RESEARCH PAPER

Stability indicating HPLC-UV method for the simultaneous quantification of Moxifloxacin and Loteprednol in pure drug and eye drop formulations

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Abstract
A combination of moxifloxacin and loteprednol, formulated as ophthalmic eye drops at a concentration of 0.5% (w/v) for both drugs, is prescribed to address eye infections accompanied by inflammation. A literature review revealed the absence of reported methods for quantifying moxifloxacin and loteprednol. Therefore, the study expected to propose a straightforward and sensitive RP-HPLC method for determination in ophthalmic formulations. Method development trials confirmed the effective separation of analytes on an Oyster BDS Premium C18 column (250 × 4.6, 5 µm) using acetonitrile and 0.1% aqueous ortho-phosphoric acid in 65:35 (v/v), pH 5.7, at 0.8 mL/min flowrate and 243 nm wavelength. This study enables the detection of moxifloxacin and loteprednol at retention times of 8.69 min and 7.65 min, respectively within 12 min run time. Calibration curves were linear within 12.5–75 µg/mL for both moxifloxacin and loteprednol. Notably, the method exhibited a highly sensitive detection limit of 0.095 µg/mL for the analytes. The procedure successfully meets all the validation criteria outlined in the guidelines, demonstrating its validity. It exhibits minimal degradation percentages in diverse stress scenarios, including acidic, basic, peroxide-induced, thermal, and UV light conditions. Furthermore, it efficiently distinguishes between various stress-induced degradation products, confirming its ability to indicate stability. The method's suitability yields satisfactory assay percentages for both compounds suggest that the method was enough fit for quantification of moxifloxacin and loteprednol in bulk drug and ophthalmic drops formulations.

Keywords: Moxifloxacin, Loteprednol, HPLC method, Stress study, Ophthalmic solution

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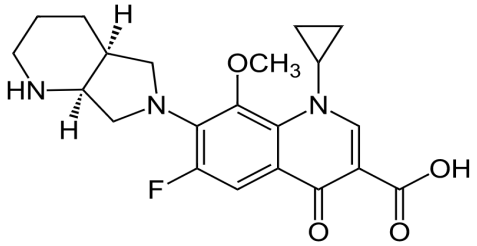
1. Introduction

Moxifloxacin is a quinolone antibiotic with a broad spectrum of activity that treats a variety of infections due to gram-positive bacteria and gram-negative bacteria, including tuberculosis, pneumonia, sinusitis, and endocarditis[1]. Moxifloxacin is also used for conditions like meningitis, cellulitis, anthrax, respiratory tract infections, and intra-abdominal infections. Moxifloxacin can be found in the oral, injectable, and ophthalmic (eye drop) forms[2]. Its antibacterial action is due to its capacity to block DNA gyrase, a vital enzyme involved in bacterial DNA replication[3]. But moxifloxacin has been linked to severe adverse effects like exacerbation of myasthenia gravis, peripheral neuropathy, and tendon rupture with spontaneous rupture, although other significant side effects are diarrhea, dizziness, and headache[4].

Loteprednol belongs to corticosteroids class drug used for the treatment of eye infections. It was used to reduce inflammation of eye after eye surgery, seasonal allergic conjunctivitis, vernal keratoconjunctivitis, uveitis, episcleritis, chronic forms of keratitis and giant papillary conjunctivitis[5]. It accelerates the release of certain natural substances that causes swelling, itching and pain[6]. The significant side effects during the usage of loteprednol include eye pain, foreign body sensation and chamber inflammation. The most common side effects include headache, runny nose, teary eyes, dry, red, or itchy eyes and burning feeling[7].



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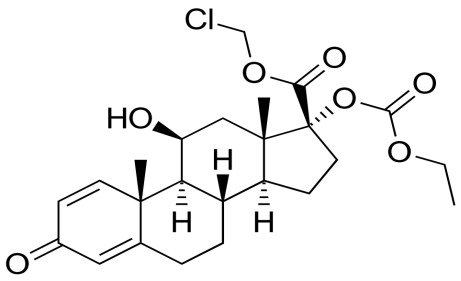


A B

Fig. 1: Chemical structure of moxifloxacin (A) and loteprednol (B)

Moxifloxacin (antibiotic) and loteprednol etabonate (corticosteroids) was available as fixed dose combined eye drop formulation at 0.5% (w/v) of loteprednol etabonate and 0.5% (w/v) of moxifloxacin. This combination was prescribed for the treatment of bacterial eye infection with inflammation. This combination was also effective for treatment of various eye problems such as chemical burns, allergies, shingles, eye injury, severe acne, iritis, uveitis and radiation. The available literature for the available analytical methods confirms that one analytical spectrophotometer Q-absorbance ratio method for quantification of moxifloxacin and loteprednol[8]. Number of methods reported for estimation of moxifloxacin in single[9-12] or in combination with other drugs such as prednisolone[13,14], flavoxate[15], bromfenac sodium and moxifloxacin[16]. Few methods reported for the estimation of loteprednol in single[17,18] or in combination with levofloxacin[19], tobramycin[20] and gatifloxacin[21-23]. Based on the reports available in literature, it was confirmed that there is no analytical method has been documented for measuring moxifloxacin and loteprednol. Hence, we planned to propose a straightforward and precise HPLC method to assess the stability and quantify these drugs in ophthalmic formulations.

2. Materials and Methods:

2.1. Reagents and chemicals:

The pure moxifloxacin (98.49 %) and loteprednol (98.71 %) were procured from Alembic pharmaceuticals Ltd, Hyderabad, Telangana. The eye drop formulation with brand Mflotas® containing 0.5 % (w/v) of moxifloxacin and 0.5 % (w/v) of loteprednol was purchased from local market. The HPLC solvents like methanol, acetonitrile, Milli-Q® water and LR grade chemicals like sodium hydroxide, hydrogen peroxide, hydrochloric acid, phosphoric acid, formic acid was procured from Merck chemicals, Mumbai.

2.2. Instruments:

The assay performed on Agilent 1100 HPLC instrument (USA) equipped with programmable solvent delivery quaternary pump (G1311), temperature programmable auto-injector with sample injectable capacity of 0.1 – 1500 µL and wavelength programmable UV detector. Different configurations of C18 columns were used to resolving the analytes and Agilent chem-station software was used for detecting and integration of column eluents.

2.3. Standard solution preparation:

Accurately weighed 25 g of moxifloxacin and loteprednol were separately transferred into 25 mL volumetric flasks. To dissolve the drugs, 15 mL of methanol which serves as diluent was added to each flask. The mixtures were then subjected to sonication for two minutes to ensure that both compounds fully dissolved in the solvent. After complete dissolution, they were carefully filtered through membrane filter (0.2 µm) into separate, clean, and dry flasks to remove any undissolved particles or impurities. The final volume in each flask was adjusted to 25 mL by adding additional methanol yields 1000 µg/mL solution of moxifloxacin and loteprednol separately. To prepare a combined standard solution, equal volumes of these individual stock solutions were accurately measured and mixed in a separate flask. This combined solution was subsequently utilized for method optimization followed by validation study.

2.4. Assay solution preparation:

The ophthalmic preparation containing 0.5% (w/v) moxifloxacin and 0.5% (w/v) loteprednol, branded as Mflotas® was used to create the formulation solution. Precisely measured 1 mL of ophthalmic formulation was carefully shifted into a 10 mL flask having 5 mL of methanol. Proper dissolution of the components was ensured by subjecting to sonication in an ultrasonic bath for 2 min. After sonication, the solution was filtered through a 0.2µm filter into a 10 mL flask to eliminate any particulate matter or impurities and final volume was making till 10 mL through same solvent. This procedure results a formulation stock solution with a concentration of 500 µg/mL for both moxifloxacin and loteprednol. The required concentration for analysis was prepared with this stock solution by appropriate dilution. The final diluted solution was then utilized for the quantification of moxifloxacin and loteprednol in the ophthalmic formulation.

2.5. Development of analytical method:

The optimization of method for resolution of moxifloxacin and loteprednol was performed by adopting systematic strategies as per ICH guidelines[24]. A UV-visible spectrophotometer was employed to determine iso-absorption wavelength for detection of moxifloxacin and loteprednol. To achieve this, standard solutions of both drugs, each at a 10 µg/mL were individually scanned over 200–400 nm and the overlay of the UV absorption spectra confirmed the iso-absorption wavelength, which was then selected for further analysis. Since moxifloxacin and loteprednol are polar compounds that exhibit efficient resolution on non-polar columns, C18 columns from different manufacturers were tested to achieve optimal

separation. To establish the most suitable mobile phase, different compositions were evaluated by varying solvents and adjusting pH levels within a defined range. Initially, 1.0 mL/min mobile of mobile phase was fixed for the study and further optimization was performed in 0.5 mL/min to 1.5 mL/min range to identify the ideal conditions for chromatographic separation. At each optimized parameter, standard solutions containing known concentrations of moxifloxacin and loteprednol were injected and corresponding responses were recorded. The recorded data included peak area, intensity, shape, and overall system suitability under various conditions. The method conditions that produced the most favorable results such as well-defined peaks, strong signal intensity, and minimal background noise were selected as the optimal parameters for separating and analyzing moxifloxacin and loteprednol. These optimized conditions were then subjected to method validation to ensure accuracy, precision, and robustness.

2.6. Method Validation:

The optimized method was validated for various parameters that include specificity, system suitability, range of analysis, repeatability, reproducibility, accuracy and sensitivity. The method applicability for resolution of various stress degradation products was assessed by performing various stress studies. Further the method applicability for evaluation of moxifloxacin and loteprednol in formulations was evaluated.

The blank, 100 % concentration solution of moxifloxacin and loteprednol was studied in the proposed method. Chromatographic response observed in each analysis was compared for the conformation of method specificity and system suitability. The range of the analysis for moxifloxacin and loteprednol in the proposed method was evaluated by analyzing 25 to 200 % level to the standard concentration. The accurate fit concentration level was considered as range of analysis for both analytes in the developed method. The 100 % concentration solution of moxifloxacin and loteprednol was analyzed in the one day (n = 6) for intraday precision, for three consecutive days (n = 2 in each day) in interday precision and three different analysts for in the same day (n=2 for each analyst) in ruggedness study. The % relative standard deviation (RSD) of less than 2 in each study for each analyst was considered as acceptable as per the guidelines. The same level solution was analyzed by both positive and negative change in the proposed method condition. The peak area response in each changed condition was compared with the results observed in the same level concentration solution analyzed in the proposed method condition. The % change of less than 2 for moxifloxacin and loteprednol in each changed condition was considered as acceptable.

The 50%, 100 % and 150% levels in the calibration range was prepared and analysed in the developed for evaluating the accuracy of the developed method. The spiked level solution was prepared and analysed in the proposed method. The % recovery was calculated by comparing the peak area response of the individual analyte with its corresponding standard calibration curve. The % RSD of the recovery results in each spiked level for both moxifloxacin and loteprednol was calculated. The % recovery of 98-102 % and the % RSD of less than 2 was acceptable. The lowest concentration of moxifloxacin and loteprednol in the developed method that can detect and quantify was evaluated in terms of detection limit (LOD) and quantification limit (LOQ). The LOD and LOQ were assessed by adopting signal (s) to noise (n) ratio approach. The s/n of 3 and 10 was confirmed as LOD and LOQ respectively that can be expressed in terms of µg/mL for both moxifloxacin and loteprednol.

The method's effectiveness for separating and identifying various stress degradation compounds was assessed through different stress degradation studies, including acidic, basic, peroxide, thermal, and UV light conditions[25]. Accurately weighed 50 mg samples of standard timolol, dorzolamide, and latanoprost were separately mixed with 50 mL of different degradation agents to evaluate their stability under various stress conditions. Hydrochloric acid (0.1 N) was used for acidic degradation, sodium hydroxide (0.1 N) for basic degradation, and hydrogen peroxide (3%) for oxidative degradation. These prepared solutions were incubated in the dark for 24 hours to allow sufficient reaction time. After incubation, the solutions were neutralized and diluted to the required standard concentration before proceeding with the analysis. In thermal and UV degradation studies, standard moxifloxacin and loteprednol samples were exposed to elevated temperatures and UV light. Specifically, both drugs were subjected to 60°C in an air oven for 24 hours to assess thermal stability, while separate samples were exposed to UV light at 254 nm for the same duration to evaluate photostability. After exposure, the degraded samples were diluted to standard concentrations before analysis. All stress-degraded samples were analyzed using the developed chromatographic method, and the resulting chromatograms were carefully examined. The analysis aimed to verify the reliability of the method in detecting degradation products while ensuring accurate quantification of the parent compounds under stressed conditions. The applicability of the developed method was further assessed by analyzing a formulation solution prepared from a commercially available moxifloxacin and loteprednol ophthalmic product. The prepared solution was subjected to chromatographic analysis under the established conditions. The peak area response obtained from the chromatogram was then compared with the standard calibration curve to determine the percentage assay of each analyte. The results were carefully evaluated to verify the method's accuracy and effectiveness in quantifying moxifloxacin and loteprednol in the marketed formulation, confirming its suitability for routine quality control analysis.

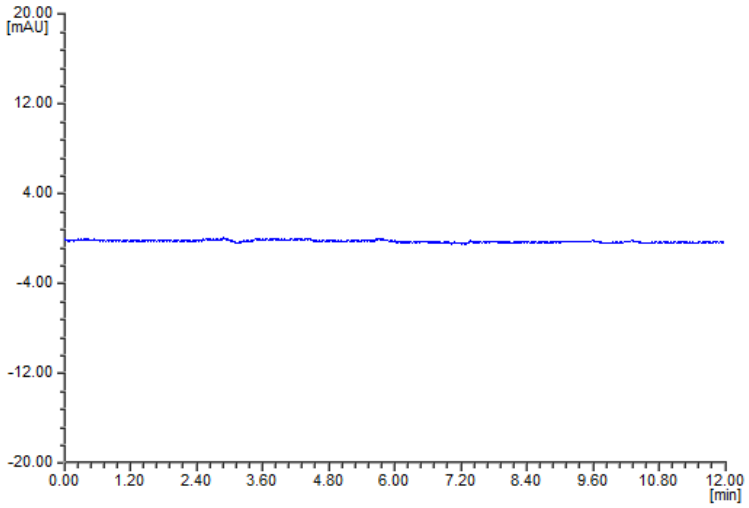
3. Results and Discussions:

The method development was initiated by identifying the suitable detector wavelength for detection of both analytes. The iso-absorption wavelength of moxifloxacin and loteprednol in methanol solution confirmed 243 nm as suitable wavelength for detection of both analytes. Hence the method optimization studies were performed by fixing 243 nm as suitable detector wavelength. The method development trails was performed by change in various solvent compositions of mobile phase such as methanol, acetonitrile and water containing less strength of formic acid, ortho-phosphoric acid etc. Various configurations of columns and mobile phase flow rate changes were also performed for the effective separation and sensitive detection of moxifloxacin and loteprednol. The optimization of the method was concluded by achieving optimum separation of moxifloxacin and loteprednol with acceptable system suitability. The optimized conditions obtained after the completion of method development trails along with system suitability results were summarized in table 1. The method passes the system suitability and hence was studied for further validation.

Table 1. Optimized HPLC conditions for the analysis of moxifloxacin and loteprednol along with system suitability results

S No	**Method Parameter**	**Results achieved**	
1	Stationary phase	Oyster BDS Premium C18 (250 × 4.6 mm, 5 µm particle size) column	
2	Mobile Phase	Acetonitrile and 0.1% aqueous ortho-phosphoric acid in 65:35 (v/v)	
3	pH	5.7	
4	Flow rate	0.8 mL/min	
5	Elution	Isocratic	
6	Wavelength	243 nm	
7	Run time	12 min	
System suitability Parameter		**Results noticed**	
		Moxifloxacin	**Loteprednol**
8	Concentration	50 µg/mL	50 µg/mL
9	Elution Time	8.69 min	7.65 min
10	Resolution	4.85	--
11	Tailing Factor	1.03	0.98
12	Plate count	5817	4219

The developed chromatographic method was applied to analyze a standard solution containing both moxifloxacin and loteprednol at a concentration of 50 µg/mL. The resulting chromatogram exhibited distinct, well-separated peaks with retention times of 8.69 minutes for moxifloxacin and 7.65 minutes for loteprednol. The baseline remained clear and stable throughout the analysis, with no interference or unexpected peaks observed. Additionally, the blank chromatogram showed no detectable signals across the entire run time, confirming that the method is highly specific for the quantification of moxifloxacin and loteprednol. Figures 4A and 4B present the chromatograms of the blank and standard solutions, respectively, under the optimized analytical conditions.



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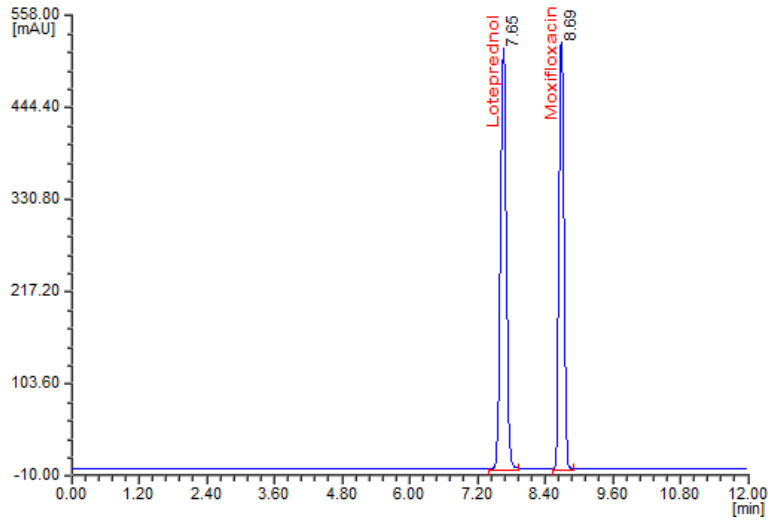


B

Figure 4. Chromatogram noticed for analysing blank (A) and standard solution (B) of moxifloxacin and loteprednol in the proposed method

Calibration curve solutions for moxifloxacin and loteprednol were evaluated through this optimized method. A highly correlated calibration curve was obtained for both analytes in the range of 12.5 – 75 µg/mL. The regression equations were determined to be y = 8564.3x - 7462.7 (R^2 = 0.9991) for moxifloxacin and y = 7316.3x - 4116.1 (R^2 = 0.9997) for loteprednol (Table 2). These results confirm the excellent linearity of the method indicates its reliability for the accurate quantification of moxifloxacin and loteprednol

Table 2. Linearity results

S. No	Moxifloxacin Concentration in µg/mL	Area response	Loteprednol Concentration in µg/mL	Area response
1	12.5	97848.5	12.5	89475.8
2	25.0	204516.7	25.0	179415.2
3	37.5	312518.3	37.5	269105.3
4	50.0	427953.8	50.0	357942.7
5	62.5	534156.2	62.5	450919.5
6	75.0	626351.5	75.0	548986.3

The repeatability and ruggedness of the developed method were evaluated using a standard solution of moxifloxacin and loteprednol at a concentration of 50 µg/mL. The % RSD values were calculated for intraday and interday precision, as well as for ruggedness. In intraday precision, the % RSD values were 0.32 for moxifloxacin and 0.23 for loteprednol whereas interday precision, the values were 1.03 for moxifloxacin and 0.56 for loteprednol. The % RSD values for ruggedness were 0.45 for moxifloxacin and 0.53 for loteprednol. All the % RSD values were within the acceptable limits, indicating that the method is both precise and rugged.

A robustness study was performed to assess the impact of small variations in method conditions on the chromatographic response. The percentage change in the peak area response for each analyte was calculated, and the results were found to be within acceptable limits, as shown in Table 3. Additionally, the system suitability of each analyte under the modified conditions was summarized, confirming that the method is robust and can withstand small changes in the analytical conditions without affecting its performance.

Table 3. Robustness results

S No	Parameter changed	Changed condition	Moxifloxacin		Loteprednol	
1	Mobile phase composition	Acetonitrile and ortho-phosphoric acid in 60:40	433166.9	1.22	353849.4	1.14
2		Acetonitrile and ortho-phosphoric acid in 70:30	425321.7	0.62	357923.6	0.01
3	Mobile phase	5.6	429851.0	0.44	357547.1	0.11

4	pH	5.8	432093.6	0.97	353707.9	1.18
5	Detector	238 nm	430077.0	0.50	357347.6	0.17
6	wavelength	248 nm	429524.7	0.37	353503.6	1.24

The spiked recovery was conducted by considering 25, 50 and 75 µg/mL in the linearity range as 50, 100 and 150 % spiked level for both moxifloxacin and loteprednol. As summarized in table 4, the % recovery results of moxifloxacin and loteprednol were observed to be under the acceptable level of 98-102% in each spiked level. The % RSD of recovery results were within the acceptable level of less than 2% in each spiked levels. This proved that method proposed for assay moxifloxacin and loteprednol was confirmed to be accurate.

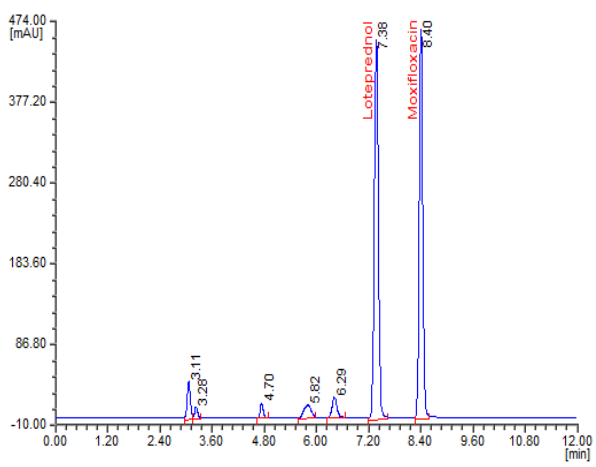
Table 4. Recovery results

S. No.	Analyte	Accuracy Level	Solution concentration µg/mL	Amount estimated* Mean ± SD	% Recovery* Mean ± SD	% RSD
1	Moxifloxacin	50 %	25	24.63 ± 0.082	98.53 ± 0.327	0.34
2		100 %	50	49.78 ± 0.046	99.56 ± 0.092	0.73
3		150 %	75	74.16 ± 0.640	98.88 ± 0.853	0.39
4	Loteprednol	50 %	25	24.63 ± 0.083	98.52 ± 0.330	0.33
5		100 %	50	49.45 ± 0.362	98.90 ± 0.725	0.09
6		150 %	75	74.67 ± 0.288	99.55 ± 0.384	0.86

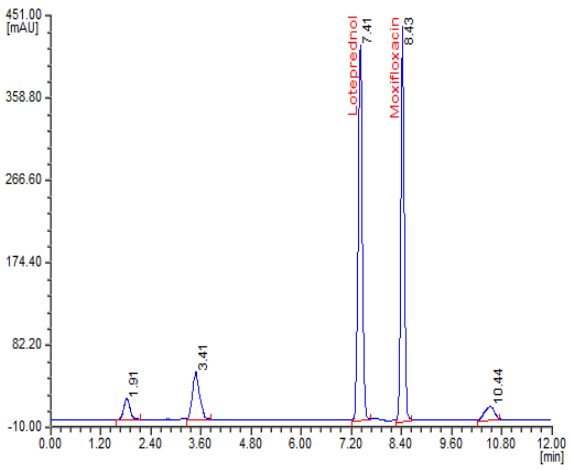
* n=3

The s/n approach confirmed LOD as 0.095 µg/mL for both moxifloxacin and loteprednol whereas 0.303 µg/mL as LOQ for both analytes. These results demonstrate that the developed method has sufficient sensitivity for the detection and accurate analysis of moxifloxacin and loteprednol in pharmaceutical formulations.

The proposed method was studied for its applicability to solve different stress degradation compounds formed due to the stress expose of moxifloxacin and loteprednol. The stressed sample was analysed after 24 hours of stress exposer and the chromatograms were verified to observed method efficiency to resolve stress degradation products. The stress degradation study results proved that, high % degradation of 6.02 and 7.15 % was noticed for moxifloxacin and loteprednol respectively in base degradation study. In these five degradation products were retained at 3.1, 3.2, 4.7, 5.8 and 6.2 min. In acid degradation three degradation products were well resolved and retained with a % degradation of 4.85 and 3.76 min respectively for moxifloxacin and loteprednol. The % degradation of 4.72 and 3.85 % for moxifloxacin and loteprednol respectively was calculated in peroxide degradation with 4 additional degradation products detected in the chromatogram. The % degradation of 3.05 and 2.57 % was noticed in peroxide degradation study for moxifloxacin and loteprednol respectively. The % degradation of 5.72 and 6.91 % was achieved for moxifloxacin and loteprednol respectively in UV stress study with four stress degradation products recognised in the chromatogram. In all the stressed conditions studied, no interference of excipients and the stress degradation compounds with moxifloxacin and loteprednol. The % degradation of less than 10% was noticed for both analytes in all the stress conditions studied proved that the method was enough suitable for the separation and resolution of degradation products of moxifloxacin and loteprednol. The chromatograms observed in stress degradation study of moxifloxacin and loteprednol in the developed method was presented in fig. 5.



Base conditions



Acid conditions

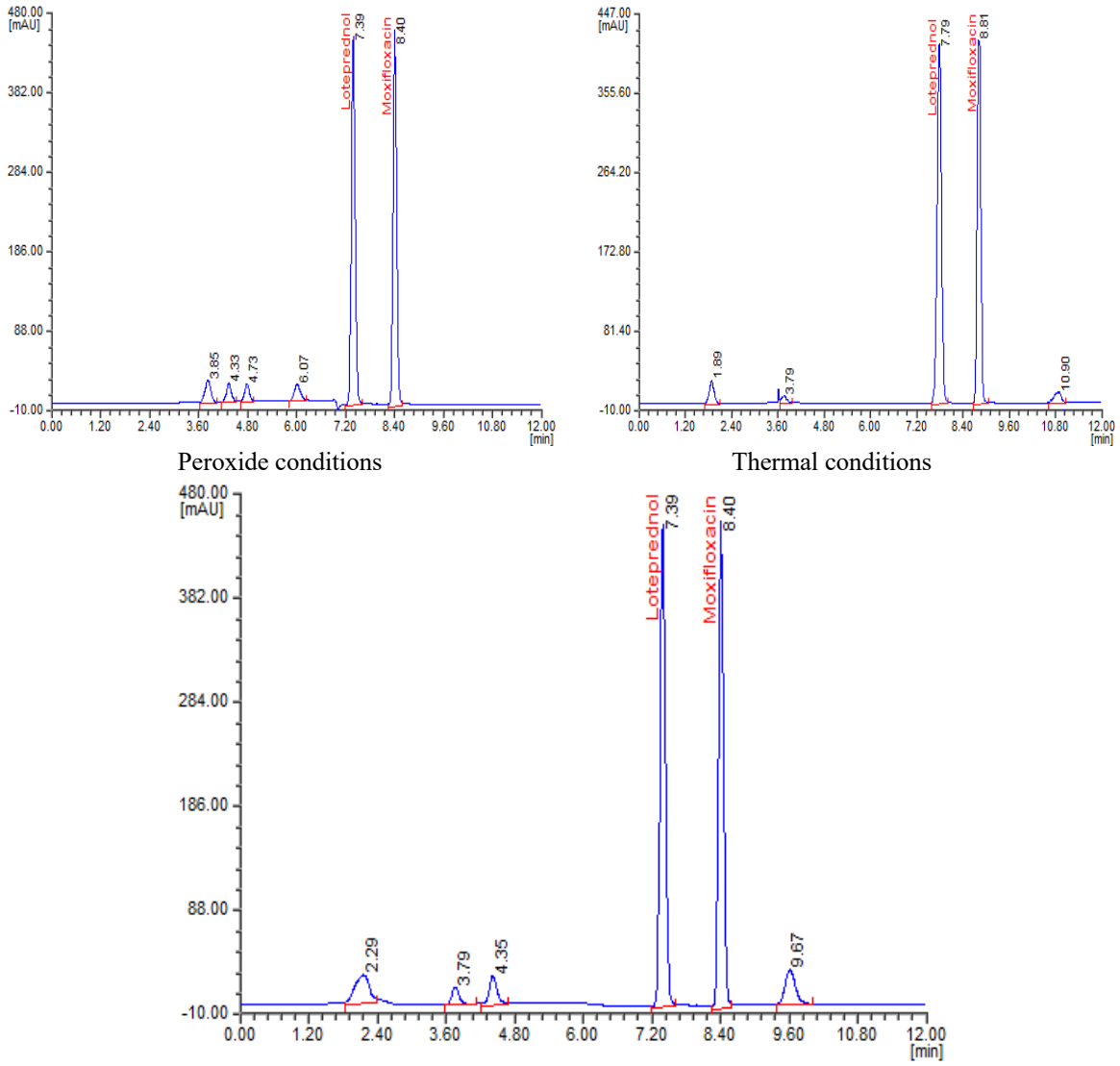


Figure 5. Chromatograms noticed in forced degradation study test of moxifloxacin and loteprednol

The developed method was applied to quantify moxifloxacin and loteprednol in ophthalmic formulations. The test solution at 50 µg/mL concentration of moxifloxacin and loteprednol that was prepared using Mflotas® formulation sample solution was analysed. The chromatogram observed for sample analysis (Fig. 6) shows peaks corresponds to moxifloxacin and loteprednol was identified at a retention time very close to the standard. There is no peaks corresponds to formulation excipients or the other ingredients used for the preparation of formulation was identified in the sample chromatogram. There is no baseline disturbances throughout the run time of sample analysis proves the method specificity. The area results of moxifloxacin and loteprednol in the sample chromatogram was compared with its corresponding calibration for the calculation of % assay of analytes in the sample. The % assay was obtained as 98.81 % and 98.46 % for moxifloxacin and loteprednol respectively. The high % assay with acceptable validation proved that the method was enough suitable for the detection and quantification of moxifloxacin and loteprednol in ophthalmic formulations.

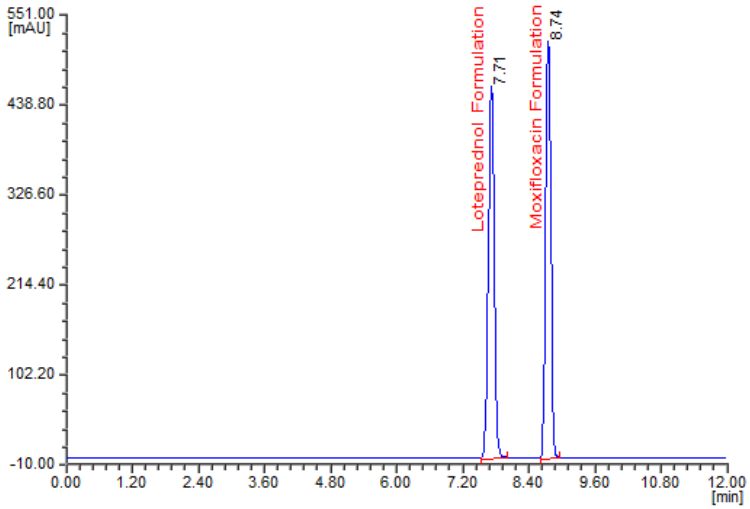


Figure 6. Formulation solution analysis chromatogram of moxifloxacin and loteprednol

4. Conclusion

This study presents a straightforward, accurate, and sensitive stability-indicating HPLC method for the identification and quantification of moxifloxacin and loteprednol in both pure drug forms and ophthalmic dosage forms. The method utilizes a simple and convenient mobile phase composed of acetonitrile and 0.1% aqueous ortho-phosphoric acid in a 65:35 (v/v) ratio, with a flow rate of 0.8 mL/min, which minimizes the usage of the mobile phase. The Oyster BDS Premium C18 (250 × 4.6 mm, 5 µm particle size) column was chosen as the stationary phase, allowing the separation of moxifloxacin and loteprednol with retention times of 8.69 minutes and 7.65 minutes, respectively, and a total run time of 12 minutes. The method offers several advantages, including the simultaneous separation of both analytes, reproducibility, wide linearity ranges, and relatively short retention times (less than 8 minutes). The HPLC technique is cost-effective due to the low cost of the mobile phase and the use of isocratic elution. Additionally, HPLC–UV equipment is commonly available in many laboratories, making it accessible for routine use. The proposed method was successfully applied to marketed eye drop formulations and achieves satisfactory percentage recoveries. These results demonstrates that the proposed method is efficient, easy-to-use and robust friendly analytical tool for high-throughput analysis in quality control laboratories by ensuring the accurate determination of moxifloxacin and loteprednol in pharmaceutical formulations.

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