate) used for Gatifloxacin as well as 263.20 nm (ZCP of

Gatifloxacin) for Difluprednate. The linearity was achieved in the concentration range of 5–35 $\mu\text{g/mL}$ intended for Difluprednate as well as 10–70 $\mu\text{g/mL}$ for Gatifloxacin. These techniques were sequentially useful to pharmaceutical formulations because no interferences from the ophthalmic emulsion recipients were found. The appropriateness of these techniques for the quantitative estimation of the compounds was demonstrated by validation [33].

S. Lakshmana Prabu., *et al.* (2010) narrative, straightforward, sensitive, rapid spectrophotometric technique has been developed for instantaneous estimation of Gatifloxacin (GA) and Ambroxol hydrochloride (AMB). The technique implicated solving simultaneous equations based on extent of absorbance having two wavelengths at 286nm as well as 242 nm, λ_{max} of GA and AMB in that order. Beer's law was obeyed in the concentration range of 4–16 $\mu\text{g/ml}$ and 10 – 50 $\mu\text{g/ml}$ for GA and AMB respectively. The method was validated for accuracy, precision and recovery studies. Statistical analysis proved the method was precise, reproducible, selective, specific, and accurate for analysis of GA and AMB. The wide linearity range, sensitivity, accuracy, and simple procedure imply that the proposed technique demonstrated to be appropriate for routine analysis and quality control assays of tablets [36].

B.Prathap, G. Nagarajan., *et al.* (2011) a simple, fast and precise simultaneous estimation method using Vierordt's method has been developed for the simultaneous determination of Gatifloxacin and Ambroxol hydrochloride in pure and combined tablet dosage form. Shimadzu UV-1700 instrument was used and λ_{max} of Gatifloxacin and Ambroxol hydrochloride was found to be 289 and 246nm, respectively using methanol and 0.1M sodium hydroxide in the ratio of 8:2. Gatifloxacin and Ambroxol hydrochloride were found to be linear in the concentration of 2–10 $\mu\text{g/ml}$ and 5–15 $\mu\text{g/ml}$, respectively at their wavelengths. Amount found for Gatifloxacin and Ambroxol hydrochloride was found to be 397.61 and 73.91mg/tablet, respectively. Percentage recovery range was found to be within 99.45–100.3% for Gatifloxacin and 99.73–103.42% for Ambroxol hydrochloride. The percentage RSD was found to be lower than 2% proves that the method is precise. The application of simultaneous equation method by UV spectroscopy can be employed for the estimation of Gatifloxacin and Ambroxol hydrochloride for routine analysis for a combination containing these two components in pure and tablet dosage forms [37].

Jugalkishor Vijay Bhandari., *et al.* (2018) UV spectrophotometric technique has been developed as well as validated meant for the determination of Gatifloxacin and Prednisolone Acetate into bulk

and eye drop. The λ_{max} of Gatifloxacin and Prednisolone Acetate were found to be 292 nm and 242nm, respectively, in methanol. Beer's law was complied through the conc. range of 0.6-3 $\mu\text{g}/\text{ml}$ and 2-10 $\mu\text{g}/\text{ml}$ with correlation coefficient of 0.999 and 0.999 for Gatifloxacin and Prednisolone Acetate, respectively. The result of analysis has been validated as per the ICH guidelines. The developed method is simple, selective and reproducible and can be used for routine analysis of formulations containing Gatifloxacin and Prednisolone Acetate [38].

Spectrofluorometric Methods

Fathy M.M. Salama, *et al.* (2018) a extremely correct and precise Spectrofluorimetric method was recognized for quantitation of Gatifloxacin in pure substance, pharmaceutical formulations as well as in the continuation of its oxidative degradation product. The emission was recorded at 487 nm after the excitation at 290 nm. Using micelle, sodium dodecyl sulphate (SDS), enhanced fluorescence intensity of Gatifloxacin-SDS complex. The optimization of numerous experimental conditions was carried out. The improved emission showed a suitable linear correlation between derivative synchronous fluorescence power and concentration of Gatifloxacin over the range of 10 to 100 ng/mL with a determination coefficient equals 0.9996. Studying cytotoxicity and antimicrobial susceptibility for oxidative degradation product of Gatifloxacin was carried out using Gatifloxacin as a control. In comparison, the proposed method presented a superior sensitivity and enhanced stability over the reported method [40].

Juan Antonio Ocana, *et al.* (2018) a Spectrofluorimetric method to determine gatifloxacin has been developed and applied to the quantification of this fluoroquinolone in spiked human urine and serum. The native fluorescence of Gatifloxacin allow the determination of 0.040-0.700 $\mu\text{g}/\text{mL}^{-1}$ of this molecule in aqueous solution containing acetic acid-sodium acetate buffer (pH 3.5), with $\lambda_{\text{exc}} = 292$ nm and $\lambda_{\text{em}} = 484$ nm. Micelle-enhanced fluorescence led to 75% higher analytical signals in presence of 12mM sodium dodecyl sulphate, which allow the determination of 0.020-0.450 $\mu\text{g}/\text{mL}^{-1}$ fluoroquinolone with $\lambda_{\text{exc}} = 292$ nm and $\lambda_{\text{em}} = 470$ nm. Both methods were successfully applied to gatifloxacin determination in spiked human urine and serum [41].

Electrochemical methods

In the last decade, bio sensing has rapidly evolved and become one of the most important research priorities in analytical chemistry and chemical sensors. Numerous techniques have been re-

ported for the fabrication of the biosensor interface and for constructing whole bio-sensing platforms. The most common modes of transduction include fluorescence, surface plasmon resonance, photoluminescence, surface-enhanced Raman scattering, electrochemiluminescence, photo electrochemistry, and electrochemistry. Amongst these techniques, electrochemical sensors have attracted considerable interest of analysts due to advantages such as rapid sample-to-answer time, high sensitivity, low cost and potential translation in point-of-care settings.

Zhiming Jiang, *et al.* (2016) constructed a new electrochemical sensor for Gatifloxacin based on one-pot electro-polymerization of β -cyclodextrin (β -CD) and reduced-graphene oxide (rGO) modified glassy carbon electrode (GCE) (β -CD/rGO/GCE) was built for the first time. Scanning electron microscope (SEM) image and Infrared spectroscopy (IR) show that polymer of β -cyclodextrin and reduced graphene oxide (rGO) has been successfully modified on electrode. The electrochemical properties of this polymer were characterized by electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV). The optimization of the electro-polymerized cycle, the pH of supporting electrolyte and the accumulation potential and time were discussed in details. Underneath most favourable circumstances, the degree of difference pulse voltammogram (DPV) demonstrated the oxidation peak currents were linearly proportional to Gatifloxacin concentrations into the ranges of 0.05 μM to 150 μM with sensitivity of 0.33 $\mu\text{A } \mu\text{M}^{-1}$. This electrochemical sensor had a low detection limit of 0.02 μM (S/N = 3). Moreover, this proposed sensor exhibited good reproducibility, long-term stability and fast current response. To further study the practical applicability of the proposed sensor, the modified electrode was successfully applied to detect Gatifloxacin in tablets and human urine samples [42].

Jian Y., *et al.* (2012) development of an electrochemical immunoassay to detect Gatifloxacin (GA) residue in swine urine, an electrochemical immunoassay was established. An indirect competitive immunoassay was developed, in which the coating antigen is immobilized in an enzyme linked immunosorbent assay (ELISA) plate and GA residue from the sample competes with the limited binding sites in added anti-GA antibody. Horseradish peroxidase (HRP) conjugated to goat anti-rabbit IgG was used as the enzymatic label. A carbon fibre working electrode was constructed and current signals were detected by using hydrogen peroxide as a substrate and hydroquinone as an electrochemical mediator. The electrochemical immunoassay was evaluated by analysis of GAT in buffer or swine

urine and an average value of half inhibition concentration (IC₅₀) of 8.9 ng/ml was obtained. Excellent specificity of the antibody was achieved with little cross-reaction with Lomefloxacin (3.0%), ciprofloxacin (3.0%), and ofloxacin (1.9%) among commonly used (fluoro) quinolones. In conclusion, the immunoassay system developed in this research can be used as a rapid, powerful and on-site analytical tool to detect GAT residue in foods and food products [43].

Pradeep Kumar Brahman, *et al.* (2012) the electrochemical oxidation of an antibacterial drug, gatifloxacin (GA), at multi-walled carbon nano-tube paste electrode was studied employing cyclic and differential pulse voltammetry methods. The effects of scan rate, pH, different electrolytes, and pulse amplitude and accumulation time on electrochemical behaviour of GA were investigated. GA shows a well-defined oxidation peak at + 1.05 V in acetate buffer of pH 5.0 ± 0.01. Underneath optimized circumstances, the peak current is linear over the concentration range 2.13×10^{-5} – 1.7×10^{-4} M through detection limit of 4.5×10^{-9} M. The applicability of the proposed method is further extended to in vitro determination of the drug in biological fluids. Differential pulse voltammetry and UV-VIS absorption techniques were employed to probe the interaction between GA and calf thymus DNA. The addition of ds-DNA to the analyte containing GA results in a decrease of the peak current and a positive shift of the peak potential of GA in differential pulse voltammetry analysis, indicating the dominance of the intercalating interaction. The spectroscopic data also confirm the interaction between GA and ds-DNA. The combining constant (β) and combining number (m) of GA-mDNA were also determined [44].

Fenfen Zhang, *et al.* (2013) initiate new cysteine acid customized carbon paste electrode (cysteine acid/CPE) lying on electrochemical oxidation of L-cysteine was urbanized to simultaneously determine of Ofloxacin as well as Gatifloxacin within the occurrence of sodium dodecyl benzene sulfonate (SDBS). Fourier transform infrared spectra (FTIR) pointed out that L-cysteine was oxidated to cysteine acid. Electrochemical impedance spectroscopy (EIS) and cyclic voltammogram (CV) designated so as to cysteine acid was effectively modified on electrode. The bulky peak separation (116 mV) among Ofloxacin and Gatifloxacin was achieved on cysteine acid or CPE while merely one oxidation peak was originate on bare electrode. And the peak currents enlarged 5 times measure up to bare electrode. Furthermore, the current might be auxiliary improved in the existence of an anionic surfactant, sodium dodecyl benzene sulfonate. The degree of difference pulse voltammogram (DPV) demonstrated that the oxidation peak currents were linearly com-

parative to their concentrations into the range of 0.06–10 μ M for Ofloxacin and 0.02–200 μ M for gatifloxacin, as well as the detection limits of Ofloxacin and Gatifloxacin were 0.02 μ M and 0.01 μ M (S/N=3), correspondingly. This projected technique was effectively useful to determine Ofloxacin and Gatifloxacin in pharmaceutical formulations as well as in human serum samples [45].

HPTLC methods

Sanjay K. Motwani, *et al.* (2006) straightforward, susceptible, selective and stability indicating high-performance thin-layer chromatographic technique used for determination of Gatifloxacin not in bulk drug but also in polymeric nano-particles was developed and validated for same as per the International Conference on Harmonization (ICH) guidelines. The technique utilized thin-layer chromatography (TLC) aluminium plates permeated with silica gel 60F-254 like the stationary phase and the mobile phase contained n-propanol: concentrated ammonia solution: methanol (5:0.9:1, v/v/v). This solvent system was established to provide solid spots for Gatifloxacin (R_f value of 0.60 ± 0.02). Densitometric assessment of Gatifloxacin was accepted having absorbance mode at 292 nm. The linear regression investigation information for the calibration plots demonstrated good linear relationship through $r = 0.9953$ having the concentration range of 400–1200 ng/spot. The mean value (\pm S.D.) of slope and intercept were 9.66 ± 0.05 and 956.33 ± 27.67 , respectively. The technique was validated for precision, ruggedness, accuracy, and recovery. The limits of detection as well as quantitation were found to be 2.7 and 8.2 ng/spot, in that order. Gatifloxacin was subject to acid as well as alkali hydrolysis, photo degradation, oxidation and dry heat treatment. The drug go through degradation beneath acidic as well as basic conditions and upon wet and dry heat treatment. The degraded compounds were well separated among the pure drug. The numerical assessment display that the developed process for Gatifloxacin as bulk drug and from polymeric nanoparticles is reproducible as well as selective. The technique possibly will successfully separate the drug among its degradation products, be able to employed as stability-indicating one [46].

N. Satheeshkumar, *et al.* (2006) a straightforward and sensitive high-performance thin-layer chromatography (HPTLC) technique was intended for the quantitative assessment of Gatifloxacin as well as Ornidazole in pharmaceutical formulation. Gatifloxacin and Ornidazole were chromatographed on silica Gel 60 F254 TLC plate having n-butanol: ammonia: methanol (8:1.5:1 v/v) mobile phase in addition to detected at 302 nm with a Camag TLC Scanner 3. The R_f value for Gatifloxacin and Ornidazole was observed as 0.21 ±

0.02 and 0.76 ± 0.04 , correspondingly. The linearity of Gatifloxacin and Ornidazole having in the range of 100 - 500 ng/spot and 250 -1250 ng/spot, correspondingly. The LOQ for Gatifloxacin was obtained 40 ng/spot and for Ornidazole was obtained 100 ng/spot. The projected technique was useful for the determination of Gatifloxacin and Ornidazole in combined dosage forms [47].

Figure 3: Overview of analytical methods for estimation of Gatifloxacin in biological and pharmaceutical samples.

Conclusion

In conclusion, abroad ranges of techniques are available for the analysis of Gatifloxacin in biological samples and pharmaceutical formulations. The analysis of the published data revealed that the HPLC was extensively used for the determination of Gatifloxacin in various matrices like plasma, serum and urine. For determination of Gatifloxacin in biological samples, were commend the HPLC-MS/MS method, since this method combines the HPLC separation ability with MS sensitivity and selectivity, allowing the unambiguous identification of Gatifloxacin and its metabolites. For analysis of Gatifloxacin in pharmaceuticals, HPLC with UV detection is applicable because this method provides accurate results and low cost compared to more advanced detection techniques. This review carried out an overview of the current state-of-art analytical methods for the determination of Gatifloxacin.

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