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A COMPREHENSIVE REVIEW OF ANALYTICAL AND BIO-ANALYTICAL METHODS FOR ETORICOXIB DETERMINATION

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ABSTRACT
A selective COX-2 inhibitor is etoricoxib. The way non-steroidal anti-inflammatory medications (NSAIDs) work is by inhibiting the inflammatory mediator COX enzyme. Etoicoxib is used to treat primary dysmenorrhea, rheumatoid arthritis, and osteoarthritis. Thus, the primary goal of this work is to investigate the use of etoricoxib in biological and pharmaceutical formulations through the application of qualitative and quantitative methodologies. We have summarized the methods for estimating etoricoxib based on UV/visible spectroscopy, high-performance liquid chromatography (HPLC), and liquid chromatography-mass spectrometry (LC-MS) in this review paper. We also talked about bioanalytical techniques for etoricoxib analysis. In conclusion, this review article will help scientists create fresh approaches to determining drug concentrations in pharmaceutical dose forms and biological fluids.

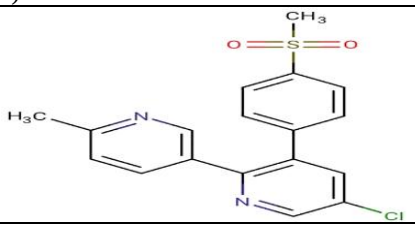
KEYWORDS: Bioanalytical methods, liquid chromatography - mass spectroscopy, high - performance liquid chromatography, etoricoxib, and analytical procedures.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat the pain and inflammation associated with rheumatoid arthritis. Their chemo preventive effects and analgesic and anti-inflammatory qualities stem from their inhibition of cyclooxygenase (COX) enzymes, which change arachidonic acid into prostaglandins.

[1]A very specific inhibitor of cyclooxygenase–2 (COX–2) is etoricoxib, also known as 5-chloro-3-(4-methane sulfonyl phenyl)-6-methyl-[2,3] bipyridyl.[2] Cyclo-oxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are the two kinds of the enzyme. Normal physiological prostaglandin-mediated processes like platelet aggregation and stomach cytoprotection are regulated by COX-1. The suppression of COX-1 by nonselective NSAIDs has been linked to stomach damage and platelet inhibition. It is commonly recognized that COX-2 plays a major role in the production of prostanoid mediators of pain and inflammation.[2] Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, dysmenorrhea, acute gouty arthritis, and chronic low back pain are among the conditions that are treated with etoricoxib. Cyclo-oxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are the two kinds of the enzyme. Normal physiological prostaglandin-mediated processes like platelet aggregation and stomach cytoprotection are regulated by COX-1. The suppression of COX-1 by nonselective NSAIDs has been linked to stomach damage and platelet inhibition. It's common knowledge that prostanoid pain mediators.[3]

Drug Profile[4,54,55,56,57]

Sr. No.	Physiochemical Properties of Etoricoxib	
1.	Drug Name	Etoricoxib (ETX)
2.	Molecular Structure	

3.	Molecular Formula	$C_{18}H_{15}ClN_2O_2S$
4.	IUPAC Name	5-chloro-2-(6-methylpyridin-3-yl)-3-(4-(methylsulfonyl) phenyl) pyridine
5.	Class	Pyridines and Derivatives
6.	Category	COX-2 Inhibitors
7.	CAS No.	NCT06517823
8.	Molecular Weight	358.8g/mol
9.	Official Status	European Medicines Agency (EMEA) FDA Global substance Registration system(GSRS)
10.	Appearance	Solid dispersion
11.	Solubility	3.28e-03 g/L
12.	Pka	16.19
13.	Melting Point	127-138ºC
14.	Partition Coefficient	Between 2.3 & 3.9
Therapeutic Properties of Etoricoxib		
15.	Uses	Osteoarthritis, Rheumatoid Arthritis, Alkylosing spondylitis, Acute gouty arthritis
16.	Side Effects	Erythema, Acute generalized exanthematous pustulosis, Erythema multiforme
17.	Dosage and Dosage form	Administered orally, 1 pill a day for 7 days.
Pharmacokinetics of Etoricoxib		
18.	Absorption	Bioavailability is 100% following oral administration.
19.	Distribution	-
20.	Metabolism	Hepatic, primarily via CYP3A4
21.	Excretion	Kidney 70% and fecal 20%
22.	Half-Life	22 hours
Drug Profile of Etoricoxib		
23.	Toxicity	Aloeolar Bone Loss, Rheumatoid, Cerebral Infraction, Cystitis, Diarrhea Arthritis
24.	Protein Binding	92%

Mechanism of Action

The suppression of prostaglandin synthesis is one reason for the analgesic, antipyretic, and anti-inflammatory properties of NSAIDs. Although the precise mode of action is yet unknown, it seems that these effects are brought about by inhibiting the COX-2 isoenzyme at the sites of inflammation, which in turn results in a decrease in the amount of prostaglandins that are formed from arachidonic acid, the precursor to numerous prostaglandins. The COX-2 enzyme, which is crucial for the regulation of pain and inflammation, is specifically inhibited by etoricoxib. It does not prevent platelet aggregation, in contrast to non-selective NSAIDs. Furthermore, affinity is negligible to nonexistent for COX-1.[4]

A Comprehensive Analysis

Etoricoxib RFX in bulk and pharmaceutical formulations can be determined using a range of analytical techniques, including UV/Visible Spectrophotometry, HPLC, HPTLC, UPLC, LC-MS/MS, and bioanalytical methodologies, according to a thorough literature search. The following medications are assessed both independently and in combination with ETX: celecoxib (CXB), paracetamol (PCT), salicylic acid (SCA), ketoprofen (KPF), nemesulide (NMS), riluzole (RLZ), drotaverine (DRT), thiocholchicoside (THC), pregabalin (PGBN), and tolperisone (TOP).

Method of bioanalysis for Etoricoxib

"Bio-analysis" is a subfield of analytical chemistry that studies the quantitative assessment of biotics (drugs and their metabolites, proteins, DNA, macromolecules, and metabolites) and xenobiotics (drugs and their metabolites) in biological systems. The bioanalytical approaches mentioned are summarized as follows: shown in Table 1.

Table 1: Etoricoxib medication and combination bio analytical determination.

Sr. No.	Title	Method	Description	Ref. No.
1.	Development and validation of an HPLC method for analysis of etoricoxib in human plasma.	HPLC	Sample: Human Plasma Column: Hypersil BDS, C18 column Detection: 235nm Standard: Valdecoxib in acetonitrile	5
2.	Validated liquid chromatographic ultraviolet method for the quantitation of Etoricoxib in	HPLC	Sample: Human Plasma Column: Waters symmetry® C18 column	3

	human plasma using liquid-liquid extraction.		Detection: 284nm Standard: Zaleplon	
3.	High Performance Liquid Chromatographic Determination of Etoricoxib in Human Plasma.	HPLC	Sample: Human Plasma Column: Waters symmetry® C18 column Detection: 284nm Standard: Rofecoxib	6
4.	Stability indicating high performance liquid chromatographic assay for the pharmacokinetics of cyclooxygenase (COX-2) inhibitor etoricoxib in rats.	HPLC	Sample: Rat Plasma Column: Novapack- C8 column Detection: 245nm Standard: Flurbiprofen	7
5.	Determination of etoricoxib in human plasma using automated on-line solid-phase extraction coupled with LC-APCI/MS/MS.	LC-APCI/MS	Sample: Human Plasma Column: Luna C18 column Standard: Antipyrin	8
6.	Determination of etoricoxib in human plasma by liquid chromatography-tandem mass spectrometry with electrospray ionisation.	LC-MS	Sample: Human Plasma Column: Narrow bore RP C column Standard: Phenazone	9
7.	Development of Simple and Rapid LC-MS/MS Method for Determination of Etoricoxib in Human Plasma and its Application to Bioequivalence Study.	LC-MS	Sample: Human Plasma Column: Thermo hypurity, C18 column Standard: Etoricoxib D3	10
8.	Validation of an LC-Tandem MS/MS Method for the Determination of Etoricoxib in Human Plasma and Pharmaceutical Formulations.	LC-MS	Sample: Spiked Human Plasma Column: C18 analytical column Detection: 234nm Standard: Piroxicam	11
9.	A liquid chromatography-mass spectrometry method for quantifying both etoricoxib and valdecoxib in human plasma	RP-HPLC	Sample: Human Plasma Column: Nucleosil C8 guard column	12
10.	Simultaneous quantitation of etoricoxib, salicylic acid, valdecoxib, ketoprofen, nimesulide and celecoxib in plasma by high-performance liquid chromatography with UV detection.	HPLC	Sample: Human Plasma Column: Kromasil KR 100-5C18 column Detection: 235nm Standard: DRF-4367	13
11.	Rapid quantitative analysis of etoricoxib in human plasma by UPLC-MS/MS and application to a pharmacokinetic study in Chinese healthy volunteers.	UPLC-MS	Sample: Human Plasma Column: ACQULTY UPLC HSS T3 column Standard: Etoricoxib d3	14
12.	LC-MS/MS assay of riluzole and etoricoxib in rat plasma and brain tissue with applications for sampling and evaluation in pre-clinical rat model of traumatic brain injury.	LC-MS	Sample: Rat Plasma and brain tissue Column: ACQULTY UPLC BEH C18 column Standard: Etoricoxib D4	15

UV-Visible Spectroscopy Method for Etoricoxib

The ETX Tablet has been determined using spectrophotometric methods. The basic concept, sample matrix, lambda max, solvent linearity range, and correlation coefficient of spectrophotometry are all determined in detail and are summarized below in Table 2.

Table 2: Spectrophotometric methods used for determination of Etoricoxib medication.

Sr No.	Title	Method	Discription	Ref No.
1.	Development and validation of UV spectrophotometric method for the determination of etoricoxib in bulk and tablet formulation.	0.1 N HCL	Method Matrix: Bulk and tablet Formulations λmax (nm): 233nm Linearity(µg/ml): 2-24 Correlation coefficient (R2): 0.9996	16
2.	Spectrophotometric Methods for the Determination of Etoricoxib in Pharmaceutical Formulations.	0.1 N HCL	Method Matrix: Tablet dosage form λmax (nm): 271.6nm Linearity(µg/ml): 1-25 Correlation coefficient (R2): 0.9981	17
3.	Development and validation of a UV spectroscopic method to estimate	Methanol	Method Matrix: Bulk and tablet Formulations λmax (nm) : 234nm	18

	Etoricoxib in bulk and tablet formulation.		Linearity(µg/ml) : 1-11 Correlation coefficient (R2): 0.9986	
4.	A simple Ultraviolet spectrophotometric method for the determination of etoricoxib in dosage formulations.	0.1 N HCL	Method Matrix: Pharmaceutical Formulations λmax (nm): 233nm Linearity(µg/ml): 0.1-0.5 Correlation coefficient (R2): 0.997	19
5.	Development and validation of UV-Visible spectrophotometric baseline manipulation methodology for simultaneous analysis of drotraverine and etoricoxib in pharmaceutical dosage forms.	Methanol	Method Matrix: Combined tablet Dosage form λmax (nm) : 274-351nm Linearity(µg/ml) : 4.5-22.5	20
6.	Spectrophotometric methods for simultaneous estimation of etoricoxib and thiocolchicoside in bulk and combined pharmaceutical dosage form.	0.1 N HCL	Method Matrix: Bulk and combined dosage form λmax (nm) : 240-260nm Linearity(µg/ml) : 2.5-30 Correlation coefficient (R2): 0.9999	21

Methods for ETX using liquid chromatography-mass spectrometry (LC-MS) The combination of LC/MS has drawn a lot of attention lately for its enhanced performance in the analysis of target analytes in complicated samples. After a careful analysis, LC/MS interfaces are separated into two groups: those for direct and indirect column effluent input. The column effluent is transferred to the MS vacuum at an indirect introduction interface via a mechanical mechanism. The transportation system is a prime illustration of an indirect introduction type of interface. When using a direct introduction method, a tube allows the column effluent to enter the mass spectrometric vacuum system directly. Generally, the direct introduction seems to be the easiest way to connect LC and MS. We have covered the LC-MS techniques for determining ETX in a dosage form in this part Table 3.

Table 3: Summary of LC-MS methods for the determination of Etoricoxib in a dosage form.

Sr No.	Title	Method	Ref. No.
1.	Validation of liquid chromatography and liquid chromatography/tandem mass spectrometry methods for the determination of etoricoxib in pharmaceutical formulations.	Method Matrix: Pharmaceutical dosage form Stationary Phase: Synergi fusion C18 column Mobile Phase: 0.01M phosphoric acid- acetonitrile (62+38, v/v) Standard: Piroxicam Linearity(µg/ml) : 0.02-150	22

HPLC technique for tablet etoricoxib

The HPLC method has good selectivity and can also achieve adequate precision at the same time. It must be acknowledged, nevertheless, that the astounding specificity, precision, and accuracy are only possible if extensive system compatibility testing are conducted prior to the HPLC analysis. Because of this, there is a substantial cost associated with the high specificity, precision, and accuracy. Table 4 displays the summary of the HPLC procedures that have been described.

Table 4: Summary of HPLC methods for the determination of Etorocoxib in a single and combined Tablet dosage form.

Sr. No.	Title	Method	Ref. No.
1.	Development and Validation of HPLC assay method for etoricoxib in bulk drug and tablet formulation.	Column: Hyper ODS 2 C18 Column Mobile Phase: Methnol λmax (nm): 233nm Linearity(µg/ml): 20-55µg/ml Retention time(nm): 3.28min Flow rate(mL/m): 1 ml/min Detector: UV-Visible	23
2.	Method development and validation of RP-HPLC method of etoricoxib in bulk and its tablet dosage forms.	Column: Reverse phase C18 column Mobile Phase: Acetonitrile: Ammonium acetate buffer (50:50) λmax (nm): 235nm Linearity(µg/ml): 20-75µg/ml Retention time(nm): 5.337min Flow rate(mL/m): 1ml/min Detector: UV-Visible	24

3.	Development and validation of RP-HPLC method for the dissolution and assay of etoricoxib in pharmaceutical dosage forms.	Column: Intersil ODS-4 column Mobile Phase: 0.01 M sodium perchlorate monohydrate and acetonitrile (48:52v/v) λmax (nm): 235nm Linearity(µg/ml): 34.44-63.96µg/ml Retention time(nm): 4.299min Flow rate(mL/m): 1.5 ml/min Detector: UV Detector	25
4.	Reverse Phase High Performance Liquid Chromatographic Method for the Analysis of Etoricoxib in Pharmaceutical Dosage Form.	Column: Reverse Phase C18 column Mobile Phase: Methanol: Phosphate buffer (90:10v/v) λmax (nm): 235nm Linearity(µg/ml): 10-20075µg/ml Retention time(nm): 3.428min Flow rate(mL/m): 1 ml/min Detector: UV Detector	26
5.	Determination of etoricoxib in pharmaceutical formulations by HPLC method.	Column: Kromasil 100, RO- C18 column Mobile Phase: Acetonitrile: Methanol: 10mm potassium dihyadrogen phosphate (35:35:30 v/v) λmax (nm): 234nm Linearity(µg/ml): 25-400ng/injection Flow rate(mL/m): 1 ml/min Detector: UV/VIS Detector	27
6.	Development, Validation & Stress degradation studies of etoricoxib using diclofenac as an Internal standard by HPLC.	Column: Phenomene x ODS 2 C18 column Mobile Phase: Methanol : 10mm potassium dihydrogen phosphate (75:25% v/v) λmax (nm): 287nm Linearity(µg/ml): 4.99-99.70µg/ml Retention time(nm): 3.2min Flow rate(mL/m): 0.8ml/min Detector: UV Detector	28
7.	High Performance Liquid Chromatographic and Ultra Violet Spectroscopic Determination of Etoricoxib in Pharmaceutical Formulations.	Column: BDS Hypersil C8 column Mobile Phase: Water: Acetonitrile: Methanol (50:25:25v/v/v) λmax (nm): 284nm Linearity(µg/ml): 5-50µg/ml Retention time(nm): 4.8min Flow rate(mL/m): 1.25 ml/min Detector: UV Detector	29

HPTLC Technique for Etoricoxib

Thin-layer chromatography is a popular technique for the analysis of a wide variety of organic and inorganic materials, because of its distinctive advantages such as minimal sample clean-up, a wide choice of mobile phases, flexibility in sample distinction, high sample loading capacity and low cost. The summary of the reported HPTLC methods is shown in Table 5.

Table 5: Summary of HPTLC methods for the determination of Etoricoxib medication in a single and combined dosage form.

Sr. No.	Title	Method	Ref. No.
1.	Development and validation of HPTLC method for the estimation of etoricoxib.	Stationary Phase: Percoated silica gel 60 F_{254} Mobile Phase: Chloroform: methanol: toluene (4:2:4 v/v) Detection: 289nm Linearity(µg/ml): 100-600 ng/spot	49
2.	High-performance thin-layer chromatographic determination of etoricoxib in the bulk drug and in pharmaceutical dosage form.	Stationary Phase: Percoated silica gel 60 F_{254} Mobile Phase: Toluene-1,4-dioxane-methanol (8:5:1.0:0.5 v/v) Detection: 235nm Linearity(µg/ml): 100-1500ng/spot	50
3.	Validated HPTLC Method for Simultaneous Estimation of Paracetamol and Etoricoxib in Bulk Drug and Formulation.	Stationary Phase: Percoated silica gel 60 F_{254} Mobile Phase: Toluene: ethyl acetate: methanol in the ratio of (6:4:1 v/v/v) Detection: 263nm Linearity(µg/ml): 60-360 ng/spot , 50-300 ng/spot	51

UPLC Technique for Etoricoxib

Ultra-performance liquid chromatography (UPLC) is a new category of separation based on well-established principles of liquid chromatography, which utilizes sub-2-mm particles for the stationary phase. The developed UPLC method is validated and therefore could be further used for quantitative analysis of Etoricoxib. UPLC method development and validation for simultaneous estimation of Etoricoxib and Thiocolchicoside in tablets. UPLC was carried out in Hibar, C18 column of dimension 100 × 2.1 mm, 1.8 at 30°C, by using mobile phase 0.1% orthophosphoric acid (pH 2.5) and acetonitrile in a ratio of 90:10 (v/v). The column effluents were monitored at 256 nm using an Acquity Tunable UV detector at a flow rate of 0.3 ml/minute. The linearity of the calibration curve ranged from 1–6 g/ml of Thiocolchicoside and 15–90g/ml of Etoricoxib and the regression coefficient (r2) was 0.999 for both Etoricoxib and Thiocolchicoside drugs.[53]

CONCLUSION

The present review article provides a comprehensive overview of the several analytical and bioanalytical methods—single and combined—developed for etoricoxib. For analytical reasons, many new analytical techniques have been published, such as UV spectroscopy, UPLC, HPLC, and HPTLC. For the convenience of the researchers, the procedure has been tabulated and includes details about the mobile phase, stationary phase, retention time, etc. With the knowledge gathered, future analytical methods for the bio-analysis of etoricoxib in pharmacological and biological formulations can be created. Finally, it provides a chance to learn more about previous successes as well as potential future projects and changes meant to deepen our comprehension of etoricoxib.

CONFLICT OF INTEREST

The authors declare that no conflict of interest.

ABBREVIATIONS

1. UV/VIS – Ultra violet/visible spectroscopy
2. HPLC – High-performance liquid chromatography
3. HPTLC – High-performance thin layer chromatography
4. LC-MS/MS – Liquid chromatography-mass spectroscopy-mass spectroscopy
5. UPLC – Ultra performance liquid chromatograpy
6. RP – Reverse phase
7. nm – Nanometer
8. g/mL – Micro gram per Milliliter
9. PDA – Photo diode array
10. VDX – Valdecoxib
11. SCA – Salicylic acid
12. KPF – Ketoprofen
13. NMS – Nimesulide
14. CXB – Celecoxib
15. RLZ – Riluzole
16. DRT – Drotraverine
17. THC – Thiocholchicoside
18. PCT – Paracetamol
19. PGBN – Pregabalin
20. TOP – Tolperisone

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