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UV Spectrophotometric and Stability Indicating RP-HPLC Assay Methods for the Estimation of Etodolac in Bulk and Tablet Dosage Form

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ABSTRACT

Objectives: The present article involved the development of sensitive and validated reverse phase liquid chromatographic and UV-spectrophotometric method for the determination of etodolac in bulk and pharmaceutical dosage form. **Methods:** The presents UV method is based on measurement of absorption at maximum at 226 nm using methanol and water (70:30) as a solvent. The stock solution of etodolac was prepared and subsequent suitable dilution was prepared in distilled water to obtained standard curve. The standard solution of Etodolac shows absorption maxima at 226 nm. **Results:** The drug obeyed beer lambert's law in the concentration range of 2-20 µg/ml with regression coefficient 0.9998 at 226 nm. The chromatographic method was optimised using Phenomenex Luna C_{18}, 100A, 5mm, 250mm x 4.6mm i.d. column with UV detection at 226 nm and Acetonitrile: Methanol in 65:35 ratio at a flow rate of 1.0 ml/ min. The proposed method was successfully applied to the determination of Etodolac in bulk and pharmaceutical dosage form. The method was found linear over the range of 0 – 48 µg/ml. The recovery was observed in the range of 98% to 102% and limit of detection and limit of quantification were found to be 0.08 µg/ml and 0.26 µg/ml. Different analytical performance parameters such as precision, accuracy, limit of detection, limit of quantification and robustness were determined and found satisfactory according to International Conference on Harmonization (ICH) guidelines. **Conclusion:** The developed methods were found reliable, easy and validated for the estimation of etodolac in bulk and tablet dosage form.

Key words: RP-HPLC, Etodolac, UV-spectrophotometry, Validation, ICH Guidelines.

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INTRODUCTION

Etodolac is a non-steroidal anti-inflammatory agent (NSAIDs). It is a white crystalline compound insoluble in water but soluble in alcohols and chloroform. Chemically etodolac is 2-{1,8-diethyl-1H,3H,4H,9H-pyrano[3,4-b]indol-1-yl}acetic acid[1,2] (Figure 1). It is used as anti-inflammatory agent, cyclooxygenase inhibitor, analgesic and antipyretic.[3] A review of the literature on numerous clinical studies showed that etodolac (200 to 600 mg/day) is effective in the treatment of osteoarthritis and rheumatoid arthritis.[4,5] The combination of etodolac with ibuprofen is more effective for treating osteoarthritis than etodolac alone. Etodolac is used to relieve pain from various conditions.[6] It also reduces pain, swelling and joint stiffness from arthritis. This medication is known as a nonsteroidal anti-inflammatory drug (NSAID).[7,8] It works by blocking your body's production of certain natural substances that cause inflammation. The pharmacological effects of the etodolac are due to the inhibition of synthesis of prostaglandins which are involved in the fever, swelling, pain and the inflammation[9] Extensive literature survey reveals that some UV and HPLC method has been developed for the etodolac with other combination. Only two UV methods was found for the estimation of etodolac only. That reported methods has huge disadvantages and found ambiguity in their reported empirical evidences. One reported method[10] the authors even did not cited any spectrum evidences for tablet assay and etodolac. Reported simultaneous HPLC method[11,12] utilized gradient elution technique and clearly understood about the inclusion of fabricated peak for the optimization. Another simultaneous HPLC method[13] not performed limit of detection and quantification study, therefore the question should raised on sensitivity issues. In the Simultaneous estimation of another method by UV and HPLC,[14,15] the authors has not included any HPLC optimization peak for API and also for the fixed dose tablet. Stability indicating method for etodolac was not reported till now. After considering the above ambiguity and disadvantages in the reported methods for etodolac estimation, there is really a need to developed reliable, easy, fast and validated method for the estimation of etodolac. Therefore, efforts has been take by the authors to develop a reliable, fully validated and stability indicating method for the estimation of etodolac in bulk and marketed dosage form in accordance with the International Conference on Harmonization (ICH) Guidelines Q2B for the validation of analytical procedure.[16]

MATERIALS AND METHODS

HPLC Instrumentation and Conditions

The Spectroscopic analysis was carried out using double beam UV-Visible Spectrophotometer (UV 1800) ELICO SL-159 with 1mm pathlength matched quartz cells was used for analytical purpose. The HPLC system employed was Waters 717 autosampler, isocratic, Empower 2 Software along with UV-Visible Detector.

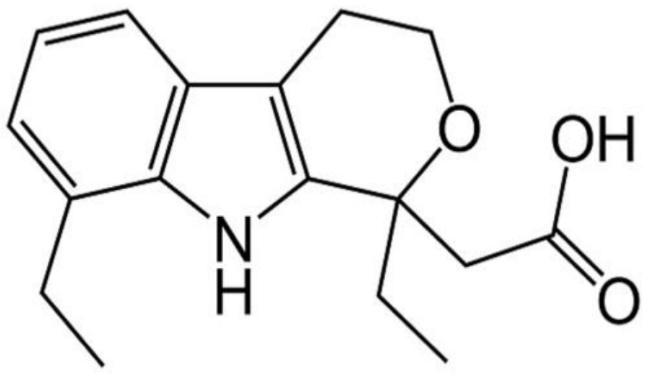

Figure 1: Chemical structure of etodolac.

Chemicals / reagents used

The active pharmaceutical ingredient etodolac (99.46% purity) was kindly obtained from the Dr. Reddy's Laboratories, Hyderabad, India. The marketed dosage form Etura-500 (etodolac 500mg) was purchased for the local market in Hyderabad, India. Methanol, acetonitrile used were HPLC grade form Loba chemicals, Mumbai, India. Dipotassium hydrogen phosphate, orthophosphoric acid, hydrochloric acid were analytical grade and from SD- fine chemicals, Mumbai. HPLC grade distilled water was used from Millipore.

Preparation of standard solution of etodolac

Weighed accurately 100 mg of Etodolac, transferred into 100 ml Standard flask, dissolved and made up to the volume-using methanol and water (70:30). This solution had a Concentration of 1 mg per ml of etodolac. Accurately pipetted out 10ml of aliquot separately into 100 ml standard flask and the volume was made up to 100 ml using methanol and water (70:30). The resulting solution had a concentration of 100µg/ml of etodolac. Accurately pipetted out 1ml of solution B separately into 10 ml standard flask and the volume was made up to 10 ml using methanol and water (70:30). The resulting solution had a concentration of 10µg/ml of etodolac.

Study of spectral characteristic of etodolac

After enabling the initial adjustments and Blank correction-using methanol the solution C was scanned separately in the UV region ranging from 200 nm to 350 nm. A broad band of Absorption spectrum was observed with maximum absorption at 226nm for etodolac.

Calibration curve of etodolac in methanol by UV absorption method

Accurately pipette 0.2 – 2 ml of solution B separately in to each ten 10 ml standard flasks and volume were made up using methanol. The absorbance of each solution was measured at 226nm for Etodolac with methanol and water (70:30) as blank.

Estimation of etodolac in pharmaceutical dosage form

Twenty tablets containing each of 500mg Etodolac was accurately weighed and finely powdered in a glass mortar. A weight equivalent to 100mg Etodolac was accurately weighed and transferred to a 100 ml standard flask. 40 ml of methanol and water (70:30) was added and swirled gently for a period of 10 min. The clear supernatant solution was then transferred to 100ml standard flask through a Whatman No 1 filter paper. The residue was further extracted twice with 20 ml each of methanol and passed through the same filter paper and the volume was made up to 100ml with methanol. The resulting solution had a concentration of 1mg/ml (solution A). Accurately pipetted 1 ml of the above solution into a 50 ml standard flask and made up to volume with methanol and water (70:30). The final solution had a concentration of 100 µg/ ml Etodolac (solution B). Accurately pipetted out 1ml of solution B into 10ml standard flask and the volume was mad up using methanol and water (70:30) to obtain concentration of 10µg/ml of Etodolac. The absorbance of this solution was measured at 226 nm. The concentration of each drug is calculated using absorbance ratio method.

Validation of the proposed method

Linearity and Range

Calibration curves were prepared for the drug at 226nm and entire calibration data at the selected analytical wavelength. The solutions were prepared in the concentration range 2-20 µg/ml at 226nm.

Repeatability / Precision

The preparation of calibration graph of Etodolac at 226 nm was repeated 5 times in a day for inter-day precision and on five different days for inters day precision. The average % RSD was calculated.

Limits of Detection and Quantification

Calibration curve was prepared for 5 times at 226 nm and SD of the intercept was calculated for the drug. The LOD and LOQ are calculated.

Recovery Studies

Accuracy of the proposed method was determined by performing recovery studies. A fixed amount of drug from dosage form was taken and pure standard drug at different concentrations within Beer's range was added the total concentration was found by the proposed method. The determination with each concentration was repeated three times and average percent recovery of the added standard was calculated.

Method development and validation for etodolac by RP-HPLC

Selection of wavelength

The standard and sample stock solutions were prepared separately by dissolving standard and sample in a solvent in mobile phase diluting with the same solvent. (After optimization of all conditions) for UV analysis. It scanned in the UV spectrum in the range of 200 to 400nm. This has been performed to know the maxima of etodolac, so that the same wave number can be utilized in HPLC UV detector for estimating the Etodolac. While scanning the Etodolac solution we observed the maxima at 226 nm.

Sample and standard preparation for the analysis

25 mg of etodolac standard was transferred into 25 ml volumetric flask, dissolved and make up to volume with mobile phase to obtain 1µg/ml. Further dilution was done by transferring 1 ml of the above solution into a 10ml volumetric flask and subsequent dilution was made to obtain 10 µg/ml with mobile phase.

Mobile phase preparation

650mL (65%) of acetonitrile and 350mL of methanol (35%) were mixed well and degassed in ultrasonic water bath for 15 min. The solution was filtered through 0.45 µm filter under vacuum filtration.

Estimation of etodolac in marketed pharmaceutical dosage form

Twenty pharmaceutical dosage forms were taken and the I.P. method was followed to determine the average weight. Above weighed tablets were finally powdered and triturated well. A quantity of powder equivalent to 25 mg of drugs were transferred to 25 ml volumetric flask, make and solution was sonicated for 15 min, there after volume was made up to 25 ml with same solvent. Then 10 ml of the above solution was diluted to 100 ml with mobile phase. The final concentration for the sample was prepared 40 mg/ml. The solution was filtered through a membrane filter (0.45 mm) and sonicated to degas. The solution prepared was injected in five replicates into the HPLC system and the observations were recorded. A duplicate injection of the standard solution was also injected into the HPLC system and the peak areas were recorded.

Method Validation

Accuracy

To determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts (80%, 100% and 120%) of pure drug of Etodolac were taken and added to the pre-analysed formulation of concentration 40mg/ml. From that percentage recovery values were calculated.

Precision

Repeatability

The precision of each method was ascertained separately from the peak areas and retention times obtained by actual determination of six replicates of a fixed amount of drug. Etodolac (API). The percent relative standard deviation was calculated for etodolac.

Intra day and Inter day

To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day. The standard solutions prepared in the precision was injected on the other day, for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits. The percent relative standard deviation was calculated.

Specificity

The specificity study was carried out by placebo interference test of the sample solution using 500 mg of placebo equivalent to one tablet dissolved in 100ml of mobile phase and the placebo solution was treated like a standard solution. The solution was injected to the chromatographic system to evaluate the possible interfering peaks.

System suitability

To verify whether analytical system is working properly, this study was evaluated by injecting the standard drugs of etodolac six times. The RSD of the parameters like theoretical plates, peak area, retention time and asymmetric factor were calculated.

Linearity and Range

The linearity of an analytical procedure is its ability to obtain test results which are directly proportional to the concentration of analyte in the sample. For this study the solution was prepared in the range of 0.5-50 µg/ml and injected. Regression coefficient was calculated by plotting a graph between concentration of the test solution on X-axis and response of the corresponding solutions on Y-axis.

LOD and LOQ

Limits of Detection [LOD] and Quantification [LOQ] were calculated directly from the calibration plot. LOD and LOQ were calculated as 3.3σ/S and 10σ/S respectively. Where σ is the standard deviation of intercept and S is the slope of the calibration plot.

Robustness

Influence of small changes in chromatographic conditions such as change in flow rate (± 0.1ml/min), Temperature (±2°C) and organic phase content in mobile phase (±2%) studied to determine the robustness of the method are also in favour of (% RSD < 2%) the developed RP-HPLC method for the analysis of etodolac (API).

Stability Studies

Acid degradation

An accurately weighed 10 mg of pure drug was transferred to a clean and dry round bottom flask. 30 ml of 0.1 N HCl was added to it and it was refluxed in a water bath at 60°C for 4 hr. Allowed to cool to room temperature. The sample was then neutralized using dilute NaOH solution and final volume of the sample was made up to 100ml with mobile phase to prepare 40 µg/ml solution. It was injected into the HPLC system against a blank of mobile phase (after optimizing the mobile phase compositions). This experiment was repeated several times using same concentration of HCl (0.1N) and observed its degradation profile.

Basic hydrolysis

An accurately weighed 10 mg of pure drug was transferred to a clean and dry round bottom flask. 30 ml of 0.1N NaOH was added to it. And it was refluxed in a water bath at 60°C for 4 hr. Allowed to cool at room temperature. The sample was than neutralized using 2N HCl solution and final volume of the sample was made up to 100ml with mobile phase to prepare 40 µg/ml solution. It was injected into the HPLC system against a blank of mobile phase after optimizing the mobile phase compositions. This experiment was repeated several times using same concentration of NaOH such as 0.1N to observe its degradation profile is the degradation profile of Etodolac in 0.1N NaOH.

Thermal degradation

Accurately weighed 10 mg of pure drug was transferred to a clean and dry round bottom flask. 30 ml of HPLC water was added to it. Then, it was refluxed in a water bath at 60°C for 6 hr uninterruptedly. After the reflux was over, the drug became soluble and the mixture of drug and water was allowed to cool to room temperature. Final volume was made up to 100 ml with HPLC water to prepare 40 µg/ml solution. It was injected into the HPLC system against a blank of mobile phase.

Photolytic degradation

Approximately 10 mg of pure drug was taken in a clean and dry Petri dish. It was kept in a UV cabinet at 254 nm wavelength for 24 hrs without interruption. Accurately weighed 1 mg of the UV exposed drug was transferred to a clean and dry 10 ml volumetric flask. First the UV exposed drug was dissolved in methanol and made up to the mark with mobile phase to get 40 µg/ml solution. Finally this solution was injected into the HPLC system against a blank of mobile phase and chromatogram was obtained, Figure 7.

Oxidative hydrolysis (3% H_2O_2)

Accurately weighed 10 mg of pure drug was taken in a clean and dry 100 ml volumetric flask. 30 ml of 3% H_2O_2 and a little methanol was added to it to make it soluble and then kept as such in dark for 24 hrs. Final volume was made up to 100 ml. using water to prepare 40 µg/ml solution. The above sample was injected into the HPLC system against a blank of mobile phase and chromatogram was obtained.

RESULTS

UV Optimization

To optimised the suitable solvent system for the ideal and linear UV spectrum of etodolac, various solvents, mixture of solvents with buffer systems at several volume ratio were tested. Finally, the solvent system, methanol and water at the volume ratio of 70:30 was selected. With this solvent system the linear UV spectrum were obtained at the λ_{max} 226nm as shown in optimised spectrum Figure 2. The above solvent system was used for the subsequent validation studies and testing of marketed dosage form of etodolac.

Method validation by developed UV spectroscopy method

The developed method was applied for the estimation of etodolac in marketed dosage form Etura Tablets (500mg) (Dr. Reddy's Laboratories). The recover amount was 499 mg and the percentage purity was 99.79%, shown in Table 1 and Figure 3. In the study of linearity, the developed method was found linear in the range of 2-20 µg/ml, with a regression coefficient (R^2) of 0.999 as cited in Figure 4. The accuracy of the developed method was conducted by recovery study, the average percentage recovery of etodolac was found 99.415 ± 0.339, as shown in Table 2. The average % RSD for the precision study was found 1.23. In the study of LOD and LOQ, the detection limit was found 0.315 µg/ml and quantitation limit was found 0.389 µg/ml. The details are shown in summary of validation parameters as shown in Table 3.

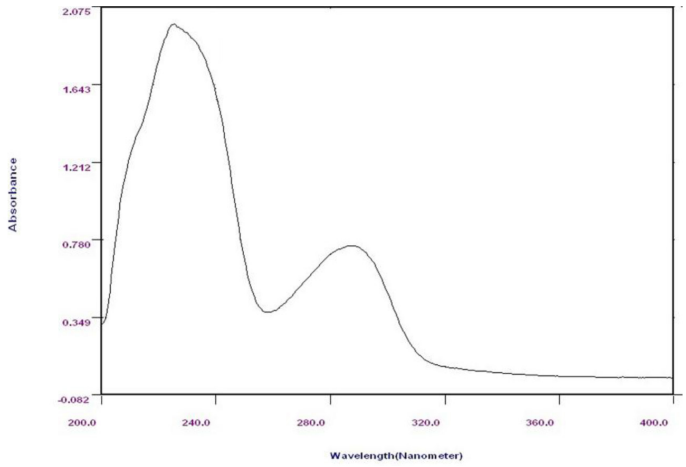

Figure 2: Optimised UV spectrum of etodolac.

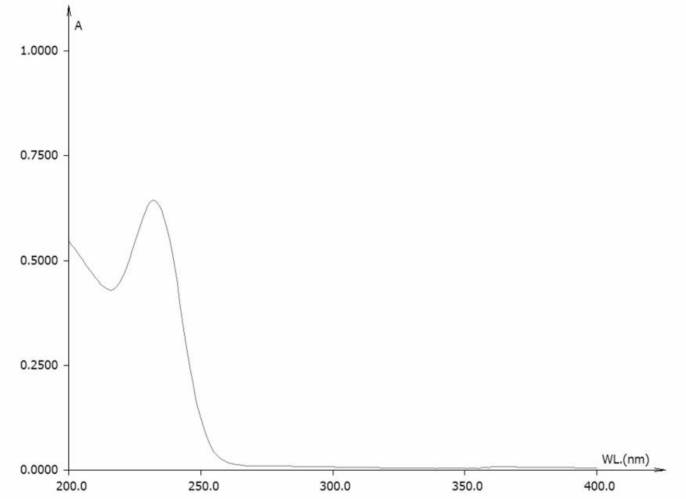

Figure 3: Assay of marketed dosage form by developed UV method.

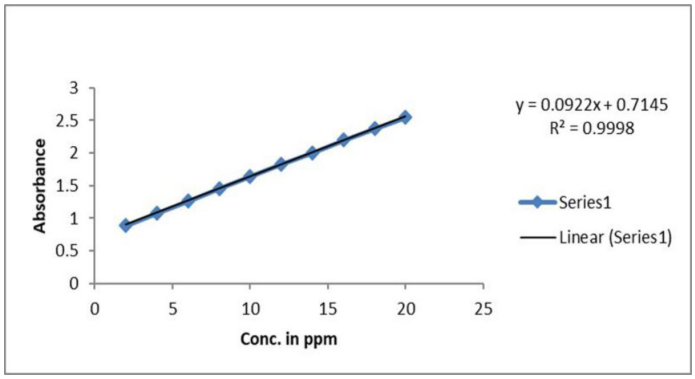

Figure 4: Linearity of etodolac in UV method.

Table 1: Assay of marketed dosage form by UV method.

Formulation	Label Claim (mg)	*Amount found (mg)	% purity
Etura (Etadolac -500mg)	500	499.68	99.79

* Average of Three experiments.

Table 2: Recovery studies of etodolac by UV method.

Formulation	Label Claim in mg	Conc. of pure drug added in mg	* Amount of drug found in mg	% Recovery ± SD	Avg % ± SD
Etura (Etadolac 500 mg)	500	--	499.86	99.68±0.1524	99.415±0.3394
	--	100	599.34	98.96±0.1652	
	--	200	699.75	99.75±0.1587	
	--	300	800.03	99.27±0.1631	

* Average of three determinations.

HPLC Method optimization

In the HPLC method development strategy, before selection of the optimised chromatographic condition, numbers of preliminary trials were conducted with different combination of solvents, various buffers, pH, flow rate, temperature and columns in order to justify the peak shape, retention time, resolution and other chromatographic parameters. The mobile phases used in the optimization procedure were prepared by mixing various buffer system with organic solvents. Several solvents (methanol, acetonitrile), buffers (orthophosphoric acid pH 2, 8, ammonium acetate pH 5 and 7, potassium dihydrogen orthophosphate pH 5, 6.8) used in different volume ratio. Various analytical columns were tested with U.V detection at 226 nm. Finally, a selected mobile phase consisting of acetonitrile and methanol in the volume ratio of 65:35(v/v) using Phenomenex Luna C_{18}, 100A, 5mm, 250mmx4.6mm i.d. analytical column was found optimum condition. With the isocratic elution with 226 nm UV detection and at the flow rate of 1 mL/min, the chromatographic conditions were fully separated within 3.521 min retention time for etodolac with a better sensitivity and excellent peak shape, shown in Figure 5.

Method Validation by developed HPLC method

The optimised chromatographic condition was utilized for the subsequent validation study and force degradation study as per ICH guidelines for the method development and validation. System Suitability is a test to verify the adequate working of the equipment used for analytical measurements. Parameters like tailing and theoretical plates were be taken into consideration. The %RSD of area, theoretical plates, tailing factors and retention time were 0.32%, 0.33%, 0.31% and 0.55% respectively. In the study of specificity no correspond peak was found at the retention time of the analyte.

The assay of marketed dosage form using developed HPLC method was conducted and the amount of drug in Etura Tablets was found 499.876 (±0.854) mg and % assay was 99.674%. The details was given in Table 4 and chromatogram was shown in Figure 6. The result of system suitability study using standard drugs of Etodolac six times shows that % RSD of several parameters like theoretical plate, retention time, peak area, asymmetric factor were in the range of 0.45-1.09. The calibration curve showed linearity in the range of 0.5 – 40 µg/ml, for Etodolac (API) with correlation coefficient (r^2) of 0.999. The Minimum concentration level at which the analyte can be detected (LOD) and quantified (LOQ) were found to be 0.08 and 0.26 µg/ml respectively. In the study of repeatability, intra and interday precision, the % RSD was found 0.85, 0.86 and 0.82. The accuracy of the developed method was proved by conducted the recovery study. The average recovery of the etodolac using HPLC method was 100.57%. The method was robust with the change in flow rates from ±0.1 mL/min, acetonitrile and methnol ratios (63: 37, 65: 35 and 67: 33), Detection wavelength (224, 226 and 228). The details of the study results are presented in Table 5. The stress degradation study were conducted in various stressed condition and % degrading was calculated. It was found that in acidic and alkaline stressed conation the percentage degradation were 8.18% and 7.55%. Where as in the thermal and UV photolytic condition the % degradation were 3.02% and 3.79%. The percentage degradation 9.37% was found in peroxide induced stressed condition. The details was given in Table 6 and degradation chromatograms were cited in Figure 7.

Table 3: Summary of validation parameters.

Parameters	Etidolac at 226nm
Beer's law limit in mg/ml	2 to 20
Molar Absorptivity	10.05 X 10^3 L mol^{-1} cm^{-1}
Regression equation	Y= 0.092 X + 0.714
Slope	0.092
Intercept	0.714
Co-relation co-efficient	0.999
LOD mg/ml	0.3158
LOQ mg/ml	0.3896
Precision (% RSD)	1.238

Table 4: Assay of marketed formulation by RP-HPLC method.

Tablet Formulation	Labelled amount of Drug (mg)	Mean (±SD) amount (mg) found by the proposed method (n=6)	Assay % (±SD)
Etura Tablets (500mg) (Dr. Reddy's Laboratories)	500mg	499.876 (±0.854)	99.674 (±0.524)

Table 5: Robustness study.

Change in parameter	% RSD
Flo w (1.1 ml/min)	0.96
Flow (0.9 ml/min)	0.75
Mobile phase ratio (+2)	0.61
Mobile phase ratio (-2)	0.92
Wavelength of Detection (224 nm)	0.85
Wavelength of detection (228 nm)	0.98

Table 6: Stress degradation study.

Stress condition	Time	Assay of active substance	% degradation	Mass Balance (%)
Acid Hydrolysis (0.1 M HCl)	4Hrs.	91.84	8.16	100.0
Basic Hydrolysis (0.I M NaOH)	4Hrs.	92.45	7.55	100.0
Thermal Degradation (60°C)	6Hrs.	96.98	3.02	100.0
UV (254nm)	24Hrs.	96.21	3.79	100.0
3 % Hydrogen peroxide	24Hrs.	90.63	9.37	100.0

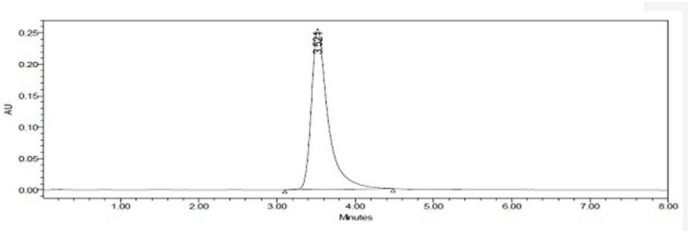

Figure 5: Optimised Chromatogram of etodolac.

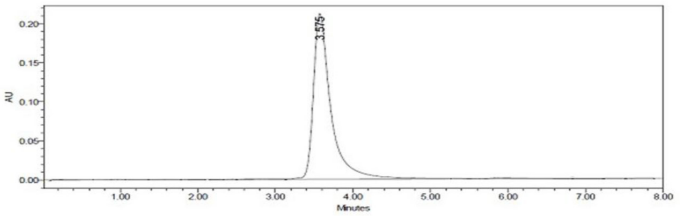

Figure 6: Assay of tablet dosage form by developed HPLC method.

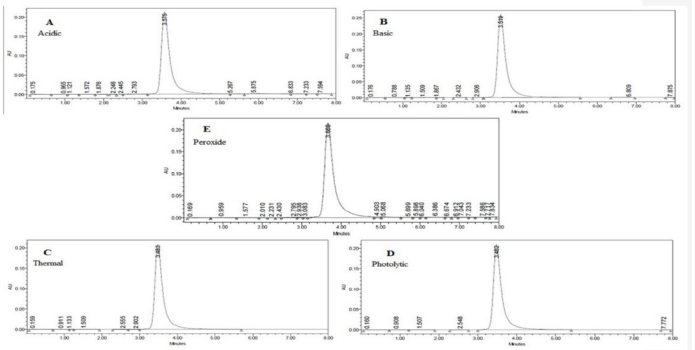

Figure 7: Degradation chromatograms of etodolac.

DISCUSSION

The chosen solvent system for the UV method, ethanol: water at the volume ratio 70: 30 was found suitable to optimised the UV spectrum of Etodolac at 226nm. Similarly in the optimised chromatographic conditions, with a mobile phase acetonitrile and methnol in the ratio of 65:35(v/v) using Phenomenex Luna C_{18}, 100A, 5mm, 250mmx4.6mm i.d. analytical column, with 226 nm UV detection and the flow rate of 1 mL/min was found optimum. Etodolac was separated within 3.521 min with a better sensitivity and excellent peak shape. In the study of linearity for the both UV and HPLC method, the regression coefficient value were 0.999, which is very close to 1, indicated the linearity of the developed methods. The percentage of RSD for the precision study using UV and HPLC method were found less than 2, which indicated that the developed UV and HPLC methods was found precise. The results of average percentage recovery 99.415% for UV method and 100.57% for HPLC method indicated the accuracy of the developed methods because the values are within the acceptance limit. Results of LOD and LOQ study indicated that the both the developed methods was found sensitive and easily quantifiable of etodolac. In the assay of marketed dosage form using both the UV and HPLC method were found significantly suitable, because the % assay was found 99.67% for HPLC and 99.79% for UV method. The result of the robustness study indicates that there is no significant changes in the result on small deliberate changes in mobile phase ratio, column temperature and flow rate of the mobile phase in chromatographic system, which indicated that the developed method was robust. The force degradation study results shown that there is a very narrow level degradation happens in most of the decomposition conditions. In comparison to photolytic and thermal degradation, acidic alkaline and oxidation caused more decomposition to the etodolac. The result indicating that the drug is highly resistant towards the above degradations.

CONCLUSION

The results of the analysis of pharmaceutical dosage form indicated that the developed spectrophotometric and RP-HPLC method is highly accurate, precise and robust and are in good agreement with the labeled claim of the drug and obtained assay results. The empirical evidences from the validation studies for both the developed method, indicated that the results are within the acceptance criteria and found validated as per ICH guidelines. Furthermore, the authors can designate that the proposed UV and RP-HPLC method has excellent sensitivity, precision and reproducibility.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

RP HPLC: Reverse phase High performance liquid chromatography; **LOD:** Limit of detection; **LOQ:** Limit of quantitation; **RSD:** Relative standard deviation; **UV:** Ultra violet; ICH: International conference on Harmonization.

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