CHAPTER – 2

LITERATURE REVIEW
2. LITERATURE REVIEW

2.1 Literature review of Gatifloxacin

❖ In pharmaceutical formulations

• Non-aqueous titration method

Marona et al (56) reported a non-aqueous titration method for estimation of gatifloxacin in pharmaceutical formulations. 0.1 M perchloric acid was used as a titrant and glacial acetic acid as media.

• Spectrophotometric methods

Reddy et al (57) developed a colorimetric method for determination of gatifloxacin in pharmaceutical formulations. The method was based on reaction between gatifloxacin and ferric alum under acidic conditions to form a colored chromogen with $\lambda_{\text{max}}$ 425 nm.

Rao et al (58) reported three spectrophotometric methods for determination of gatifloxacin. These methods were based on oxidation of gatifloxacin with excess of oxidant. In method A and B N-bromo-succinimidine (NBS) was used as oxidant while in method C, chloramine-T (CAT) was used. The unreacted oxidant was then estimated calorimetrically by an oxidizable dye Celestine blue (CB) in method A; p-N-Me-aminophenol-sulphate (p-MAP)-sulphanilamide (SA) reagent in method B; and gallocyanine (GC) in method C. Linearity range: Method A: 2.0 - 10.0 mg/mL. Method B: 4.0 - 20.0 mg/mL. Method C: 1.0 - 5.0 mg/mL.

Prasad et al (59) reported methods for assay of gatifloxacin in bulk and formulations by visible spectrophotometry. These methods were based on oxidation of drug with excess of NBS and reaction of
unreacted NBS with celestine blue (CB) in method A; with p-N-methyl aminophenol sulfate (PMAP)-sulphanilamide (SA) in method B. Method C was based on reaction of gatifloxacin and folin-ciocalteau reagent and formation of blue colored complex.

Xu et al (60) developed a UV spectrophotometric method for determination of gatifloxacin in capsules dosage form by UV. Gatifloxacin was estimated at $\lambda_{\text{max}}$ 284 nm. Linearity range: 3.0 - 15.0 µg/mL.

Salgodo et al (61) reported a UV spectrophotometric method for determination of gatifloxacin in tablets at 287 nm. Water was used as solvent. Linearity range: 4.0 - 14.0 µg/mL.

Reddy et al (62) developed a method for spectrophotometric determination of gatifloxacin in dosage forms. This method was based on reaction between gatifloxacin and cerric ammonium sulphate to form a yellowish orange colored chromogen which was stable for a long time with $\lambda_{\text{max}}$ 455 nm. Linearity range: 40 - 160 µg/mL.

Venugopal et al (63) developed UV-spectrophotometric method of gatifloxacin in bulk and pharmaceutical formulations. Gatifloxacin was estimated at 286 nm in 100 mM phosphate buffer (pH 7.4) and at 292 nm in 100 mM hydrochloric acid (pH 1.2). Linearity range was found to be 1 - 18 µg/mL in the phosphate buffer (pH 7.4) and 1 - 14 µg/mL in hydrochloric acid medium (pH 1.2).

• Electrophoresis method

Sane et al (64) used capillary zone electrophoresis for the determination of gatifloxacin from its pharmaceutical preparation (tablets), using fused silica capillary. Separation was performed after hydrodynamic injection; the separation was achieved by applying 21 Kv voltage. Phosphate buffer solution (pH 9.5) was
used as separation electrolyte. Detection was done at 280 nm using a UV-detector. Under these experimental conditions the analysis takes 8 min. A linearity range for gatifloxacin was between 20 - 60 \( \mu \text{g/mL} \).

Zhu et al (65) determined gatifloxacin by using developed High performance capillary electrophoresis (HPCE) method. Fused-SiO\textsubscript{2} capillary of 50 \( \mu \text{m} \) x 56 cm (50 cm of effective length) with 100 mmol/L NaHPO\textsubscript{4}-MeOH (85:15, pH 9 adjusted with 1 mmol/L NaOH) as running buffer. Sample injected hydrodynamically (15s, 138 kpa) into the capillary, applied voltage 15 KV, detection 293 nm, running time 30 min. Linearity range 0.05 - 2 mg/mL.

- **Spectrofluorimetric method**

Shah et al (66) developed a spectrofluorimetric method. Drug dissolved in 0.1N HCl/Acetate buffer pH 4/Phthalate buffer pH 4. The fluorescence intensity of the solutions was measured at the excitation and emission wavelengths as given below:

<table>
<thead>
<tr>
<th>Solution</th>
<th>Excitation wavelength (nm)</th>
<th>Emission wavelength (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1N HCl</td>
<td>295</td>
<td>498</td>
</tr>
<tr>
<td>Acetate buffer pH 4</td>
<td>295</td>
<td>489</td>
</tr>
<tr>
<td>Phthalate buffer pH 4</td>
<td>337</td>
<td>488</td>
</tr>
</tbody>
</table>
• Chromatographic methods

HPTLC method

Shah et al (66) developed a HPTLC method for estimation of gatifloxacin. Mobile phase: n-butanol: methanol: ammonia (6 M) (5:1:2 v/v); Stationary phase: Silica gel 60 F254 aluminum plates; Linearity range: 400-1200 ng/spot; LOD: 10 ng/spot; LOQ: 50 ng/spot; RF value: 0.47; Detection wavelength: 292 nm.

HPLC method:

<table>
<thead>
<tr>
<th>Column</th>
<th>Specification</th>
<th>Detection</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shim-pack CLC-ODS column</td>
<td>Mobile phase: 0.02 mol/L KH2PO4 buffer solution (pH 4.0): Acetonitrile (85:15) containing 2 mmol/L Tetra butyl ammonium bromide. Linearity range: 4-32 pg/mL.</td>
<td>293 nm</td>
<td>67</td>
</tr>
<tr>
<td>Shim-Pack LC-ODS C18</td>
<td>Mobile phase: MeCN:H2O:SDS Linearity range: 5-40 µg/mL</td>
<td>UV</td>
<td>68</td>
</tr>
<tr>
<td>Reversed phase ODS</td>
<td>Mobile phase: 0.003 mol/L tetra butyl ammonium bromide, 0.02 mol/L KH2PO4 buffer, acetonitrile.</td>
<td>293 nm</td>
<td>69</td>
</tr>
</tbody>
</table>

Maria et al (70) developed a chromatographic method and validated for quantitative determination of four quinolone antibiotics in tablets and injection preparations. The fluoroquinolones studied were gatifloxacin (GAT), levofloxacin (LEV), lomefloxacin (LOM) and
The quinolones were analyzed by using a LiChrospher® 100 RP-18 column (5 μm, 125 mm × 4 mm) and a mobile phase constituted of water:acetonitrile (80:20, v/v) with 0.3% of triethylamine and pH adjusted to 3.3 with phosphoric acid. The flow rate was 1.0 mL/min and the analyses were performed using UV detector with wavelengths varying from 279 to 295 nm. The analyses were performed at room temperature (24 ± 2 °C). All fluoroquinolones were separated within 5 min. The calibration curves were linear (r ≥ 0.9999) over a concentration range from 4 - 24 μg/mL. The relative standard deviation was <1.0% and average recovery was above 99.54 %.

In biological fluid (In vivo study)

Overholser et al (71) reported a HPLC method for the determination of gatifloxacin concentrations in human serum and urine. Serum proteins were removed by ultra filtration through a filtering device after adding a displacing agent. Urine samples were diluted with mobile phase prior to injection. Separation was achieved with a C18 reverse-phase column and gatifloxacin concentrations were determined using ultraviolet detector. The quantitation limits of the assay were 100 ng/mL in serum and 1.0 μg/mL in urine.

Liang et al (72 Error! Reference source not found.) reported a liquid chromatographic method with UV and fluorescence detection for the determination of fluoroquinolones in human plasma. The effects of mobile phase composition, ion-pair and competing-base reagents, buffers, pH, and acetonitrile concentrations were investigated on the separation of six quinolones (cinofloxacin, levofloxacin, ciprofloxacin, gatifloxacin, moxifloxacin and trovafloxacin). Sample preparation was carried out by adding internal standard and displacing agent and processing by ultra filtration. This method uses ultraviolet and fluorescence detection
and separation using a C18 column.

Hoang et al (73) developed a Liquid chromatography with a column-switching technique for simultaneous direct quantification of levofloxacin, gatifloxacin and moxifloxacin in human serum. Serum samples were injected on a LiChroCART® 4-4 pre-column (PC) filled with a LiChrospher® 100 RP-18, 5 µm where fluoroquinolones (FQs) were purified and concentrated. The FQs were back-flushed from the PC and then separated on a Supelcosil ABZ+ Plus (150 mm x 4.6 mm i.d.) analytical column with a mobile phase containing 10 mM phosphate buffer (pH 2.5), acetonitrile (88 : 12, v/v) and 2 mM tetrabutyl ammonium bromide. The effects of ion-pair reagents, buffer type, and pH and acetonitrile concentrations in the mobile phase on the separation of the three FQs were investigated. Fluorescence detection provided sufficient sensitivity to achieve quantification limit of 125 ng/mL for levofloxacin and moxifloxacin; 162.5 ng/mL for gatifloxacin with a 5 µL sample size.

Juan et al (74) developed a spectrofluorimetric method to determine gatifloxacin 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 µg/mL of this molecule in aqueous solution containing acetic acid–sodium acetate buffer (pH 3.5), with λexc = 292 nm and λem = 484 nm. Micelle-enhanced fluorescence led to 75% higher analytical signals in presence of 12 mM sodium dodecyl sulphate, which allow the determination of 0.020 – 0.450 µg/ mL fluoroquinolone with λexc = 292 nm and λem = 470 nm. Both methods were successfully applied to gatifloxacin determination in spiked human urine and serum.

Nguyen et al (76) developed Liquid chromatography with a column-switching technique for simultaneous direct quantification of
levofloxacin, gatifloxacin and moxifloxacin in human serum. Serum samples were injected on a LiChroCART 4-4 pre-column (PC) filled with a LiChrospher 100 RP-18, 5 microm where fluoroquinolones (FQs) were purified and concentrated. The FQs were back-flushed from the PC and then separated on a Supelcosil ABZ+ Plus (150 mm x 4.6 mm i.d.) analytical column with a mobile phase containing 10 mM phosphate buffer (pH 2.5), acetonitrile (88:12, v/v) and 2mM tetrabutyl ammonium bromide. The effects of ion-pair reagents, buffer type, pH and acetonitrile concentrations in the mobile phase on the separation of the three FQs were investigated. Fluorescence detection provided sufficient sensitivity to achieve quantification limit of 125 ng/mL for levofloxacin and moxifloxacin; 162.5 ng/mL for gatifloxacin with a 5 µg sample size. The on-line process of extraction avoids time-consuming treatment of the samples before injection and run time is shortened.

K. Vishwanatan et al (78) reported a method for determination of gatifloxacin in human plasma by liquid chromatography/electrospray tandem mass spectrometry. SPE- using oasis HLB internal standard – ciprofloxacin. Linearity range : 10 - 1000 ng/mL, % CV < 6%. Co-efficient of determination: > 0.99. LOD : 500 pg/mL.

Borner et al (79) reported HPLC method of estimation of gatifloxacin in human serum and urine.

Zhao et al (80) reported method of determining the contents of gatifloxacin and aminophylline simultaneously in infusion solutions by HPLC method and its application.

Patel al (81) estimated mixture of gatifloxacin and ornidazole using spectrophotometric method.

Mandal et al (82) studied pharmacokinetics of gatifloxacin in urine.
Aster-cephac, France (83) reported HPLC methods with fluorescence detection in plasma and urine. Linearity range: 0.010 – 10.0 µg/mL for plasma and 0.100 – 50.0 µg/mL for urine.

Emprexe Analyticalab (84) reported validated method for the analysis of gatifloxacin in heparinised human plasma using C\textsubscript{18} column and Mobile phase MeOH : MeCN : citrate : TBAH maintaining Flow rate: 1 mL/min with fluorescence detection. Linearity range: 0.01-8.0 µg/mL.

Dillib institute, France (85) also developed RP-HPLC method for estimation of gatifloxacin in human serum and urine with fluorescence detection.

Vimita lab (86) developed RP-HPLC method for estimation of gatifloxacin in human plasma using UV detection. Linearity range: 150-4000 ng/spot.
1.1 Literature review of Ornidazole

❖ In pharmaceutical formulation

- Spectrophotometric methods:

  Reddy et al (87) described the method for determination of Ornidazole in bulk and dosage forms. The method was based on reaction between reduced ornidazole and 3-methyl-2-benzothiazolinone hydrazone in the presence of FeCl₃ to give a green complex, which showed an absorbance maximum at 645 nm.

  Zuhri et al (88) described the method for determination of ornidazole in commercial dosage forms. This method was based on reaction between ornidazole and bromothymol blue to form a colored complex which was measured at 446 nm.

  Salman et al (89) described a method for assay of ornidazole in injection solutions and tablet dosage from by visible spectrophotometry. The method was based on reaction between reduced ornidazole with p-dimethylamino benzaldehyde.

  Manjunath et al (90) developed a method for determination of ornidazole in bulk and tablet dosage form. The method was based on formation of condensation products of ornidazole by reaction with p-dimethylaminobenzaldehyde and p-dimethylaminocinnamaldehyde which exhibited absorbance maxima at 480 nm and 460 nm respectively.

  Padhye et al (91) reported a method for estimation of ornidazole in tablets by diazotization reaction. The method was based on quantitative formation of diazonium salt of ornidazole by coupling with N-(1-naphthyl)ethylenediamine to produce a colored derivative. Two different procedures were provided, both derivatized compounds were stable, and exhibited absorption maxima at 530 nm and 500 nm respectively.
• Chromatographic methods

HPLC methods:


• Simultaneous estimation of Ornidazole and a fluoroquinolone derivative

Kale et al (94) reported two methods for spectrophotometric determination of ornidazole and norfloxacin in tablets. These methods were simultaneous equation method and derivative spectroscopy.

Nalini et al (95) reported a method for simultaneous estimation of ofloxacin and ornidazole in tablets by spectrophotometry and RP-HPLC. For RP-HPLC LC-10 ATvp, SPD 10 AVP, C18 column was used. Mobile phase Distilled water containing TEA: Acetonitrile (3 : 1). pH was adjusted 3.0 with o-phosphoric acid. Flow rate: 1 mL/min and UV detection at 284 nm.

Natarajan et al (96) reported a stability indicating HPLC method for simultaneous estimation of ofloxacin and ornidazole in tablets. Octadecyl silane column (4.6 mm x 250 mm, 5 μ) was used. Mobile phase pH 3.0 buffer: Acetonitrile (80:20). Flow rate: 1 mL/min and UV detection at 300 nm. Linearity range: Ornidazole: 100 - 350 μg/mL and Ofloxacin: 40-140 μg/mL.
In biological matrices

- Chromatographic methods

**HPLC methods**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Column</th>
<th>Mobile phase</th>
<th>Flow rate (mL/min)</th>
<th>Detection (by UV)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nucleosil 5 C\textsubscript{18} column</td>
<td>Methanol: 0.067M Phosphate buffer pH 6, (80:20) for Ornidazole, (17:83) for metabolites</td>
<td>-</td>
<td>312 nm</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Waters (\mu) Bondpack C\textsubscript{18} (300 x 3.9 mm i.d.) Packed with silica gel (10 (\mu)m) with a C\textsubscript{18} chemically bonded nonpolar stationary phase</td>
<td>Methanol: Water (50:50)</td>
<td>1</td>
<td>313 nm</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>Zorbax C\textsubscript{8}</td>
<td>MeCN : (\text{H}_2\text{O} : \text{D/4 reagent (30: 70: 1)})</td>
<td>-</td>
<td>317 nm</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Lichrosorb RP 8</td>
<td>Ethanol : Water (1: 9)</td>
<td>-</td>
<td>317 nm</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>MOS-Hypersil RP-8 column</td>
<td>Methanol : 0.01M KH\textsubscript{2}PO\textsubscript{4} (3: 7)</td>
<td>-</td>
<td>318 nm</td>
<td>101</td>
</tr>
</tbody>
</table>
**Literature review for Gatifloxacin and Ornidazole**

<table>
<thead>
<tr>
<th></th>
<th>μBondpack C18 reversed-phase column</th>
<th>Water : Ethanol (1:9)</th>
<th>2</th>
<th>318 nm</th>
<th>102</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Lichrosorb RP 18.5 µm Length 12.5</td>
<td>Ethanol : Water (20:80)</td>
<td>1</td>
<td>318 nm</td>
<td>103</td>
</tr>
<tr>
<td>7</td>
<td>LiChrospher 100 column RP 18 endcapped, particle size 5 µm, column diameter 4 mm</td>
<td>Methanol : Water (25 : 75)</td>
<td>1</td>
<td>318 nm</td>
<td>104</td>
</tr>
</tbody>
</table>

**GC method**

Bhatia et al (105) described a sensitive and selective electron capture gas chromatography method for determination of ornidazole in blood. OV-11 column was used. The hydroxyl function in the N-1 substitution was converted to its respective trimethylsilyl derivative before chromatography on OV-11 column. Blood levels as low as 50 µg/mL of ornidazole were measured using this method.