**RESEARCH ARTICLE**

# A Validated Sensitive Stability Indicating HPLC Method for the Determination of Etoricoxib in Bulk and Formulation

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## ABSTRACT

**Aim:** The current research aims to create a high-resolution and validated liquid chromatographic method used for quantitative detection of etoricoxib within dosage forms that is both easy to use and reliable in terms of accuracy, sensitivity, and reproducibility.

**Materials and Methods: A**nalysis was carried out at isocratic conditions at flow rate of 0.7 mL/min using a mobile phase consisting of 40 parts methanol to 60 parts water (0.1% OPA) at pH 3.2. The eluents were tested using UV detection at 236 nm.

**Results:** Etoricoxib had clearly separated peaks with a retention duration of 4.347 minutes in the optimized settings. The concentration range used to generate the calibration curve was 10 to 60 µg/mL. LoD was 0.0779 µg/mL, and upper LoQ was 0.23 µg/mL. The approach has been effective in separating a known quantity of etoricoxib, and the percentage of degradation was shown to be very low across all stress settings.

**Conclusion:** Etoricoxib in bulk drug and commercial formulations can be identified and quantified using the proposed method, which has been validated in accordance with ICH recommendations.

**Keywords:** Etoricoxib, HPLC Method, Forced degradation.

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**Conflict of interest:** None

## INTRODUCTION

As shown in Figure 1, etoricoxib (ETC) is a novel NSAID.[1] By blocking cyclooxygenase-2 activity, prostaglandin production is stymied.[2,3] It is selective for COX-2 and has higher margin of safety. It's less harmful to the stomach and works at low doses.[4]

When compared to traditional NSAIDs, etoricoxib is the better choice due to the increased risk of gastrointestinal problems like ulcers, severe bleeding, and perforation, which can lead to hospitalization or even death.[5] Osteoarthritis, rheumatoid arthritis, and acute gouty arthritis are the most common conditions for which it is used.[6-8] When taken as a tablet, ETC is absorbed and made accessible almost immediately; its absolute bioavailability is predictable as 100%. Urinary excretion of its oxidative metabolites is its primary route of elimination.[9] Since extent of absorption of ETC was not affected by rate of absorption. Its dosage proportionality in healthy volunteers have been investigated.[10,11]

Human plasma ETC was measured by HPLC-MS/MS between.[12-15] There were further reports of ETC being measured using high-performance liquid chromatography.[16,17]

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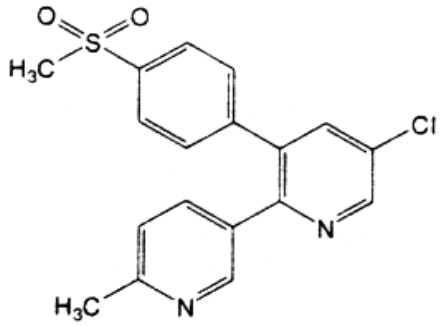

**Figure 1:** Molecular structures of Etoricoxib

spectrophotometry[18] and capillary zone electrophoresis.[19] HPTLC[20,21] method employing a chloroform: methanol: toluene (4:2:4 v/v) mobile phase were applied to quantify ETC in the samples. When exposed to UV light (254 nm), etoricoxib undergoes a photocyclization reaction, creating two main isometric photo-cyclization products with other HPLC-based methods. Matthews *et al*. were able to separate and describe the photolytic products.[22] This study provides a simple, reproducible RP-HPLC approach that has been validated in compliance with ICH criteria for the determination of etoricoxib in dosage forms.[23]

## MATERIALS AND METHODS

### Instrumentation

Agilent Gradient System by auto-injector DAD Detector was used for drug analysis. The chemstation is set up with a UV730D absorbance detector, a 20 mL injection loop, and a reverse phase (Agilent) $C_{18}$ column (4.6 mm x 100 mm, 2.5 µm). The UV-vis spectrophotometer from Analytical Technologies Limited is a double-beam, high-seed scanning spectrophotometer that requires around a minute to start up for the first time. The spectrophotometer uses a deuterium lamp as its light source, and a computer is connected to the device to analyze the collected data. They used a quartz cuvette with a route length of 1-cm. The mobile phase, standards, and samples were all weighed on a DENVER (SI-234) electronic balance before being mixed and prepared in an ultrasonic batch sonicator (1.5 L).

### Chemicals and Reagents

Ranbaxy Research Laboratories Limited, Haryana, India provided gift samples of the pharmaceutical medicine Etoricoxib (ETC). ETC tablets' brand names in India include Etody-60 tablet (Abbott pharmaceutical Pvt. Ltd.). Tablets of KINGCOX (Cadila HC), ETOZOX (Cipla) and ETROBAX (Ranbaxy) were acquired from a local pharmacy (60, 90, and 120 mg, respectively). All compounds were of analytical quality, and HPLC-grade methanol (Merck) was utilized.

### Selection of Mobile Phase

The cellular age good peak resolution for etoricoxib was obtained using a 40:60% v/v mixture of methanol and 0.1% (OPA) water at pH 3.2 and a 0.7 mL/min flow rate at 236 nm.

### Preparation of Etoricoxib Standard Solution

Weigh 10 mg standard drug (etoricoxib), transfer it in volumetric flask (10 mL), in diluent methanol and filling the flask to obtain 1000 µg/mL stock solution and sonicating for 15 minutes to dissolve it; transferring 0.1 mL of resulting stock solution to a 10 mL volumetric flask and filling. Method development and validation research made use of a solution whose concentration was previously determined.

### Linearity

Employing a 10 mL volumetric flask succession of etoricoxib standard solutions were generated by drawing off suitable aliquots of drug sample (10–60 µg/mL) from the stock solution then raising volume to 10 mL with mobile phase. Using a mixed volume loop injector, 20 µL of each ETC solution was injected into the HPLC apparatus and the resulting chromatograms were captured. In Figure 2 we have a chromatogram of ETC that is very normal. The results of ETC's peak area measurements were tabulated (Table 1). Using the ETC concentrations (x-axis) and peak area ratios (y-axis) (Figure 2), a calibration curve was generated. Table 2 shown regression data for etoricoxib.

### Preparation of Marketed Formulation Solution

Tablets (n = 10) of the commercially available brand name etoricoxib, Etody – 20 mg, were crushed and pulverized using a clean mortar and pestle. The tablet powder was weighed out and dissolved in methanol at a concentration of 4.635 g of etoricoxib. Sonicate with roughly 10 mL of diluent to achieve complete dissolution, and then top off the volume with diluent. Filter through a 0.45 µm membrane after thorough mixing. Transfer 0.4 mL of stock to 10 mL using the appropriate solvents (40 µg/mL). Test etoricoxib's uncomplicated chromatogram. Extrapolating area values from the calibration curve yielded per-tablet concentrations of etoricoxib. Tablet iterations of analysis were performed five times. Evaluation of a Tablet's %RSD label claim. Tables 3 and 4 display the results.

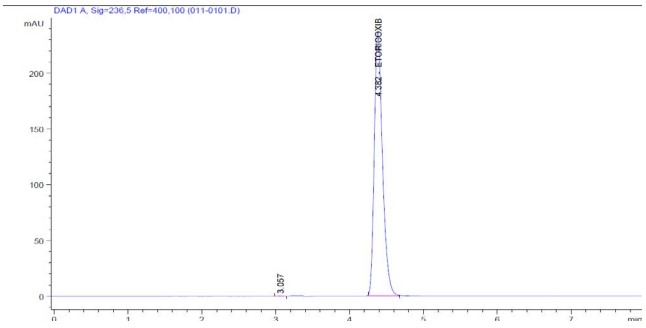


**Figure 2:** Linearity chromatogram

**Table 1:** Etoricoxib linearity

| *S. No.* | *Concentration (µg/mL)* | *Area Etoricoxib* |
|---|---|---|
| 01 | 10.00 | 1866.67 |
| 02 | 20.00 | 3719.25 |
| 03 | 30.00 | 5415.44 |
| 04 | 40.00 | 7402.90 |
| 05 | 60.00 | 10757.15 |

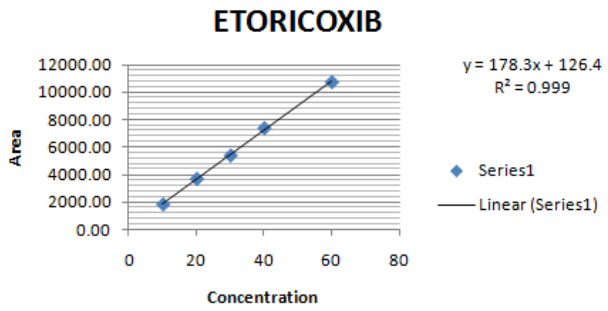


**Figure 3:** Calibration curve of etoricoxib

**Table 2:** Regression data for etoricoxib

| *Regression Data Y = mx+c* | |
|---|---|
| Intercept(c) | 126.4 |
| Slope(m) | 178.3x |
| Correlation Coefficient | 0.999 |

**Table 3:** Marketed formulation analysis

| *S. No* | *Conc.* | *Area (I)* | *Amount found in mg* | *%Label claim* |
|---|---|---|---|---|
| | *ETOR* | *ETOR* | *ETOR* | *ETOR* |
| 1 | 40 | 7407.58 | 40.83 | 101.21 |
| 2 | 40 | 7394.54 | 40.40 | 101.02 |
| 3 | 40 | 7399.56 | 40.79 | 101.97 |
| Mean | _ | 7400.56 | 40.80 | 102.00 |
| SD | _ | 6.58 | 0.04 | 0.13 |
| %RSD | _ | 0.09 | 0.09 | 0.13 |

**Table 4:** Tablet for %Label claim

| *Sample* | *Label claimed* | *%Label claimed. ± SD* | *%RSD* |
|---|---|---|---|
| Etoricoxib | 60 mg | 102.0 ± 6.58 | 0.09 |

The commercial formulation analysis %verification of the 102% label claim

Satisfactory are concluded ( Table 3).

Tablet assay for %label claim

Results from an assay of the tablet's labeled percentage of purity were found to be 102%, with an RSD of less than 2%. (See Table 4)

### Method Development

Many method development trials were carried out to identify and quantify etoricoxib in pharmaceutical formulations, including a study of forced degradation. Mobile phase composition, pH, UV detector wavelength, mobile phase flow rate and stationary phase configuration were all investigated during technique development. The characteristics of the system's suitability were evaluated in each trial condition, and the optimal settings were deemed to be those that yielded the best results.

### Method Validation

Etoricoxib was separated and quantified using this approach, and its sensitivity, accuracy, precision, ruggedness, and robustness were all determined through validation. All

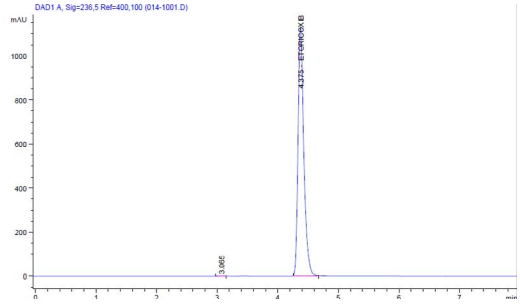

**Figure 4:** Chromatogram of marketed formulation

investigations including method development and validation were conducted in accordance with ICH standards.[23]

### Force Degradation Studies

A forced degradation study was performed on the reference medication etoricoxib to test the efficacy of the suggested method for separation and identification. Etoricoxib underwent alkaline hydrolysis with 0.1N NaOH (70°C/1 h). At 1-hour% degradation, the main etoricoxib degradation products were detected at 41.52%. For all three forms of etoricoxib, acid hydrolysis using 0.1N HCl for 1hr min showed deterioration. At 1-hour% degradation, the main etoricoxib degradation products were found to be 7.84. At RRT of 1-hour%, the degradation product was spotted. Etoricoxib was also found to have these contaminants. After being exposed to 3% $H_2O_2$ for 1-hour, the chromatogram for Etoricoxib showed no oxidative stress degradation peak at 1-hour% degradation (1-hour for 90.18%). Both etoricoxib and its inactive metabolite showed no significant photodegradation. Degradation of etoricoxib in acidic, alkaline, and oxidative stress conditions was observed using high-performance liquid chromatography. Under neutral degradation conditions, the medication was determined to be stable (Table 5).

### Formulation Analysis

The devised method was applied to an analysis of a formulation solution made by dissolving etoricoxib formulation tablets of the Etody – 20 mg brand. In the developed approach, the percent assay of etoricoxib was determined.

## RESULTS AND DISCUSSION

Quantitative analysis of etoricoxib is now impossible because no HPLC method exists to indicate stability. The goal was having simple, stability-indicating, robust and easy approach for regular evaluation of etoricoxib, including forced degradation tests in quality control laboratories.

**Table 5:** Degradation of different stress conditions

| *Sr. no* | *Degradation parameter* | *% Degradation (%)* |
|---|---|---|
| 1 | Alkali Deg. 0.1 N NaoH - after 60 minutes-30 mcg | 41.52 |
| 2 | Acid Deg.0. 1 N HCl- after 60 minutes-30 mcg | 7.84 |
| 3 | 3% $H_20_2$ DEG after 60 minutes-30 mcg | 90.18 |
| 4 | Neutral after 120 minutes-30 mcg | 0 |

Selecting the optimal wavelength to provide good sensitivity with minimal noise is the first stage in developing a method for the quantification of etoricoxib medicinal ingredient. The UV absorption spectra of etoricoxib was used to investigate this phenomenon. It has a strong UV absorption at 236 nm, which is a rather visible wavelength. Since 236 nm provides a high absorbance for the etoricoxib standard detector, this wavelength was maintained throughout the investigation.

Since etoricoxib and the standard separation medication share a chemical structure and polarity, column selectivity for etoricoxib was essential. Three distinct columns, the Phenomenex ODS $C_{18}$ (250 x 4.6 mm, 5 µ), the (Agilent) C18 column (4.6 x 100 mm, 2.5 µm), and the Spherisorb ODS2 (250 x 4.6 mm, 5 µ), were used in the preliminary studies. The investigated compounds were found to be maintained and separated on a (Agilent) C18 column (4.6 mm x 100 mm; 2.5 µm) with relatively sharp peaks. This column was thus subjected to further optimization.

Different mobile phases were tested for their ability to resolve etoricoxib, including water, methanol, acetonitrile, phosphate buffers of varying pH values, acetate buffers of varying pH values, and sodium perchlorate of varying pH values. The optimal separation for etoricoxib was achieved using mobile phase consisting of 40% (v/v) methanol and 60% (v/v) water produced with 0.1% (OPA) at a pH of 3.2. Run time and other parameters were all held constant at 0.7 mL/min and 35°C, respectively, to facilitate etoricoxib separation.

The standard medication was clearly resolved and retained at a retention time of 4.347 minutes for etoricoxib under the optimized settings, allowing for a distinct baseline to be seen. The procedure meets the conditions for system suitability (Table 6). The etoricoxib chromatogram, as optimized by the new technique, is displayed in Figure 5.

The 10 to 60 µg/mL concentration range was found to be an accurately correlated calibration range for etoricoxib. It was calculated that y = 178.3x + 126.4 ($R^2$ = 0.998). It was determined that the calibration curve was linear at the concentration used in the experiment. Table 7 displays the findings of the linearity analysis.

Intraday, interday, and ruggedness studies were conducted to examine repeatability and reproducibility. Six replicate analyses were performed on same day for intraday precision, 6 replicate analyses were performed over the course of 3 days for interday precision and 6 replicate analyses were performed at a

**Table 6:** System suitability results of etoricoxib in the developed method

| *Parameter* | *Etoricoxib* |
|---|---|
| Standard Concentration | 10 µg/mL |
| Retention time (min) | 4.347 |
| Peak Area response [mV*s] | 4822.216 |
| Resolution | 6.29 |
| Theoretical Plates | 10949 |
| Tailing Factor | 0.68 |

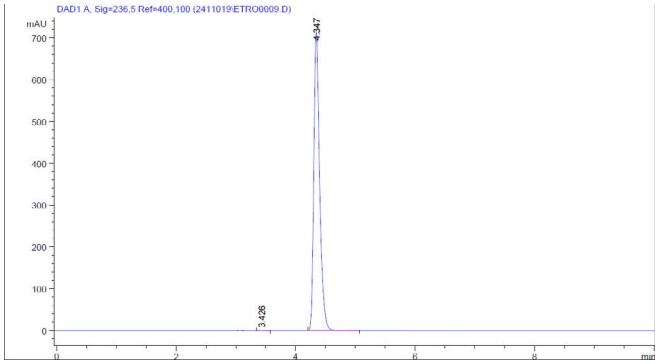


**Figure 5:** Standard chromatogram in the optimized conditions

**Table 7:** Linearity of etoricoxib

| *S. No.* | *Concentration (µg/mL)* | *Area Etoricoxib* |
|---|---|---|
| 01 | 10.00 | 1866.67 |
| 02 | 20.00 | 3719.25 |
| 03 | 30.00 | 5415.44 |
| 04 | 40.00 | 7402.90 |
| 05 | 60.00 | 10757.15 |

standard concentration of 20 µg/mL for a change in analyst for robustness research. Results from a robustness analysis showed that etoricoxib had a %RSD of 0.89, 0.03, and 0.02 for intraday accuracy, 0.89, 0.05, and 0.04 for interday precision, and 0.19, 0.06, and 0.18 for stability. This demonstrates the reliability and accuracy of the developed approach for etoricoxib analysis. Alterations to the analytical conditions were used to study the drug at its standard concentration. The computed percentage change was determined to be less than the allowable threshold of for etoricoxib, indicating the method's reliability.

The effects of spiking etoricoxib to concentrations of 80, 100 and 120% of 10 µg/mL were investigated. It was determined that the calculated values for %Recovery and %RSD of recovery at every spike level of etoricoxib were within acceptable ranges (Tables 8, and 9).

The detection and quantification results of etoricoxib validated the sensitivity of the approach. The method's LoD was calculated as follows: LoD = 3.3 S/m (S=standard deviation, m=slope) of calibration curve. Using acquired LoD values (LoQ=3.3 x LoD), LoQ was determined. The devised technique's detection and quantification limits were found to be extremely low at 0.0779 and 0.23 µg/mL, respectively. All three forms of observed etoricoxib degradation were subjected to acid hydrolysis with 0.1N HCl for 1-hour. At 1-hour% degradation, the main etoricoxib degradation products were found to be 7.84. At RRT of 1 hour, the degradation product was spotted. Illustration 6 etoricoxib underwent alkaline hydrolysis with 0.1N NaOH at 70°C for 1-hour etoricoxib deterioration. At 1-hour% degradation, the main etoricoxib degradation products were detected at 41.52% (Figure 6 and 7). After being exposed to 3% $H_2O_2$ for 1-hour, the chromatogram for Etoricoxib showed no oxidative stress degradation peak at 1-hour% degradation (1 hour for 90.18%). Neither etoricoxib

**Table 8:** Recovery data for etoricoxib

| *Drug* | *S. No.* | *Level (%)* | *Taken Amount (µg/mL)* | *Added Amount (µg/mL)* | *Found Amount (Mean* ± S.D.)* | *Recovered Amount (Mean * ± S.D.)* | *% Recovery Mean* ± S.D.* |
|---|---|---|---|---|---|---|---|
| ETOR | 1 | 80 | 10 | 8 | 18.06 ± 0.01 | 8.06 ± 0.01 | 100.75 ± 0.18 |
| | 2 | 100 | 10 | 10 | 20.01 ± 0.04 | 10.01 ± 0.04 | 100.09 ± 0.38 |
| | 3 | 120 | 10 | 12 | 21.94 ± 0.06 | 11.94 ± 0.06 | 99.51 ± 0.55 |

*Mean (n=30)

**Table 9:** Statistical validation of recovery studies etoricoxib

| *Level of Recovery (%)* | *Drug* | *Mean recovery (%)* | *SD** | *%RSD* |
|---|---|---|---|---|
| 80 | Etoricoxib | 100.75 | 0.55 | 0.55 |
| 100 | Etoricoxib | 100.09 | 0.38 | 0.38 |
| 120 | Etoricoxib | 99.51 | 0.55 | 0.55 |

*mean average of three determinations

**Table 10:** Forced degradation results of etoricoxib in the developed method in different stress condition

| *S. No* | *Degradation parameter* | *%Degradation (%)* |
|---|---|---|
| 1 | Alkali Deg. 0.1 N NaoH - after 60 minutes 30 mcg | 41.52 |
| 2 | Acid Deg.0. 1 N HCl- after 60 minutes -30 mcg | 7.84 |
| 3 | 3% $H_20_2$ DEG after 60 minutes -30 mcg | 90.18 |
| 4 | Neutral after 120 minutes -30 mcg | 0 |

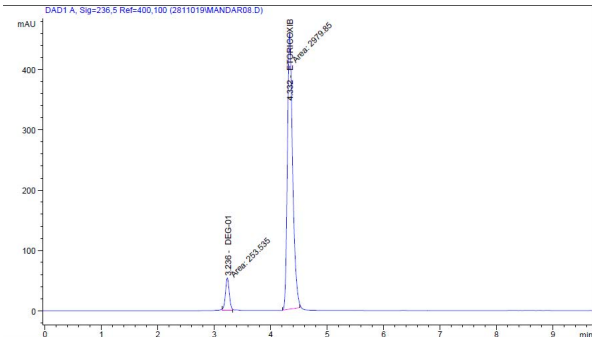


**Figure 6:** Chromatogram of acid hydrolysis

nor its metabolite were significantly degraded by exposure to light (Figure 8), suggesting that they are not photosensitive. To illustrate: (Figure 9) The fact that not only was etoricoxib detectable under all of these circumstances of degradation but that the extra degradation chemicals generated throughout the stress testing were also successfully isolated demonstrates the method's efficacy. The effects of various stresses on etoricoxib's stability are summarised in Table 10.

Etoricoxib formulation assay using the new technique was shown to be 98.83% effective. The presence of the reference medication etoricoxib was confirmed by the presence of a distinct baseline in the chromatogram depicting the formulation. The formulation chromatogram showed no traces of excipients. Hence the approach should be fine for routine analysis of etoricoxib. Figure 10 displays the chromatogram of the final formulation.

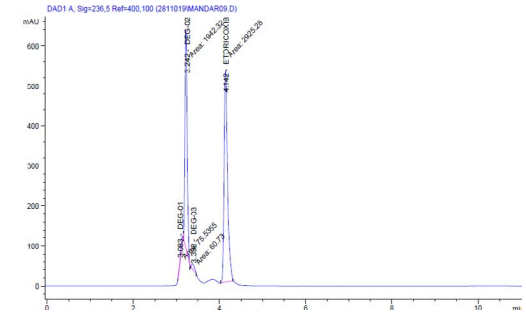


**Figure 7:** Chromatogram of base hydrolysis

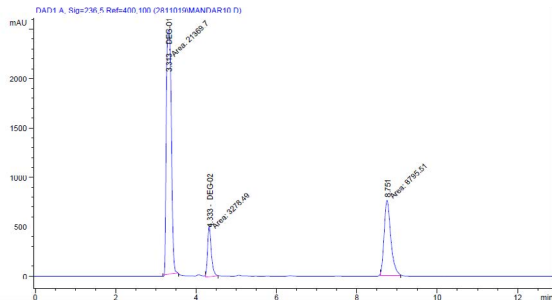


**Figure 8:** Chromatogram of oxidative degradation

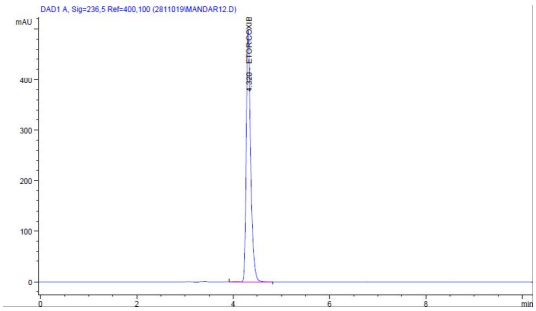


**Figure 9:** Chromatogram of neutral degradation

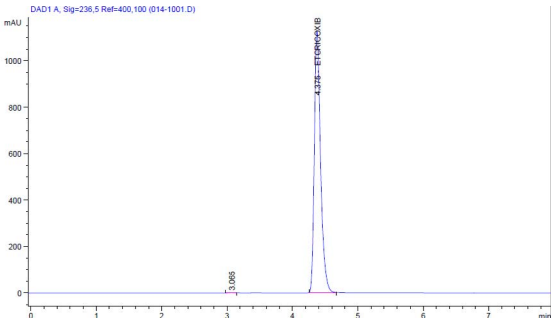


**Figure 10:** Formulation chromatogram

## CONCLUSION

The separation, quality, and quantity of etoricoxib were effectively analyzed using a straightforward and stable RP HPLC method. All validation parameters were found to be acceptable, and they successfully differentiated between the known medication and the force in a stress experiment. The separation was accomplished without the use of an ion-pair reagent, and the experiment used a previously unreported combination of conditions, including a simple mobile phase in isocratic elution. The established LoD and LoQ by this method are lower than those published in the literature. It is determined that the approach is linear in the given range, accurate, and stable. The method's reliability is demonstrated, and the formulation's validity is confirmed. Therefore, this technology can routinely analyze etoricoxib in supplied products and formulations.

## ACKNOWLEDGEMENTS

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