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RESEARCH ARTICLE

A Stability-Indicating Validated RP-HPLC Method for the Determination of Etoricoxib and It's Degradants: Investigation of Greenness and Functionality of the Developed Method

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ABSTRACT

Etoricoxib is a novel NSAID that belongs to selective COX-2 inhibitors. The aim of this research is to develop a precise, selective, cost-effective, and validated HPLC analytical method for the quantitative determination of Etoricoxib and its degradants. The analysis was implemented on a C18 column (150 × 4.6 mm, 5 μm particle size) using a mobile phase containing methanol and ammonium acetate (60:40) at a flow rate of 0.9 mL/min, with the Photodiode Array detector wavelength set at 234 nm. The method was validated according to USP43-NF38 guidelines and the International Conference on Harmonization recommendations. Linearity was established with a correlation coefficient value of 0.9999. The selectivity, accuracy, precision, and robustness of the method showed results within the acceptance criteria. Detection limit (DL) and quantification limit (QL) were 0.21 μg/ml and 0.72 μg/ml, respectively. Etoricoxib was subjected to several forced degradation factors, such as alkali and acid hydrolysis, heat degradation, photolytic degradation, and oxidative degradation. The degradants were successfully separated from the drug using the developed analytical method. Degradation of Etoricoxib was observed in oxidation, thermolysis, photolysis, and basic hydrolysis, while it was found stable in acid hydrolysis. Stress studies showed that maximum degradation of Etoricoxib was observed upon exposure to oxidation. Assessment of greenness was investigated using AGREE (Analytical greenness Metric approach). The Method approach's functionality was evaluated using BAGI (Blue applicability Grade Index). Hence, the results indicated that the method can be used as an efficient tool for routine testing in QC laboratories and the pharmaceutical industry.

Keywords: Degradants, Etoricoxib, High performance liquid chromatography, Quality control, Stability indicating

Introduction

Etoricoxib, a new selective COX-2 inhibitor, was developed with the goal of relieving pain and inflammation without gastrointestinal safety concerns associated with the use of conventional NSAIDs.[1,2] Chemically known as 5-chloro-2-(6-methylpyridin-3-yl)-3-[4-(trideuteriomethyl sulfonyl) phenyl] pyridine,[3] Fig. 1.

An essential step in the process of developing a medicinal product is stability testing. The purpose of stability testing is to show how an active substance or pharmaceutical product's quality will be affected over time as a result of numerous environmental influences, including temperature, humidity, and light. With the help of this information, storage guidelines, retest intervals, and the drug's shelf life can be determined.[4,5]

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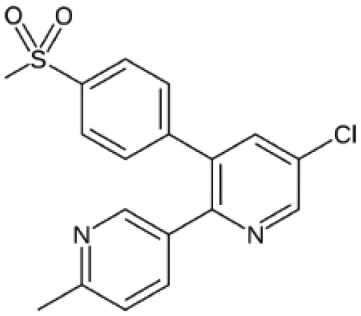

Fig. 1. Etoricoxib chemical structure.

Etoricoxib is not yet officially listed in the USP43 or the British pharmacopeias.[6] Moreover, in literature, a few analytical techniques were mentioned for determining Etoricoxib using UV,[7] HPTLC,[8] and HPLC.[9–11] Most of them take a long time for analysis, which leads to waste in the solvents or depends upon expensive solvents such as acetonitrile.[12] Few stability-indicating methods[13,14] are reported for determining Etoricoxib[15,16] and its degradation products.[17–19]

Collected literature surveys, regarding stability indicating methods that developed earlier, are listed in Table 1.

Therefore, there is a need to develop a stability-indicating RP-HPLC analytical estimation of Etoricoxib and its degradation products. This method aims to overcome the issues of long retention time to save solvents and costs, as well as to minimize the use of toxic and expensive solvents. Therefore, the objective of this research is to develop a rapid, specific, economic, and stability-indicating RP-HPLC method for the estimation of Etoricoxib and its degradants, validated as per ICH and USP recommendation guidelines.

The contributions of this article are as follows.

This method reduces retention time and consequently saves solvents and costs. Furthermore, it minimizes the use of toxic and expensive solvents. In addition, the proposed method has stability-indicating capability due to its ability to separate the drug from degradation products after forced degradation studies. Finally, this method shows good features of greenness and functionality after applying AGREE and BAGI assessment.

Materials and methods

Etoricoxib standard was obtained from Bahri Company, sourced from Kekule-Pharma, India. HPLC grade methanol, ammonium acetate, and acetic acid were purchased from Panreac. Hydrochloric acid and sodium hydroxide were purchased from SIGMA-ALDRICH®. Hydrogen peroxide (30%) was purchased from a local pharmacy.

Devices

HPLC water from Siemens Water Technologies (LaboStar). The analysis was performed with the HPLC system (Shimadzu, Japan) provided with a PDA detector. Sartorius sensitive analytical balance (with a sensitivity of 10^{-4} mg) was used.

The photostability study was performed in a photostability chamber (Camag). The thermal stability study was performed in a dry air oven (Memmert, Germany).

Methods

Preparing solutions

The mobile phase is made of a mixture of methanol and ammonium acetate as buffer solution (pH 3.6) in the ratio of 60:40 (methanol: ammonium acetate) filtered using HPLC filters.[3]

Buffer solution preparation

To prepare 25 mmol of ammonium acetate, 1 g of ammonium acetate was weighed, placed into a 500 ml beaker, mixed with HPLC water, and then glacial acetic acid was added to achieve the required pH. The resulting solution was filtered using HPLC filters.[20]

Stock solution of Etoricoxib

A total of 180 mg of Etoricoxib standard was weighed and placed in a 100 ml flask, then diluent (mobile phase) was added to make up the volume. Consequently, the Etoricoxib concentration in the solution will be 1.8 mg/ml.[3]

Standard solution preparation

A total of 5 ml of the Etoricoxib stock solution was pipetted into a 100 ml flask. The solution was diluted up to the required level with the diluent (mobile phase), resulting in an Etoricoxib concentration of 90 μg/ml.[3]

Solutions preparation of forced degradation studies

The stress conditions carried out for degradation studies according to ICH recommendations include photolytic, oxidation, thermolysis, base, and acid hydrolysis.

- **Acid Hydrolysis Studies:** 25 ml of the Etoricoxib stock solution was mixed with 25 ml of 2N HCl, which was then kept for 48 hours at 60°C. The obtained solution was diluted to

Table 1. Literature survey of stability-indicating methods of Etoricoxib.

Stationary phase	Mobile phase	Wavelength detection	Forced degradation conditions	Results	Year of publication	Ref
Phenomenex®C18, 5 μm, 250 mm × 4.6 mm	acetonitrile, methanol and water (60:15:25, v/v/v)	UV detector 236 nm	acid hydrolysis: 1 N HCl / 24 h / 50 ˚C alkali hydrolysis: 1 N NaOH / 24 h / 50˚C oxidative stress: 3% H_2O_2 / 24h / 50˚C Thermal stress: dry heat /60˚C / 24h	Eto was stable against oxidative and thermal stress. No additional peaks were seen in acid and alkali hydrolysis.	2011	13
zorbax SB CN (250×4.6 mm) 5 μm	Na2HPO4 (0.02M) & ACN (60:40, v/v)	UV detector 235 nm	Acid hydrolysis: 1 N HCl/ 4 h/ 80 ˚C alkali hydrolysis: 1 N NaOH / 2 h / 80˚C oxidative stress: 50% H_2O_2 / 1h / 80˚C Thermal stress: 105˚C/ 4 days Photolytic stress: (UV 254/ 4 days)	The degradation of Etoricoxib was observed under base and oxidation environment. The drug was stable in other stress conditions.	2011	14
Stationary phase	Mobile phase	Wavelength detection	Forced degradation conditions	Results	Year of publication	Ref
Agilent C18 column	Acetonitrile: water (50: 50)	PDA detector 230 nm	Acid hydrolysis: 0.1N HCl/ 75˚C/ 30 min Alkali hydrolysis: 0.1N NaOH/ 75˚C/ 30 min Oxidative stress: 30% H_2O_2 / 75˚C/ 30 min Thermal stress: 75˚C/ 30 min	The degradation of Etoricoxib was observed under thermolysis, oxidation, acid and base hydrolysis.	2022	15
C18, 150×4.6 mm, 2.7 μ column	buffer (0.1 % v/v ortho phosphoric acid, pH 3.6), acetonitrile and isopropyl alcohol (65.3:29:5.7 v/v	UV detector 285 nm	Acid hydrolysis: 1 N HCl/ 60˚C/ 30 min Alkali hydrolysis: 1N NaOH 60˚C/ 30 min Thermal stress: 80˚C/ 2 days Photolytic stress: UV light Oxidative stress:3% H_2O_2/ 30 min	Etoricoxib was found to be stable to all degradation conditions.	2022	16
Hypersil C18 (250 mm×4.6 mm, 5 μ)	Acetonitrile: Water (55:45 v/v)	UV/VIS detector 269 nm	Acid hydrolysis: 0.1N HCl/ 50˚C/ 24h Alkali hydrolysis: 0.1N NaOH/ 50˚C/ 24h Oxidative stress: 3% H_2O_2 50˚C/ 24h Thermal stress: 60˚C/ 24h Photolytic stress: UV light/ 24h	Etoricoxib was stable on exposure to various stress conditions.	2011	17
AQ-ODS column (15 cm_4.6 mm i.d., 3 mm)	Acetonitrile with KH_2PO_4, pH 3.1 Gradient separation	PDA detector 220 nm	Oxidative stress by using 5% H_2O_2 Photolytic stress by using solution containing 0.1N HCl, then exposed to ICH photolytic conditions	The degradation of Etoricoxib was observed under photolytic and oxidative stress only.	2003	18
C18 column (150 _ 4.6 mm, 5 μm	Buffer: acetonitrile methanol: (40:15:45)	UV detector 235 nm	Acid hydrolysis: 1 N HCl/Alkali hydrolysis: 1N NaOH Oxidative stress: 30% H_2O_2 Thermal stress: 70˚C/ 4 hours Photolytic stress: sunlight/ 1 hour	Degradation of Etoricoxib was observed in oxidation and light degradation only.	2023	19

(Continued)

make a 90 μg/ml solution, then it was injected into HPLC. Chromatograms were recorded and analyzed to evaluate the stability of the material.[3]

- **Alkali Hydrolysis Studies:** 25 ml of the Etoricoxib stock solution was mixed with 25 ml of 2N NaOH, which was then kept for 48 hours at 60˚C. The obtained solution was diluted to make a 90

Table 1. Continued

Stationary phase	Mobile phase	Wavelength detection	Forced degradation conditions	Results	Year of publication	Ref
C18 column (150 _ 4.6 mm, 5 μm	Methanol :ammonium Acetate (60:40)	PDA detector 234 nm	Acid hydrolysis: 2 N HCl/ 60˚C/ 48h Alkali hydrolysis: 2N NaOH /60˚C/ 48h Oxidative stress: 30% H_2O_2 60˚C/ 48h Thermal stress: 105˚C/ 7days Photolytic stress: UV light/7 days	Degradation of Etoricoxib was observed in oxidation, thermolysis, photolysis, and basic hydrolysis while it was found stable at acid hydrolysis. (present work)		

μg/ml solution, then it was injected into HPLC. Chromatograms were recorded and analyzed to evaluate the stability of the material.[3]

- **Thermal Degradation Studies:** To study heat degradation, the standard of Etoricoxib was kept in an oven at 105˚C for 7 days. Then, a solution of 90 μg/ml of Etoricoxib was prepared for the RP-HPLC investigation. Chromatograms were recorded and analyzed to evaluate the stability of the material.[3]
- **Photolytic Degradation Studies:** The standard of Etoricoxib was placed in a UV chamber for 7 days. Then, a solution of 90 μg/ml of Etoricoxib was prepared for the RP-HPLC investigation. Chromatograms were recorded and analyzed to determine the sample's stability.[3]
- **Oxidation:** 25 ml of the Etoricoxib stock solution was mixed with 25 ml of 30% hydrogen peroxide, which was then kept for 48 hours at 60˚C. The obtained solution was diluted to make a 90 μg/ml solution, then it was injected into HPLC. Chromatograms were recorded and analyzed to evaluate the stability of the material.[3]

All of the degradation study samples were analyzed using the developed method. The percent assay, percent of degradants, and mass balance of all stress samples of Etoricoxib were determined. Fig. 2 illustrates the solutions preparation of forced degradation studies.

Results and discussion

The method mentioned in the article "Development and Validation of HPLC Method for the Assay of Etoricoxib in Pharmaceutical Dosage Form,"[21] with chromatographic conditions:

– Stationary phase: C18 (150×4.6) mm 5μm
– Mobile phase: 60% Methanol and 40% Ammonium acetate with pH = 3.5
– Temperature: 35˚C

Table 2. Summary of method validation results for Etoricoxib.

Parameters	Etoricoxib
Retention time	3.1 min
Theoretical plate	2800
Tailing factor	1.3
Accuracy	100.9%
Precision RSD	99.8% 0.55
Intermediate Precision RSD%	100.2% 0.57
Linearity	72_108 μg/ml
Correlation coefficient	0.9999
DL μg/ml	0.21 μg/ml
QL μg/ml	0.72 μg/ml

was adopted with adjustments to the flow rate to 0.9 ml/min and pH to 3.6 to make the method more suitable for the separation of Etoricoxib and its degradants. The method was then validated based on USP guidelines. The outcomes and parameters were all confirmed to meet the requirements for acceptance. Table 2. summarizes the outcomes of method validation. Fig. 3 depicts a chromatogram of an Etoricoxib standard solution.

After subjecting Etoricoxib to the forced degradation tests under the applied conditions, as shown in Table 3, which summarizes the degradation conditions and results, the damaged samples were analyzed using the same previous analytical method. This method enabled the separation of Etoricoxib from the resulting degradation products, demonstrating the stability-indicating ability of the method.

These tests demonstrated that no degradation occurred to Etoricoxib when applying the conditions listed in Table 3, for a period of 24 hours at room temperature. Likewise, no degradation occurred at 40˚C for half an hour. Therefore, degradation was monitored after two hours at 40˚C, and no degradation occurred, which is consistent with the results of studies by Bagade et al. and Kolla et al. that confirmed the high stability of Etoricoxib. Therefore, the occurrence of degradation was monitored for a period of 48 hours at 60˚C for acid and alkaline hydrolysis and oxidation, and for a period of 7 days for thermal and light degradation. The results were as follows:

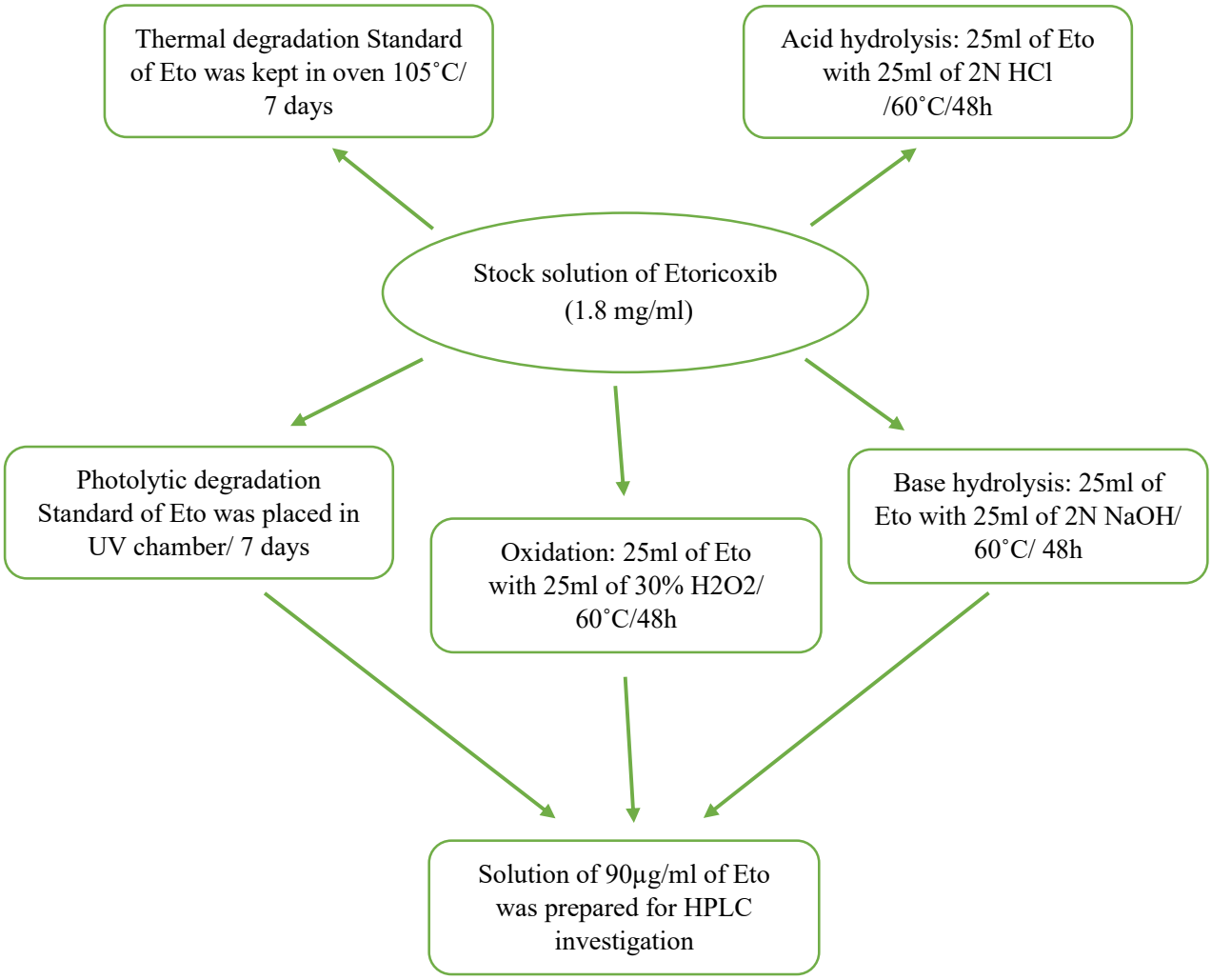

Fig. 2. The solutions preparation of forced degradation studies.

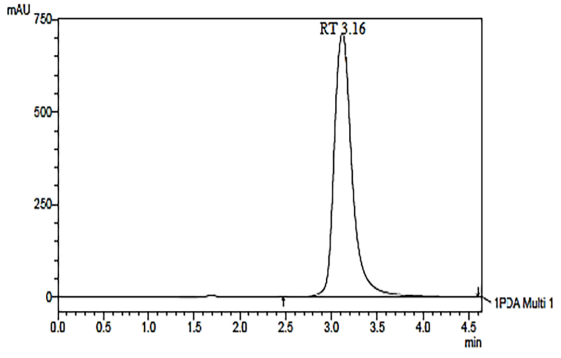

Fig. 3. A chromatogram of an Etoricoxib standard solution with a concentration of 90 μg/ml.

- No degradation of the drug substance occurred by applying acid hydrolysis, while slight degradation appeared by alkaline hydrolysis at a retention time of 2.103.
- Degradation products appeared when applying harsh conditions of heat and UV, with retention times of 2.1 and 1.69 when applying heat, and a retention time of 1.6 when applying UV.
- Degradation of the drug appeared when oxidation was applied using 30% hydrogen peroxide at a retention time of 2.4. All degradation products had separate retention times from the main peak, indicating the ability of the developed method to separate Etoricoxib from its degradation products, demonstrating the stability-indicating tendency of the method.

It is important to highlight that Etoricoxib exhibits remarkable stability toward different degradation factors and does not degrade unless exposed to harsh conditions.

These findings were compared to those of other studies in the literature survey, and it was found that each study in which degradation occurred differed according to the conditions followed. However, they all agreed that the material was stable and did not easily degrade. Additionally, it confirmed that

Table 3. Summary of forced degradation outcomes of Etoricoxib.

Condition of degradation	Time	Assay of Etoricoxib %	Total degradants %	Mass balance	Notes
Acid hydrolysis (2N HCl/ 60˚C)	48 hours	99.91%	–	99.91	No degradation
Base hydrolysis (2N NaOH/ 60˚C)	48 hours	98.8%	0.06%	98.8	
Oxidation (30% H_2O_2/ 60˚C)	48 hours	94.21%	3.998%	98.2	
Thermal (105˚ C)	7 days	96.3%	0.499%	97.2	
Photolytic (UV light)	7 days	98.79%	0.51%	99.3	

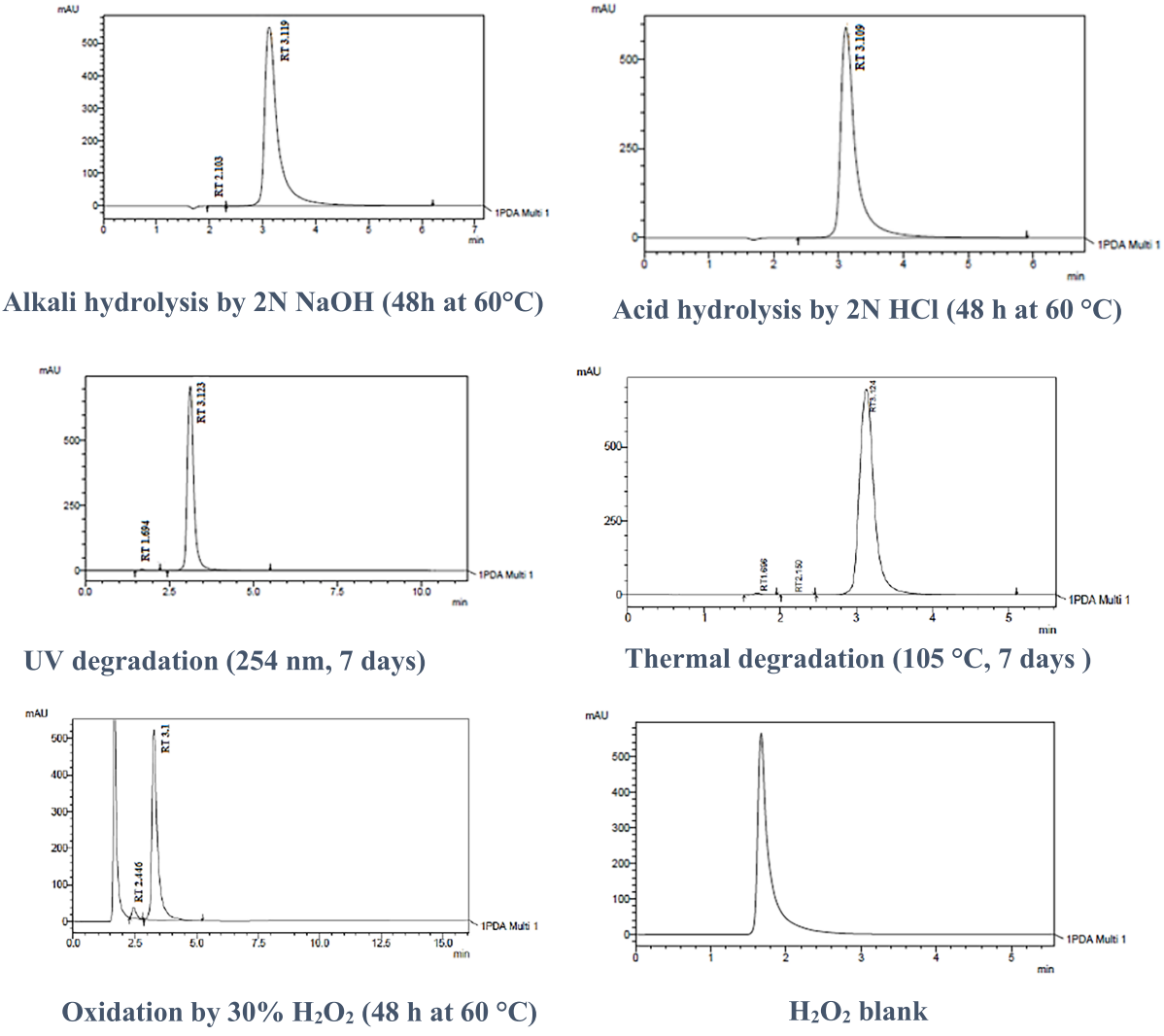

Fig. 4. A chromatograms of forced degradation of Etoricoxib.

Etoricoxib was degraded by oxidation and varied with the rest of the factors according to the conditions applied due to the high stability of the substance. Hence, the main objective of the research was that, in the event of degradation, even if it was a small percentage, the method would be able to detect it and separate the drug from its degradants.

As a result, degradation of Etoricoxib was observed in oxidation, thermolysis, photolysis, and basic hydrolysis, while it was found stable in acid hydrolysis. Stress studies showed that maximum degradation of Etoricoxib was observed upon exposure to oxidation. The chromatograms of all samples showed that all degradation peaks were separated from the Etoricoxib peak and that there was no interaction with Etoricoxib retention time under stressful conditions.

Mass balance, which is the sum of the assay percent and the percent of total degradation products of each condition, is within the acceptance criteria as shown in Table 3. The chromatograms produced under

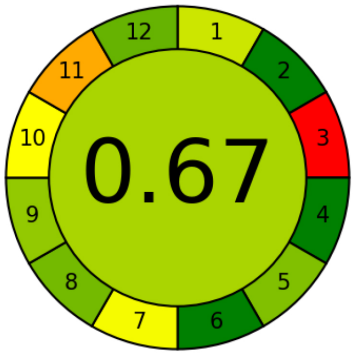

Fig. 5. AGREE pictogram of the developed method.

various stress situations are shown in Fig. 4. The details of the forced degradation studies of Etoricoxib are detailed in Table 3.

Greenness assessment applying AGREE tool

The analytical method was then evaluated using AGREES analytical greenness assessment tool

AGREE parameters[22,23]

1. at-line analysis
2. amount of sample (0.09 g)
3. location of the analytical device (off-line)
4. number of steps of chemical analysis(3)
5. degree of automation (semi-automatic) and sample preparation (miniaturized)
6. no derivatization agents used
7. waste amount (3.69)
8. number of samples determined (15 samples per hour)
9. energy of system (0.1–1.5 kWh per sample)
10. some reagents are bio-based source
11. toxic reagents (yes)
12. highly flammable.

The AGREE score was found to be 0.67, which revealed good greenness features of the method.

Fig. 5 illustrates a representative pictogram for the AGREE score of the developed method.

Functionality assessment applying BAGI tool

BAGI metric tool was adopted to evaluate the applicability and functionality of the analytical method. The information from the analysis was both quantitative and confirmatory due to the employment of the Diode Array Detector as mentioned in the BAGI Index criteria.[24]

BAGI Metric Tool Evaluation:

The short retention time (3.1 min) resulted in a sample throughput of more than 10 h^{-1}. Common, commercially available reagents were used, and current instrumentation in most labs was employed. Simultaneous sample preparation of approximately 13–95 samples was assumed. Pre-concentration was required. Semi-automation and simple, low-cost sample preparation were chosen. The BAGI score of 82.5 for the method demonstrates its good applicability.

Fig. 6. A pictogram of the BAGI index for the developed method.

Fig. 6 illustrates a representative pictogram for the BAGI index of the developed method.

Conclusion

A precise, stability-indicating, and rapid RP-HPLC analytical method was developed and validated for the estimation of Etoricoxib and its degradants.

After applying various stress conditions to Etoricoxib, the method efficiently separated the degradation products created during the degradation study. Thus, the method can be applied effectively in QC laboratories and pharmaceutical industries.

The method shows good features of greenness and functionality after applying AGREE and BAGI assessment.

Therefore, it is recommended to continue work to determine the structure of the degradation products by using LC-MS. It is also recommended to apply the developed method to assay Etoricoxib in biological fluids and ensure it can be used in bioavailability studies.

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Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the figures and tables in the manuscript are ours. Furthermore, figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- No animal studies are presented in the manuscript.
- No human studies are presented in the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Damascus, Syria.

Authors' contribution statement

The authors confirm contribution to the paper as follows: Conception, design, acquisition of data, analysis, drafting the MS, interpretation were done by L. G. Revision and proofreading were done by I. A. and M. A. A.

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طريقة مؤشرة للثبات لتحديد إيتوريكوكسيب ومنتجات تحلله باستخدام كروماتوغرافيا العمود السائلة عالية الأداء: دراسة مدى خضرة ووظيفة الطريقة المطورة

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الخلاصة

يعد إيتوريكوكسيب من مضادات الالتهاب غير الستيروئيدية الحديثة، ذات التثبيط الإنتقائي لأنزيم سيكلو أوكسيجيناز. يهدف البحث لتطوير طريقة اقتصادية ودقيقة لتحديد إيتوريكوكسيب ومنتجات تحلله. تم العمل باستخدام (HPLC) من خلال عمود (C18) وطور متحرك مؤلف من ميتانول وأسيتات الأمونيوم بنسبة (60:40) ومعدل تدفق 0.9مل/د وباستخدام متحري (PDA) بطول موجة 234. تم التحقق من مصدوقية الطريقة التحليلية من حيث الخطية والدقة والمضبوطية والنوعية وحد الكشف وحد الكم وكانت النتائج متوافقة مع المعايير الدستورية. أجريت دراسة تخريب قسري تحت شروط مختلفة من الحموضة والقلوية والأكسدة والضوء والحرارة للتحقق من كون الطريقة المطورة مؤشرة للثبات وقد استطاعت الطريقة فصل إيتوريكوكسيب عن منتجات تحلله وتحديد عوامل التحلل تجاه هذه المادة.

الكلمات المفتاحية: نواتج تحلل، إيتوريكوكسيب، الاستشراب السائل عالي الأداء، مراقبة الجودة، مؤشرة للثبات.