Simultaneous determination of gatifloxacin and prednisolone acetate in ophthalmic formulation using first-order UV derivative spectroscopy

Rúbia A. Sversut, Isabella C. Alcântara, Aline M. Rosa, Adriano C.M. Baroni, Patrik O. Rodrigues, Anil K. Singh, Marcos S. Amaral, Nájla M. Kassab

Universidade Federal de Mato Grosso do Sul, Centro de Ciências Biológicas e da Saúde, Campo Grande-MS, Brazil

Universidade de São Paulo, Faculdade de Ciências Farmacêuticas, Departamento de Farmácia, São Paulo-SP, Brazil

Universidade Federal de Mato Grosso do Sul, Instituto de Física, Campo Grande-MS, Brazil

Received 20 April 2013; accepted 3 November 2014

KEYWORDS
Drug; Fluoroquinolone; Glucocorticoid; Spectrophotometry; Validation

Abstract  A simple method for simultaneous determination of gatifloxacin and prednisolone acetate in ophthalmic formulation was developed and validated using UV spectrophotometry. Gatifloxacin and prednisolone acetate were quantified using the first-order derivative of the UV spectra. The proposed method was validated according to the guidelines of the International Conference on Harmonization and the Association of Official Analytical Chemists International. The measurements were made in acetonitrile/water (70:30 v/v) at 348 nm for gatifloxacin and at 263 nm for prednisolone acetate. The calibration curves were linear in the concentration range of 3–21 µg mL⁻¹ for gatifloxacin and 6–42 µg mL⁻¹ for prednisolone acetate with Sandell's sensitivities of 0.349 µg cm²/C₀ and 0.402 µg cm²/C₀, respectively. The mean recovery and the limit of quantification for gatifloxacin were 99.76 ± 0.41% and 1.11 µg mL⁻¹ and for prednisolone acetate were 99.52 ± 0.87% and 0.55 µg mL⁻¹, respectively. The method was precise, with a relative standard deviation of less than 2.50% for both drugs. For robustness, the factors analyzed did not significantly affect the quantification of gatifloxacin and prednisolone acetate. The results of the validated method did not differ significantly from high-performance liquid chromatography (HPLC), which
1. Introduction

Gatifloxacin (GFN) is chemically known as 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (O’Neil, 2006). The empirical formula of GFN is \( \text{C}_{19}\text{H}_{22}\text{FN}_{3}\text{O}_{4} \) and the molecular weight is 384.40 g mol\(^{-1}\) (Fig. 1a). GFN is a fourth-generation fluoroquinolone that has been widely used in the prophylaxis and treatment of ocular infections (Long et al., 2003; Donnenfeld et al., 2004; Bucci et al., 2008; Callegan et al., 2009; Cervantes and Mah, 2011).

Prednisolone acetate (PRED) is chemically known as 1,4-pregnadiene-11\(\beta\),17\(\alpha\),21-triol-3,20-dione 21-acetate (O’Neil, 2006). It has an empirical formula of \( \text{C}_{23}\text{H}_{30}\text{O}_{6} \) and a molecular weight of 402.48 g mol\(^{-1}\) (Fig. 1b). PRED is one of the most effective drugs of the synthetic glucocorticoid group used for treatment of ocular inflammatory diseases (Akram et al., 2010; Ibrahim et al., 2010).

Various pharmaceutical combinations of fluoroquinolones and topical corticosteroids have been proposed in recent years (Roland and Wall, 2008; Wall et al., 2009; Campos et al., 2011). Clinical studies have demonstrated the safety and efficacy of these combinations in the treatment and prophylaxis of ocular infections caused by Gram-positive (Staphylococcus aureus, Staphylococcus epidermidis and Streptococcus pneumoniae) and Gram-negative (Haemophilus influenzae) bacteria (Mohan et al., 2001; Belfort et al., 2012). In the Brazilian market, Allergan Inc. launched the first and still the only fixed-dose combination containing GFN (0.3%) and PRED (1.0%) in ophthalmic suspension (Zypred). This formulation was approved by ANVISA (National Agency of Sanitary Surveillance) in April 2010 for the treatment and prophylaxis of ocular infections (Anvisa, 2013).

Various analytical methods have been described for the estimation of GFN or PRED in biological fluids (Vishwanathan et al., 2001; Al-Dgither et al., 2006; Zhang et al., 2006; Srinivas et al., 2008; Li et al., 2012). Determinations of GFN in pharmaceutical formulations by high-pressure liquid chromatography (HPLC) (Venugopal et al., 2007; Abida et al., 2011), UV spectrophotometry (Salgado and Oliveira, 2005; Venugopal and Saha, 2005; Jane et al., 2006; Amin et al., 2007; Kanakapura and Rangachar, 2007; Darwish et al., 2010) and capillary zone electrophoresis (Sane et al., 2005) were reported. UV spectrophotometric and HPLC methods have been used to estimate PRED in pharmaceutical dosage forms (Singh and Verma, 2007; Ghosh et al., 2011). A few methods were also given for the simultaneous determination of fluoroquinolones and corticosteroids in combined dosage form (Sireesh and Prakash, 2011; Prakash and Sireesh, 2012; Barot et al., 2012; Patel and Sejal, 2013; Razzaq et al., 2012).

No analytical method has yet been reported in the official compendia for the simultaneous determination of GFN and PRED in ophthalmic formulations. The present study attempted to develop a rapid, economical, precise and accurate method for simultaneous determination of GFN and PRED in ophthalmic formulation. The first-derivative spectrophotometry method permits simultaneous analysis of both compounds without previous separation and extraction procedures. This alternative is simpler and less expensive than HPLC methods (Paschoal and Ferreira, 2000; Sversut et al., 2014).

The results for precision obtained by this spectrophotometry method were statistically compared to those obtained by the HPLC method, which was previously developed and validated by our research group.

2. Experimental

2.1. Apparatus

A Thermo Scientific Evolution 60® UV–Visible Spectrophotometer was used for the UV measurements. All drugs and reference substances were weighed on a Shimadzu® analytical balance (AY 220, Shimadzu Corp., Japan).

Figure 1 Chemical structure of (a) GFN and (b) PRED.
2.2. Materials and reagents

The GFN and PRED reference substances (assigned purity 100.0%) were kindly donated by Allergan, Inc., São Paulo, Brazil (batch numbers 2010090113 and F20101031), respectively, and were used as reference standards without further purification. The samples of ophthalmic suspension containing 0.3% GFN and 1% PRED (declared content) were also donated by Allergan, Inc. The GFN and PRED reference substances, as well as the commercial formulations, were kept protected from light throughout all stages of the study. Analytical-grade acetonitrile (Proquímios®, Rio de Janeiro, Brazil) and freshly distilled water were used in all solution preparations.

2.3. Method development

2.3.1. Selection of the solvent

Different mixtures of solvents were investigated. For selection of the solvent, the criteria employed were the ease of preparing the standards and samples, solubility and stability of the drugs, cost of the solvent, and applicability of the method.

2.3.2. Selection of wavelengths

The working standard solutions of GFN and PRED were diluted with acetonitrile/water (70:30 v/v) to obtain a solution containing 5 µg mL⁻¹ GFN and 15 µg mL⁻¹ PRED. Approximately 3.0 mL was removed and scanned from 200 to 400 nm with the UV spectrophotometer. The first-order derivative UV spectra of GFN and PRED were calculated from the UV absorption spectra, and the best wavelengths were determined. The choice of an optimum wavelength for each drug was based on the fact that the absolute value of the first-order derivative absorption spectrum provided the best linear response, without interference from other components of the mixture.

2.3.3. Preparation of standard solutions

The standard solutions were prepared by weighing 10 mg of GFN and 15 mg of PRED in 200 mL and 100 mL volumetric flasks, respectively. Acetonitrile/water (70:30 v/v) was added to each flask to obtain the working standard solutions of 50 µg mL⁻¹ GFN and 150 µg mL⁻¹ PRED.

2.3.4. Preparation of sample solution

The sample solution was prepared in the same ratio as the labeled amounts of GFN and PRED in an ophthalmic formulation. An aliquot of 5 mL was transferred to a 100 mL volumetric flask, and the volume was completed with acetonitrile/water (70:30 v/v) to obtain a stock sample solution containing 150 µg mL⁻¹ GFN and 500 µg mL⁻¹ PRED.

From the above stock solutions, 5 mL was added to 95 mL of acetonitrile/water (70:30 v/v) to give final concentrations of 7.5 and 25.0 µg mL⁻¹ of GFN and PRED, respectively.

2.4. Method validation

Validation of the new simultaneous spectrophotometry method was carried out as recommended by the International Conference on Harmonization (ICH, 2005) and the Association of Official Analytical Chemists International (AOAC, 2005) for the parameters of linearity, limit of detection (LOD), limit of quantification (LOQ), precision, accuracy, specificity, and robustness.

2.4.1. Linearity

Seven aliquots of working standard solutions for each drug were used to determine the calibration curves. These curves were plotted in the concentration ranges of 3.0–21.0 µg mL⁻¹ for GFN and 6.0–42.0 µg mL⁻¹ for PRED. The values of the first-order derivative UV spectra at 348 nm for GFN and at 263 nm for PRED as a function of the drug concentration were used to construct the calibration curves. All spectrophotometric determinations were performed in triplicate and at room temperature (25 ± 2°C). The linear regression was calculated by the method of least squares, and the curves were evaluated by analysis of variance (ANOVA).

2.4.2. Limits of detection and quantitation

LOD and LOQ were calculated based on the standard deviation of the response and the slope of the calibration curve. They were obtained using the following equations, respectively:

\[ LOD = 3.3 \cdot SD_b/a \]  
\[ LOQ = 10.0 \cdot SD_b/a \]

where \( SD_b \) represents the standard deviation of the y-intercept and \( a \) is the slope of the calibration curve (AOAC, 2005).

2.4.3. Precision

The intra-day precision (repeatability) was evaluated by analyzing sample solutions at single concentrations of GFN and PRED, to span the linear range of the method (7.5 and 25.0 µg mL⁻¹, respectively). The analyses were performed in six replicates on the same day. To estimate the inter-day precision, the sample solutions were freshly prepared at the same concentration level for each drug, and the responses were determined in six replicates. This procedure was performed on three consecutive days. The intra- and inter-day precisions are expressed in terms of Relative Standard Deviation (%RSD).

2.4.4. Accuracy

The accuracy was calculated based on the percentage of recovery of the known amounts of GFN and PRED added to the samples (AOAC, 2005; Paim et al., 2012). Aliquots of the GFN and PRED standard solutions in concentrations of 80, 120 and 160 µg mL⁻¹ were transferred to 10 mL volumetric flasks containing 5 mL of sample solution. The volumes were completed with acetonitrile/water (70:30 v/v) and the drugs were determined in triplicate, using the proposed method.

2.4.5. Specificity

The specificity of the method was evaluated through analysis of a placebo solution. The mixture of inert components including benzalkonium chloride, dibasic sodium phosphate, monobasic sodium phosphate, ethylenediamine tetraacetic acid, hypromellose, hydrochloric acid and sodium hydroxide was prepared in the usual concentrations employed in ophthalmic formulations. These solutions were analyzed by the proposed method.
method in order to determine if any of the components of the formulation might affect the determinations of GFN and PRED.

2.4.6. Robustness

Robustness testing was performed in order to evaluate the susceptibility of measurements to deliberate variations in analytical conditions (Paim et al., 2012). The robustness test was designed according to Abdullah et al. (2014). Different volumes of known concentrations of GFN and PRED were added to pre-analyzed samples containing 3.75 and 12.50 μg mL⁻¹ of GFN and PRED, respectively. Then, the recoveries of the added standard were measured under different analytical conditions. The analytical conditions selected to examine the robustness were percentage of acetonitrile (±5.0%), temperature (room and refrigerator temperatures) and wavelength (±2 nm). While one condition was changed, the others remained unchanged (at normal level). The results were evaluated by means of the t-test.

2.5. Application of the method

The ophthalmic suspensions were analyzed at concentrations of 7.5 and 25.0 μg mL⁻¹ for GFN and PRED, respectively, following the methodology used to prepare the sample solution. All determinations were performed in 5 replicates and at room temperature. The amounts of GFN and PRED were determined by fitting the responses of the derivatives into the equations for the calibration curves of GFN and PRED.

2.6. Comparison of methods

In order to compare the UV derivative spectrophotometry method with the previously validated HPLC method, the results for precision of these methods were compared by one-way ANOVA.

3. Results and discussion

3.1. Method development

Considering the solubility and the stability, the following solvents were tested as diluents of GFN and PRED standard and sample solutions: water, basic water, acidic water, methanol, ethanol and acetonitrile. The first solvent studied was water. GFN was easily soluble in 100% water, and PRED was insoluble.

A study using the HPLC method showed the instability of GFN and PRED in acid and basic solutions (Sversut et al., 2014). Therefore, these solutions were not used. The methanol and ethanol solutions did not provide good zero crossing points for either drug.

After these preliminary tests, the mixture of acetonitrile:water (70:30, v/v) was used as the diluent to develop the method, and afforded satisfactory solubility and stability of GFN and PRED. This solvent offers an additional advantage because it shows lower absorption in the UV region, indicating that it did not affect the analysis of GFN and PRED.

The zero-order UV spectrum was inappropriate for analyzing this binary mixture because of the UV spectral overlap of GFN and PRED, which did not permit the simultaneous analysis of both drugs (Fig. 2). However, the use of the first-order derivative UV absorption spectra allowed these drugs to be determined simultaneously (Fig. 3). The derivative values were taken at 348 nm for GFN (zero-crossing of PRED) and at 263 nm for PRED (zero-crossing of GFN).

3.2. Method validation

3.2.1. Linearity

The statistical results of the linear regression and calibration curves for GFN and PRED are shown in Table 1. The correlation coefficients indicated good linearity: 0.9997 and 0.9996 for GFN and PRED, respectively. The linearity ranges were 3.0–21.0 μg mL⁻¹ for GFN and 6.0–42.0 μg mL⁻¹ for PRED. The absorbance values for these concentration ranges remained between 0.3 and 1.5, conforming to the recommendations of Vogel (2002). The UV spectrophotometric method for simultaneous determination of GFN or PRED in a combined dosage form shows a smaller range of concentrations (Patel and Sejal, 2013).
### 3.2.2. Limits of detection and quantitation

The sensitivity was determined using Sandell’s sensitivity and using Eqs. (1) and (2) to calculate the values for LOD and LOQ, respectively. Sandell’s sensitivities were of 0.349 l/gc m/C0^2 (GFN) and 0.402 l/gc m/C0^2 (PRED). The LODs were 0.33 and 0.16 l/gm L/C0^1 for GFN and PRED, and the LOQs were 1.11 and 0.55 l/gm L/C0^1 for GFN and PRED, respectively. These values show that the proposed method has good sensitivity.

The methods reported in the literature for determination of GFN or PRED in ophthalmic formulations are less sensitive, as demonstrated by Sireesha and Prakash (2011) and Barot et al. (2012), who obtained LOQ values of 1.203 l/gm L/C0^1 and 1.957 l/gm L/C0^1 respectively, for GFN and PRED.

### 3.2.3. Precision

The precision parameters (%RSD) expressed as repeatability (intra-day) and as intermediate precision (inter-day) are presented in Table 2. For GFN, the values of %RSD were 1.34%, 0.60%, and 1.07% for repeatability in analyses performed during 3 consecutive days, and 2.23% for intermediate precision. For PRED, all %RSD values were lower than 1%.

Thus, our proposed method has good precision in the simultaneous determination of GFN and PRED.

### 3.2.4. Accuracy

The recovery percentages were 99.76 ± 0.41% and 99.52 ± 0.87% for GFN and PRED, respectively (Table 3). These results indicate the accuracy of the method.

### 3.2.5. Specificity

The specificity test demonstrated that the excipients did not affect the drug determination (Fig. 2). Our method showed good specificity in the UV first-order derivative for unequivocal determination of the analyte in the presence of matrix compounds (excipients).

### 3.2.6. Robustness

The responses of GFN and PRED did not change significantly when the analytical conditions were modified (Table 4). These observations confirm the robustness of the method for determination of GFN and PRED in ophthalmic formulation.

### Table 1 Parameters for calibration curves of GFN and PRED using first-order derivative absorption spectra (dA/dλ).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>GFN</th>
<th>PRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linearity range (μg mL^-1)</td>
<td>3.0–21.0</td>
<td>6.0–42.0</td>
</tr>
<tr>
<td>Wavelength (nm)</td>
<td>348</td>
<td>263</td>
</tr>
<tr>
<td>Regression equation</td>
<td>dA/dλ = 0.0011C + 0.0001</td>
<td>dA/dλ = 0.001C – 0.0001</td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.9997</td>
<td>0.9996</td>
</tr>
<tr>
<td>p-Value^a</td>
<td>&lt; &lt;0.05 (p = 2.50 × 10^-22)</td>
<td>&lt; &lt;0.05 (p = 2.70 × 10^-22)</td>
</tr>
</tbody>
</table>

^a Theoretical value of p is based on the one-way ANOVA test at α = 0.05 level of significance.

### Table 2 Precision of intra-day and inter-day results for simultaneous determination of GFN and PRED by the first-order derivative UV spectrophotometric method.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intra-day^b</th>
<th>Inter-day^c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>GFN (μg mL^-1)</td>
<td>7.55 ± 0.11</td>
<td>7.45 ± 0.05</td>
</tr>
<tr>
<td>Content found (%)</td>
<td>100.62 ± 1.34</td>
<td>99.28 ± 0.60</td>
</tr>
<tr>
<td>PRED (μg mL^-1)</td>
<td>24.93 ± 0.07</td>
<td>25.02 ± 0.07</td>
</tr>
<tr>
<td>Content found (%)</td>
<td>99.70 ± 0.07</td>
<td>100.97 ± 0.07</td>
</tr>
</tbody>
</table>

^a Theoretical concentration: 7.50 μg mL^-1 for GFN and 25.0 μg mL^-1 for PRED.

^b Mean of 6 determinations.

^c Mean of determinations on 3 different days.

### Table 3 Recovery data for standard solutions added to the samples analyzed by the first-derivative UV spectrophotometric method.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fortified theoretical concentration (μg mL^-1)</th>
<th>Experimental concentration found^d (μg mL^-1)</th>
<th>Recovery (%)</th>
<th>Mean recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFN</td>
<td>11.75</td>
<td>11.63</td>
<td>99.96</td>
<td>99.76 ± 0.41</td>
</tr>
<tr>
<td></td>
<td>15.75</td>
<td>15.63</td>
<td>100.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19.75</td>
<td>19.51</td>
<td>99.29</td>
<td></td>
</tr>
<tr>
<td>PRED</td>
<td>20.50</td>
<td>20.28</td>
<td>98.58</td>
<td>99.52 ± 0.87</td>
</tr>
<tr>
<td></td>
<td>24.50</td>
<td>24.36</td>
<td>99.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.50</td>
<td>28.44</td>
<td>100.29</td>
<td></td>
</tr>
</tbody>
</table>

^d Mean of 3 determinations.

---

Table 1: Parameters for calibration curves of GFN and PRED using first-order derivative absorption spectra (dA/dλ).

Table 2: Precision of intra-day and inter-day results for simultaneous determination of GFN and PRED by the first-order derivative UV spectrophotometric method.

Table 3: Recovery data for standard solutions added to the samples analyzed by the first-derivative UV spectrophotometric method.
3.3. Application of the method

The proposed UV spectrophotometric method is suitable for simultaneous determination of GFN and PRED in their combined ophthalmic dosage form in routine analysis. Table 5 shows the results for simultaneous determination of GFN and PRED in an ophthalmic formulation, using this method.

3.4. Method comparison

The UV derivative spectrophotometry and HPLC methods were compared through one-way ANOVA, using the mean values obtained for the precision of the methods. The techniques did not differ significantly ($F_{calc} < F_{crit}$ and $p < 0.05$). These results show the capacity of the derivative spectrophotometry method to simultaneously quantify GFN and PRED in ophthalmic formulation with precision comparable to HPLC, which is a more expensive and complicated technique.

4. Conclusion

A UV spectrophotometric method was developed and validated for the simultaneous determination of GFN and PRED in ophthalmic formulations. The method showed specificity, precision, accuracy, sensitivity and robustness, as evaluated according to ICH and AOAC guidelines. The proposed method proved to be simpler, less expensive, and faster, because no additional pretreatment of the samples is required prior to the measuring step, thus accelerating the quality-control process. The lack of a significant difference from the previously validated HPLC method confirms that the UV derivative spectrophotometry method is suitable, useful, and an excellent alternative to assess quality in routine analysis of GFN and PRED in drug products.

Acknowledgments

The authors thank the pharmaceutical company Allergan (Brazil) for supplying the raw material and pharmaceutical formulations. They also thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES-Brazil) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-Brazil) for financial support.

Table 4 Robustness evaluation of the first-derivative UV spectrophotometric method.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal conditions</th>
<th>Percentage of acetonitrile (+5.0%)</th>
<th>Percentage of acetonitrile (-5.0%)</th>
<th>Wavelength (+2.0 nm)</th>
<th>Wavelength (-2.0 nm)</th>
<th>Refrigerator temperature (8 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFN</td>
<td>100.12 ± 1.17</td>
<td>98.83 ± 0.86</td>
<td>98.83 ± 0.86</td>
<td>98.13 ± 1.88</td>
<td>99.32 ± 0.98</td>
<td>97.38 ± 0.50</td>
</tr>
<tr>
<td>PRED</td>
<td>98.77 ± 0.64</td>
<td>100.93 ± 1.80</td>
<td>97.42 ± 1.43</td>
<td>97.90 ± 2.08</td>
<td>97.53 ± 0.25</td>
<td>96.87 ± 1.00</td>
</tr>
</tbody>
</table>

- a Mean of 5 determinations.
- b Added amount of each drug: 8 μg mL⁻¹.
- c Normal spectrophotometric conditions: first-derivative UV spectrophotometric method using the mixture acetonitrile: water (70:30, v/v) as solvent at 263 nm (for PRED) and 348 nm (for GFN). All analyses were performed at room temperature (25 ± 2 °C).

Table 5 Commercial ophthalmic formulation analysis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Theoretical concentration* (μg mL⁻¹)</th>
<th>Measured concentration* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFN</td>
<td>7.5</td>
<td>100.53 ± 0.62</td>
</tr>
<tr>
<td>PRED</td>
<td>25</td>
<td>99.94 ± 0.19</td>
</tr>
</tbody>
</table>

- a The ophthalmic formulation was Zypred® (Allergan Inc., São Paulo, Brazil) containing labeled amounts of 3.0 mg mL⁻¹ GFN and 10 mg mL⁻¹ PRED.
- b The theoretical concentration followed the same ratio as the labeled amounts of GFN and PRED in the ophthalmic formulation.

Please cite this article in press as: Sversut, R.A. et al., Simultaneous determination of gatifloxacin and prednisolone acetate in ophthalmic formulation using first-order UV derivative spectroscopy. Arabian Journal of Chemistry (2014), http://dx.doi.org/10.1016/j.arabjc.2014.11.026.
Simultaneous determination of gatifloxacin and prednisolone acetate 7


Bucci Jr., F.A., Amico, L.M., Evans, R.E., 2008. Antimicrobial efficacy of prophylactic gatifloxin 0.3% and moxifloxin 0.5% in patients undergoing phacoemulfication surgery. Eye Contact Lens 1, 39–42.


Donnenfeld, E., Perry, H.D., Chruscicki, D.A., Bitterman, A., Cohn, S., Solomon, R., 2004. A comparison of the fourth-generation fluoroquinolones gatifloxacin 0.3% and moxifloxin 0.5% in terms of ocular tolerability. Curr. Med. Res. Opin. 11, 1753–1758.


