
Brahma Reddy Gade*, Sita Ram Bandhakavi1 and Ganji Ramanaiah2

1Department of Chemistry, P.V.P. Siddhartha Institute of Technology, Kanur, Vijayawada - 520007, India
2Department of chemistry, Acharya Nagarjuna University, Guntur, India

ABSTRACT

A new rapid, precise and sensitive reverse phase high performance liquid chromatographic (RP-HPLC) method has been developed and validated for the estimation of Ofloxacin and Ketorolac tromethamine simultaneously in combined dosage form. The two components Ofloxacin and Ketorolac tromethamine were well resolved on an isocratic method, C8 column, utilizing a mobile phase composition of acetonitrile: methanol: a mixed buffer of 0.02M Potassium dihydrogen phosphate and sodium dihydrogen phosphate buffer (20:20:60), v/v, pH 4.8) at a flow rate of 1.0 mL/min with UV detection at 295 nm. The retention time of Ofloxacin and Ketorolac tromethamine were 3.2 min and 4.2 min respectively. The developed method was validated for specificity, linearity, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ) and robustness as per ICH guidelines. Linearity for Ofloxacin and Ketorolac tromethamine were found in the range of 20-60 µg/ml and 12-36 µg/ml, respectively. The percentage recoveries for Ofloxacin and Ketorolac tromethamine ranged from 97-99 % and 96-100 %, respectively. The proposed method could be used for routine analysis of Ofloxacin and Ketorolac tromethamine in their combined dosage forms.

Keywords: Liquid Chromatography, Ofloxacin, Ketorolac tromethamine, Combined dosage forms, Simultaneous estimation, Validation.
INTRODUCTION

Multidrug administration is often associated with clinically significant interaction, especially of narrow therapeutic index drugs, either at pre-absorption or post absorption stage. This can limit the desired therapeutic effect of either of the drug molecules. The present study was aimed to develop simple, rapid and precise analytical method for simultaneous estimation of ofloxacin (OFLOX) and ketorolac tromethamine (KETO).

Ofloxacin, is an antimicrobial drug and chemically it is 9-fluro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperiziny)-7-oxo-7H-pyrido [1, 2, 3-de]-1, 4-benzoxaine-6-carboxylic acid. Various analytical methods have been reported in literature for estimation of ofloxacin in single and in combination form such as spectrophotometric, potentiometry and conductometry, HPLC, electrophoresis and LC/MS/MS.

Ketorolac tromethamine, has anti inflammatory and analgesic activity. Chemically it is 5-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid, 2-(hydroxy-methyl) - 1, 3-propanediol. It is official only in USP. In literature, few analytical methods have been reported for the estimation of ketorolac tromethamine in single or combination such as spectrophotometric, HPLC, electrophoresis and LC/MS/MS.

Ketorolac tromethamine in pharmaceutical formulations by UV-spectrophotometer and RP-HPLC method. The significance of the developed methods is to determine the content of both drugs simultaneously in commercially available ophthalmic drops dosage form. The ophthalmic drops dosage form in combination containing Ofloxacin (5 mg) and Ketorolac tromethamine (3 mg) is available in the market. In this paper, we reported one reverse-phase stability indicating HPLC method for the quantification of Ofloxacin and Ketorolac tromethamine simultaneously. The present RP-HPLC method was validated as per ICH guidelines.

However there is no analytical method reported for simultaneous estimation of both drugs in their combined ophthalmic drops dosage form by reporting forced degradation studies to demonstrate stability indicating nature of the method. Present work describes rapid, simple, sensitive, accurate and reproducible stability indicating method. The present developed method was used determine the Ofloxacin and Ketorolac tromethamine present in the formulation and method validated according to the ICH guidelines.

MATERIALS AND METHODS

Materials

HPLC grade Potassium dihydrogen phosphate, sodium dihydrogen phosphate, acetonitrile, methanol and water were procured from Merck India. All dilutions were performed in standard class-A, volumetric glassware. For the estimation of commercial formulation, Ketoflox having (Ketorolac tromethamine-3mg and Ofloxacin-5mg) manufactured by Allergan India ltd were procured from the local market.
Instrumentation

Waters Alliance HPLC, with DAD detector was used for the chromatographic separation. The chromatogram was recorded at and peaks quantified by means of Empower-2 software. Chromatographic separation was carried out on a C8 column [Devlosil C-8, 150mm x 4.6mm 5µ]. Sartorius electronic balance was used for weighing the samples. Ultra-sonic bath sonicator was used for degassing and mixing of the mobile phase.

Chromatographic conditions

Chromatographic separation of Ofloxacin and Ketorolac tromethamine was carried on a C8 column. The mobile phase was composed of acetonitrile, methanol and a mixed buffer of 0.02M potassium dihydrogen phosphate and sodium Dihydrogen Phosphate buffer (pH 4.8) in the ratio of 20:20:60 v/v. It was filtered through a 0.45 µ membrane filter and degassed for 15 minutes. The flow rate of the mobile phase was maintained at 1 ml/min. Detection was carried out at 295 nm at ambient temperature.

Method development

Preparation of Standard Stock Solutions

Standard stock solutions were prepared by dissolving 40 mg of Ofloxacin and 24 mg ketorolac working standard in two separate each 50mL volumetric flasks using 30mL of mobile phase and made up to the mark with mobile phase to obtain a final concentration of 480µg/mL and 800 µg/mL of each Ofloxacin and Ketorolac tromethamine. From the above stock solutions, each 5ml of aliquots of Ofloxacin and Ketorolac tromethamine were pipette in to a 100mL volumetric flask and dissolved in 25mL of the mobile phase and made up to the mark with the solvent to obtain a final concentration of 24 µg/mL and 40 µg/mL for Ofloxacin and Ketorolac tromethamine respectively.

Preparation of Sample solutions

Collect the sample from 5 bottles and determine the density or specific gravity (wt./mL) of the sample. Accurately weighed and transferred equivalent to 5mg Ofloxacin and 3mg of Ketorolac tromethamine into a 25 mL volumetric flask, added 20 mL of diluent, and sonicated for 10 minutes with intermittent shaking at controlled temperature and diluted to volume with diluent and mix. Filter the solution through 0.45 µm membrane Filter. Transferred 5.0 mL of the above solution into a 25 mL volumetric flask and diluted to volume with diluent to obtain a concentration of 24 and 40 µg/mL of Ofloxacin and Ketorolac tromethamine respectively.

Method validation

The developed HPLC method for the simultaneous determination of Ofloxacin and Ketorolac tromethamine was validated as per the ICH guidelines. As part of method validation as per ICH guidelines, the following parameters are studied.

1. System Suitability and System Precision
2. Specificity Studies
   A. Blank Interference
   B. Placebo Interference
   C. Forced degradation studies in different stress conditions to establishing stability indication of the developed method.
3. Method Precision
4. Accuracy studies
5. Linearity Studies including LOD/LOQ determination
6. Ruggedness
7. Robustness
8. Analysis of Marketed samples by applying the developed method.

Each parameter was explained separately in different sections under results and discussions.
RESULTS AND DISCUSSION

System suitability and system precision

System suitability for chromatographic separation was checked on each day of validation to evaluate the components of the analytical system in order to show that the performance of the system meet the standards required by the method. System suitability parameters established for the developed method include number of theoretical plates (efficiency), Resolution, Tailing factor. The HPLC system was equilibrated using the initial mobile phase composition, followed by 5 injections of the standard solution of 100% concentration containing 40 µg/mL Ofloxacin and 24 µg/ml ketorolac. These 5 consecutive injections were used to evaluate the system suitability on each day of method validation. The result was given in the Table 1.

Specificity

Blank and placebo interference

A study to establish the interference of blank and placebo was conducted. Diluent and placebo was injected into the chromatograph in the defined above chromatographic conditions and the blank and placebo chromatograms were recorded. Chromatogram of Blank solution (Fig. no.-2A) and placebo solution (Fig. No.-2B) showed no peaks at the retention time of Ofloxacin and Ketorolac tromethamine peak. This indicates that the diluent solution as well as placebo used in sample preparation do not interfere in estimation of Ofloxacin and Ketorolac tromethamine in its drops formulation. Similarly typical representative chromatogram of standard is also shown (Fig. No. -3)

Forced degradation

Control sample

Accurately weighed and transferred equivalent to 3mg Ofloxacin and 3mg of ketorolac drops solution into a 25 mL volumetric flask, added 20 mL of diluent, and sonicated for 10minutes with intermittent shaking at controlled temperature and diluted to volume with diluent and mix. Filter the solution through 0.45 µm membrane Filter. Transferred 5.0 mL of the above solution into a 25 mL volumetric flask and dilute to volume with diluent. Refer (Fig. no.-4A)

Acid degradation sample

Accurately weighed and transferred equivalent to 3mg Ofloxacin and 3mg of ketorolac drops solution into a 25 mL volumetric flask, added 20 mL of diluent, and sonicated for 10minutes with intermittent shaking at controlled temperature. Then add 1.0mL of 1N acid, refluxed for 10min at 60°C, then cooled to room temperature, neutralize with 1N NaOH and dilute to volume with diluent and mix. Filter the solution through 0.45 µm membrane Filter. Transfer 5.0 mL of the above solution into a 25 mL volumetric flask and dilute to volume with diluent. Refer (Fig. no.-4B)

Base degradation sample

Accurately weighed and transferred equivalent to 3mg Ofloxacin and 3mg of ketorolac drops solution into a 25 mL volumetric flask, added 20 mL of diluent, and sonicated for 10minutes with intermittent shaking at controlled temperature. Then add 1.0mL of 1N NaOH, refluxed for 10min at 60°C, then cooled to room temperature, neutralize with 1N HCl and dilute to volume with diluent and mix. Filter the solution through 0.45 µm membrane Filter. Transfer 5.0 mL of the above solution into a 25 mL volumetric flask and dilute to volume with diluent. Refer (Fig. no.-4C)

Peroxide degradation sample

Accurately weighed and transferred equivalent to 3mg Ofloxacin and 3mg of ketorolac drops solution into a 25 mL
volumetric flask, added 20 mL of diluent, and sonicated for 10 minutes with intermittent shaking at controlled temperature. Then add 1 mL of Hydrogen Peroxide, refluxed for 10 min at 60°C, then cooled to room temperature, and dilute to volume with diluent and mix. Filter the solution through 0.45 µm membrane Filter. Transfer 5.0 mL of the above solution into a 25 mL volumetric flask and dilute to volume with diluent. Refer (Fig. no.-4D)

Thermal degradation sample

Accurately weighed and transferred equivalent to 3 mg Ofloxacin and 3 mg of ketorolac drops solution into a 25 mL volumetric flask, added 20 mL of diluent, and sonicated for 10 minutes with intermittent shaking at controlled temperature. Then expose the sample solution on a water bath at 60°C for about 10 min. cool to room temperature and dilute to volume with diluent and mix. Filter the solution through 0.45 µm membrane Filter. Transfer 5.0 mL of the above solution into a 25 mL volumetric flask and dilute to volume with diluent. Refer (Fig. no.-4E)

Similarly Humidity, UV-Light exposure, Sunlight exposure and Water hydrolysis stress samples are prepared and checked for their purity by proposed method.

Linearity and range

The standard curve was obtained in the concentration range of 20-60 µg/ml for Ofloxacin and 12-36 µg/mL for ketorolac. The linearity of this method was evaluated by linear regression analysis. Slope, intercept and correlation coefficient [r²] of standard curve were calculated and given in Figure-5A (For Ofloxacin) and Figure-5B (For ketorolac) to demonstrate the linearity of the proposed method. The result of regression analysis was given in the Table 2.

From the data obtained which given in Table-2 (For Ofloxacin and Ketorolac tromethamine) the method was found to be linear within the proposed range.

Accuracy

The accuracy of an analytical method is the closeness of results obtained by that method to the true value for the sample. It is expressed as recovery (%), which is determined by the standard addition method. In the current study recovery at three spike levels 50%, 100% and 150% were carried out. The % recovery at each spike level was calculated and was given in Table 3.

Precision

The precision of an analytical method is the closeness of replicate results obtained from analysis of the same homogeneous sample. Precision was considered at different levels, i.e. method, system, Inter day and intraday. Precision of the developed method was assessed by measuring the response on the same day (intraday precision) and next two consecutive days (inter day precision). The precision of the method was assessed by six replicate injections of 100% test concentration. Intra and inter-day precision of the method was assessed by determination of standard deviation and % RSD for the analyte response. The result was given in Table 4.

LOD and LOQ

LOD and LOQ values were determined by the formulae LOD = 3.3 σ/S and LOQ = 10 σ/S (Where, σ is the standard deviation of the responses and S is the slope of the calibration curves). In the present method σ is the mean of standard deviation of y intercepts of the three calibration curves and S is the mean of slopes of the calibration curves. The result was given in Table 5.

Robustness

The robustness of the method was determined by assessing the ability of the developed method to remain unaffected by
the small changes in the parameters such as percent organic content, pH of the mobile phase, buffer concentration, temperature, injection volume and flow rate. A deviation of ± 2nm in the detection wavelength, ± 0.1 mL/min in the flow rate, ± 5% change in the organic phase were tried individually. The result was given in the Table 5.

OVER ALL SUMMARY OF THE METHOD

Column chemistry, solvent selectivity, solvent strength (volume fraction of organic solvent (s) in the mobile phase), detection wavelength and flow rate were varied to determine the chromatographic conditions for giving the best separation. Several mobile phase compositions were tried to resolve the peaks of Ofloxacin and Ketorolac tromethamine. The optimum results were attained with acetonitrile, methanol and mixed buffer of potassium dihydrogen phosphate and sodium dihydrogen phosphate buffer (pH 4.8) in the ratio of 20:20:60 (v/v) because it could resolve the peaks of Ofloxacin with retention time at 3.2 min and ketorolac retention time at 4.2 min. The two peaks were symmetric and sufficiently resolved. System suitability was carried out by injecting 5 replicate injections of 100% concentration of Ofloxacin and Ketorolac tromethamine. The resolution was found to be greater than 2 and the other parameters are presented in Table 1.

Specificity of the chromatographic method was tested by injecting mobile phase as blank, placebo solution and sample concentration prepared from marketed formulation. The response was compared with that obtained from the standard drug. The chromatogram confirms the presence of Ofloxacin and Ketorolac tromethamine at 3.2 min and 4.2 min respectively without any interference. Thus the developed method was specific for analyzing the commercial formulations for Ofloxacin and Ketorolac tromethamine. An optimized chromatogram with the retention times of Ofloxacin and Ketorolac tromethamine was shown in the Figure 2.

The peak areas corresponding to the concentration range of Ofloxacin 20-60 µg/mL and ketorolac 12-36 µg/ml prepared in triplicate were plotted against the respective concentrations. The calibration curves were linear in the range studied for Ofloxacin and Ketorolac tromethamine, respectively, with mean correlation coefficients (n=3) of 0.999 and higher, the representative calibration curve is shown in Figure 3. The regression analysis was given in Table 2.

Accuracy of the proposed method was assessed by standard addition method at 50%, 100% and 150% levels of recovery to the pre analyzed sample in triplicate. The recovery of the added standard to the sample was calculated and it was found to be 96-99 %w/w for Ofloxacin and 97-100 %w/w for ketorolac respectively and the % RSD was less than 2 for both the drugs which indicates good accuracy of the method. The result of recovery was given in table 3.

LOD and LOQ were calculated from the average slope and standard deviation of y intercepts of the calibration curve. Limit of detection for Ofloxacin and Ketorolac tromethamine were 11.24 µg/mL and 28.20 µg/mL respectively where as limit of quantitation of Ofloxacin and Ketorolac tromethamine were 34.07 µg/mL and 85.44 µg/mL respectively indicating high sensitivity of the method. LOD and LOQ value was given in table 2. The method is precise with a %RSD of less than 2 for both Ofloxacin and Ketorolac tromethamine respectively. The results of intraday and inter day precision was given in table 4. Robustness was carried out by change in the flow rate (±1mL/min), mobile phase variation (±5%) and variation in wavelength (±2 nm).Solution of 100% concentration is prepared and injected in triplicate for each varied operational condition.
and % R.S.D was found to be less than 2. The result was given in table 5. The proposed method was applied for the assay of commercial formulation containing Ofloxacin and Ketorolac tromethamine. Each sample was analyzed in triplicate. The mean recovery values were 98.5 and 99.4 for Ofloxacin and Ketorolac tromethamine. The result of estimation was given in table 6.

**CONCLUSION**

The proposed RP-HPLC method for simultaneous assay Ofloxacin and Ketorolac tromethamine in combined dosage forms was validated, and found to be applicable for routine quantitative analysis of Ofloxacin and Ketorolac tromethamine. The results of linearity, precision, accuracy and specificity, were proved to be within the limits. The method provides selective quantification of Ofloxacin and Ketorolac tromethamine with no interference from other formulation excipients. Therefore, this method can be employed for the routine analysis for simultaneous estimation Ofloxacin and Ketorolac tromethamine in quality control of formulations and also in the diluent studies, compatibility studies etc.

**REFERENCES**


**Table 1.** System suitability parameters for ofloxacin and ketorolac tromethamine by proposed method

<table>
<thead>
<tr>
<th>Name of the Compound</th>
<th>Retention Time</th>
<th>Tailing factor</th>
<th>Theoretical plate</th>
<th>USP Resolution</th>
</tr>
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<tbody>
<tr>
<td>Ofloxacin</td>
<td>3.277</td>
<td>1.124</td>
<td>8973</td>
<td>-</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>4.186</td>
<td>1.183</td>
<td>8482</td>
<td>5.544</td>
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</table>
Table 2. Linearity studies for ofloxacin and ketorolac tromethamine by proposed method

<table>
<thead>
<tr>
<th>% Level (Approx.)</th>
<th>For ofloxacin</th>
<th>For ketorolac</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration (µg/ml)</td>
<td>Area</td>
</tr>
<tr>
<td>50</td>
<td>20.00</td>
<td>1006777</td>
</tr>
<tr>
<td>75</td>
<td>30.00</td>
<td>1507347</td>
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<tr>
<td>100</td>
<td>40.00</td>
<td>2072133</td>
</tr>
<tr>
<td>125</td>
<td>50.00</td>
<td>2564940</td>
</tr>
<tr>
<td>150</td>
<td>60.00</td>
<td>3001861</td>
</tr>
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</table>

|                   | Slope          | Intercept    | % Y-Intercept | STYEX    | Intercept    | % Y-Intercept | CC         | CC         | RSQ       | RSQ       | Residual sum of squares | Residual sum of squares |
|                   | 50478          | 11507        | 0.4           | 39202    | 7186        | 5.9           | 0.9991     | 0.9990     | 0.9982    | 0.9979    | 39202          | 61397        |
|                   | 122472         | 122472       |               |          |             |               | 0.9988     |            | 0.9992    |            |                |             |

|                   | LLD            | LLQ          |                |          |             |               |            |            |          |            |                |             |
|                   | 11.24          | 34.07        |                |          |             |               |            |            |          |            |                |             |
|                   | 28.20          | 85.44        |                |          |             |               |            |            |          |            |                |             |

Table 3A. Recovery studies for ofloxacin by proposed method

<table>
<thead>
<tr>
<th>% Level</th>
<th>Recovery range</th>
<th>% RSD at each level</th>
<th>Over all %RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>96.02-99.44</td>
<td>1.75</td>
<td>0.52</td>
</tr>
<tr>
<td>100</td>
<td>98.17-98.49</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>98.23-99.10</td>
<td>0.48</td>
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Table 3B. Recovery studies for lercanidipine by proposed method

<table>
<thead>
<tr>
<th>% Level</th>
<th>Recovery range</th>
<th>% RSD at each level</th>
<th>Over all %RSD</th>
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</thead>
<tbody>
<tr>
<td>50</td>
<td>97.56-98.54</td>
<td>0.49</td>
<td>0.54</td>
</tr>
<tr>
<td>100</td>
<td>96.44-96.89</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>98.42-99.79</td>
<td>0.95</td>
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Table 4. Method precision (Inter and intraday) studies for ofloxacin and ketorolac by proposed method

<table>
<thead>
<tr>
<th></th>
<th>For ofloxacin</th>
<th>For ketorolac</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method precision (Inter &amp; intraday)</strong></td>
<td><strong>Method precision (Inter &amp; intraday)</strong></td>
<td></td>
</tr>
<tr>
<td>96.89</td>
<td>98.56</td>
<td>97.58</td>
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<tr>
<td>97.84</td>
<td>98.72</td>
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<td>96.99</td>
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<tr>
<td>98.56</td>
<td>96.89</td>
<td>99.65</td>
</tr>
<tr>
<td>98.42</td>
<td>96.48</td>
<td>96.48</td>
</tr>
<tr>
<td>Overall Avg.</td>
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<td>97.98</td>
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<tr>
<td>Overall %RSD</td>
<td>0.81</td>
<td>1.20</td>
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Table 5. Robustness studies for ofloxacin and ketorolac tromethamine by proposed method

<table>
<thead>
<tr>
<th>Parameter</th>
<th>% RSD for Ofloxacin</th>
<th>% RSD for Ketorolac</th>
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</thead>
<tbody>
<tr>
<td>Wavelength ±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>293 nm</td>
<td>0.12</td>
<td>0.48</td>
</tr>
<tr>
<td>297 nm</td>
<td>0.23</td>
<td>0.87</td>
</tr>
<tr>
<td>Flow Rate mL/min</td>
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<tr>
<td>0.8 mL/min</td>
<td>0.56</td>
<td>0.36</td>
</tr>
<tr>
<td>1.2 mL/min</td>
<td>0.69</td>
<td>0.29</td>
</tr>
<tr>
<td>Temperature in °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30°C</td>
<td>0.34</td>
<td>0.71</td>
</tr>
<tr>
<td>40°C</td>
<td>0.36</td>
<td>0.56</td>
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Table 6. Assay of marketed samples for ofloxacin and ketorolac tromethamine by proposed method

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amount Claimed in mg per mL</th>
<th>Estimated Amount in mg/mL</th>
<th>% Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>5</td>
<td>5.12</td>
<td>97.65</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>3</td>
<td>2.93</td>
<td>102.39</td>
</tr>
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</table>
Figure 1. A, Ofloxacin. B, Ketorolac tromethamine

Figure 2A. A typical HPLC chromatogram showing the no interference of diluent for ofloxacin and ketorolac tromethamine
Figure 2B. A typical HPLC chromatogram showing the no interference of placebo for ofloxacin and ketorolac tromethamine

Figure 3. A typical HPLC Chromatogram showing the peak of Ofloxacin and Ketorolac tromethamine
Figure 4A. A typical HPLC chromatogram showing the control sample profile of ofloxacin and ketorolac tromethamine by proposed method.

Figure 4B. A typical HPLC chromatogram showing the profile of ofloxacin and ketorolac tromethamine in acidic hydrolysis by proposed method.
Figure 4C. A typical HPLC chromatogram showing the profile of ofloxacin and ketorolac tromethamine in base hydrolysis by proposed method.

Figure 4D. A typical HPLC chromatogram showing the profile of ofloxacin and ketorolac tromethamine in peroxide hydrolysis by proposed method.
Figure 4E. A typical HPLC chromatogram showing the profile of ofloxacin and ketorolac tromethamine in thermal hydrolysis by proposed method

Figure 5A. Calibration curve for Ofloxacin
Figure 5B. Calibration curve for ketorolac tromethamine