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GRADUATE REVIEW ARTICLE

A Review on Various Analytical Methodologies for Etoricoxib

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ABSTRACT

Etoricoxib belongs to the class of highly selective COX-2 inhibitor NSAIDs. It is mostly used for the treatment of pain, arthritic conditions including rheumatoid arthritis and osteoarthritis. The current study focuses primarily on analytical and bioanalytical method development methodologies, as well as numerous methods established for the estimation of etoricoxib, whether in pharmaceutical dose form or in bulk. Analytical procedures are critical for determining compositions, as they allow us to obtain both qualitative and quantitative results utilising advanced analytical tools. The analytical method for Etoricoxib may be chromatographic, electrochemical, spectral or hyphenated. These methods aid in the comprehension of critical process parameters as well as the minimization of their impact on precision and accuracy. Analytical method development is required to sustain high commercial product quality standards and to meet regulatory requirements. Following the reference, regulatory organisations in several nations have established standards and procedures for providing approval, authentication, and registration. Bioanalytical methods are designed to quantify the concentration of drug, metabolite, or typical biomarkers from various biological fluids including serum, urine, saliva and tissue extracts.

Keywords: Etoricoxib, Analytical, HPLC

1 Introduction

NSAIDs have the mechanism of action by inhibition of the prostanoid biosynthesis. It has been prescribed in the management of pain, inflammation and fever. Prostanoid is the lipid mediator which helps in the pathologic and physiologic processes. The prostanoids are synthesized from arachidonic acids and secreted from phospholipid membranes in presence of enzyme phospholipase. It is then converted into the PG-G/H (Prostaglandin) synthase into the PG-G2, further, it is converted into the unstable endoperoxide. The end products like prostanoids including PGE2, PGF2α, PGD2 and prostacyclin, these molecules interrupt cellular response and the pathophysiological process like inflammatory reaction, homeostasis, thrombosis and hemodynamic. The isoforms of the PGH-synthase are Cyclooxygenase i.e. COX-1 and 2 which are also called PGHS-1 and PGHS-2. PGHS-1 (COX-1) is expressed in various cells including mammalian, endothelium gastrointestinal mucosa and endothelium. COX-2 is characterized by its active role in

inflammatory processes and it induces the process of inflammation stimulation. It is associated with pain. NSAID acts by inhibiting the action of COX enzymes and thereby helpful in the reduction of synthesis of pro-inflammatory prostaglandin. Generally, non-selective NSAIDs can inhibit both COX enzymes [1]. Selective COX-2 inhibitors are the subclass of the NSAIDs which is used in the management of pain in Rheumatoid arthritis and osteoarthritis**.** When compared to the COX-2 inhibitors rofecoxib, valdecoxib, and celecoxib, etoricoxib has a higher selectivity for COX-2 over COX-1 [2,3]. Etoricoxib binds to COX-2 in a reversible, noncovalent manner with a 1:1 stoichiometric ratio. In vitro, etoricoxib interfered significantly less with the cardioprotective COX-1-mediated antiplatelet activity of low-dose aspirin than other NSAIDs such as rofecoxib, valdecoxib, celecoxib, and ibuprofen (in ascending order of aspirin antagonism), indicating that etoricoxib has a lower affinity for COX-1 [4].

1.1 Physicochemical Properties

Its chemical name is 5-chloro-2-[6-methyl pyridin-3-yl]-3-[4-methylsulfonylphenyl] pyridine. The structure of Etoricoxib has presented in figure 1.Colour of etoricoxib is off-white and the texture is crystalline and it is not soluble in water and a freely soluble aqueous solution of alkali [5]**.** pKa value is 4.5, absorption maximum 238nm/280nm & melting point 135-138˚C.

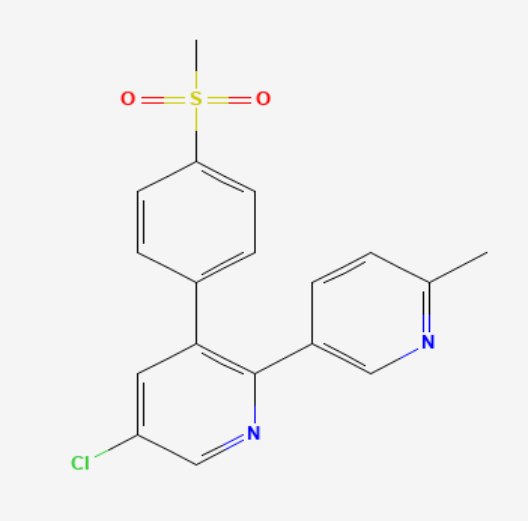

Figure 1: *Chemical structure of Etoricoxib*

1.2 Pharmacokinetic properties

A study has been done on the absorption of the etoricoxib on the single oral doses of the 5, 10, 20, 40 and 120mg. Pharmacokinetics were found to be linear regardless of the formulation [6] Oral etoricoxib is quickly and fully absorbed in healthy volunteers. It has up to 100 percent absolute bioavailability and achieves C_{max} after around 1 hour. Following a high-fat meal, absorption is slowed but not reduced, indicating that Etoricoxib can be provided without regard to diet. Etoricoxib has pharmacokinetics that is linear at doses at least 2-fold higher than the maximum clinical dose (120 mg). The study has been reported that, at a steady-state, the dose which is given intravenously showed the average volume of distribution. It was reported that cytochrome P450 (CYP) 3A4 is essential for the highest amount of (40–90%) of etoricoxib metabolism but other CYP also responsible for the metabolism which includes CYP2D6, CYP2C9, CYP1A2 and CYP2C19 [7]. From intravenous 25 mg, etoricoxib was found to be eliminated from plasma in a biphasic fashion. According to the findings, renal excretion is the main route for the removal of etoricoxib metabolites. Etoricoxib is thoroughly metabolized and excreted mostly in the urine, with just around 1% of the oral dose recovered intact [8,9].

1.3 Pharmacodynamic

Clinically, there are two categories traditional or non-selective and selective. In the non-selective method, it inhibits both COX-1 and COX-2 isoforms. PG synthesis is mediated by the COX enzyme. COX enzymes take part in the inflammation and enhance the physiological process like cytoprotection, renal hemodynamic, renin synthesis, etc [10,11]. For anti-inflammatory response inhibition of COX-2 is necessary. Etoricoxib is majorly characterized for the COX-2 selectivity [12]. In the non-selective method, their transcription factor and gets deactivated by the kappa B. Cyclic adenosine monophosphate response which is dose dependant and inhibited by etoricoxib [13].

Application: Etoricoxib is applied in the pain which is associated with RA, ankylosing spondylitis, and osteoarthritis also in cardiovascular, gastrointestinal, renal diseases. Etoricoxib has also many applications like it is applied in the treatment of acute gouty arthritis, lower back pain, and postoperative pain**.**

1.4 Approved dosage forms of Etoricoxib

The available medicines in the mark*et al.*ong with the brand name and manufacturer are presented in Table 1 [14,15].

Table 1: *Etoricoxib dosage forms along with brand names*

Sr. no	Brand Name	Manufacturer	Dosage form
1.	Coxet (60/90 mg)	Anthus pharmaceutical pvt ltd	Tablet
2.	Coxifact (60/90 mg)	Medico Healthcare	Tablet
3.	Coxnuro(60/90/120 mg)	Emenox Healthcare	Film coated tablet
4.	Ebov (60/90/120 mg)	Glenmark Pharmaceutical Ltd	Film coated tablet
5.	Ecoxib (90/120 mg)	Anglo French drug & industries Ltd	Tablet
6.	Eloxib (90/120 mg)	Emcure pharmaceuticals Ltd	Tablet
7.	Erofica (90/120 mg)	Micro labs Ltd	Tablet
8.	Nucoxia (90/120 mg)	ZydusCadila	Tablet
9.	Retoz	Dr. Reddy's Laboratories ltd	Tablet
10.	Raviza-TH Thiocolchicoside + Etoricoxib(4mg + 60 mg) FC Tablets	Wells Biosciences	Tablet

2 Need of Analytical and Bioanalytical Methods

Analytical techniques are very much important for the determination of the compositions by using advanced analytical instruments. By which we can get both qualitative as well as quantitative results. In these methods, instruments used in analysis play a very important role by which high quality and reliable analytical data can get. These methods may be spectral, electrochemical, chromatographic, hyphenated, or miscellaneous. Analytical method creation aids in the understanding of important process parameters and the reduction of their effect on precision and accuracy. Analytical methods should be formulated using the proper methods and analytical requirements outlined in the guidelines of ICH when adhering to GMP and GLP guidelines. Q2: (R1). The analytical approach refers to the task of choosing an accurate assay technique to determine the composition of a formulation which is known as the analytical method [16-19]. The selection of analytical instrumentation and its method in the creation of a fresh analytical technique must rely on the analytical methods and their scope. Specificity, linearity, limits of detection (LOD) and

quantitation limits (LOQ), range, accuracy, and precision are all essential parameters to consider when developing a process.

Bioanalytical methods aim to quantify a drug & metabolite of a drug or its biomarker concentration in biological fluids example, blood, plasma, serum, urine, and saliva, as well as tissue extracts. The bioanalytical approach must meet stringent method validation requirements set out by regulatory bodies like the US Food and Drug Administration (USFDA) the European Medicines Agency (EMA). It is essential for the development of accurate and very efficient methods for performing both qualitative and quantitative analysis, as well as cost-effective methodologies and shorter analysis times. It is essential to develop reliable and efficient procedures for performing both analysis including quality and quantity measurement, as well as methodologies that should be cheap and shorter analysis times [20]. The purpose of doing analytical method validation and its creation arose as a result of international competition, the need to maintain quality standards of high commercial and consumer value, and ethics of the consumer should be considered. Regulatory bodies have established the standard and procedure for granting approval, authentication, and registration following the reference. Method creation is a time-consuming, costly, and complex process. The steps and procedures used to conduct an analysis are detailed in an analytical process. Sample preparation, its standard solutions, and reagents; application of apparatus; calibration curve generation; application of measurement formulae, and so on. The cycle of the analytical method is shown in figure 2**.**

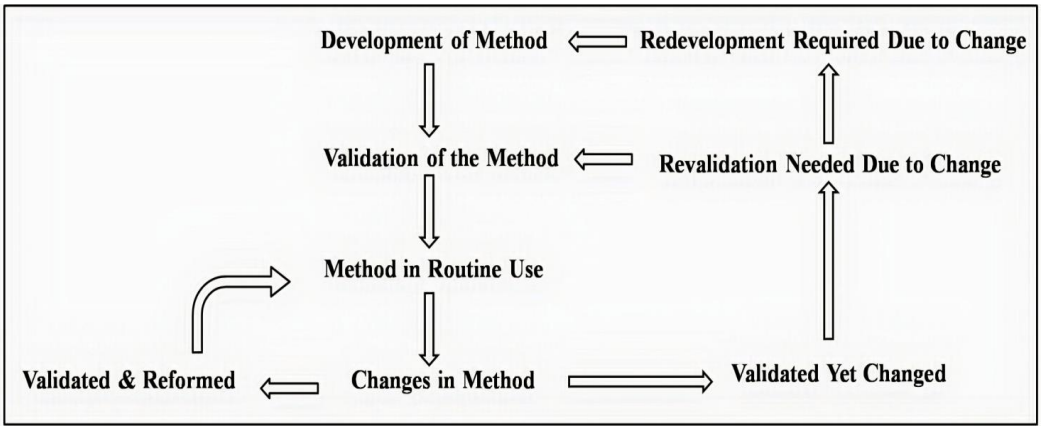

Figure 2*: Analytical method development and its cycle*

3 Analytical Method Development By UV Spectrophotometer

Shahi *et al.* developed the method UV spectrophotometrically for analysis of Etoricoxib in bulk as well tablet dosage form. Where, Dissolution studies are performed on all immediate-release tablets in HCl 0.1 N, with the guidance of by SUPAC-IR, or in a specific medium used for dissolution, which is stated in the monograph officially. The UV instrumental system, which was produced in HCL 0.1 N and is applicable for analyzing IR tablets, is quick, precise, detailed, and highly sensitive. The process has been shown to accurately determine Etoricoxib in different dosage forms as well as in bulk. The maximum absorption of etoricoxib in 0.1N HCl was measured at 233 nm. In the concentration range of 2-24 g/ml, Beer-law Lambert's was followed. The study was suggested that the process is free from impurities and also other additives were absent when calculating drug concentration in the formulation [21]. Bharatheesha*et al.* developed a reliable and sensitive extractive spectrophotometric determination of Etoricoxib in different dosage forms. Two methods were developed, method A and method B which consist of the extract of chloroform and a combination of the drug with bromocresol purple and bromothymol blue. The details for the use of instrument model, solvent and wavelength used have been mentioned in Table 2 [22]. Jat RK *et al.* studied the spectrophotometric quantification of the Etoricoxib tablet and bulk using a hydrotropic agent. The use of the hydrotropic solubilization technique increases the aqueous solubility of poorly water-soluble drugs. Summary of the instrument, solvent and wavelength has been mentioned in Table 2 [23].

Singh S *et al.* developed and validated simple and low-cost ultraviolet spectrophotometric methods [24]. Shakya AK *et al.* developed UV as well as HPLC methods for the estimation of the etoricoxib in different dosage forms [25]. Shah *et al.* studied and done the literature survey to gather the information of different analytical methods for the recently approved fixed-dose combination of drugs i.e. Pregabalin (PGB) and Etoricoxib (ETC). Various methods have been reported like HPLC, spectroscopy, HPTLC, hyphenated techniques& thin layer chromatography [26]. Many researchers develop the method by using a UV spectrophotometer. Some of the examples have been mentioned in Table 2 [27-30].

Table 2*: Analytical method development using UV spectrophotometer*

Sr no	Sample/dosage form	Method/Instrument model	Solvent/solution	Wavelength	Reference
1	Bulk and IR tablet	Shimadzu UV 1700	0.1 N HCl	233 nm	21
2	Bulk and tablet	Shimadzu 1700 UV-Visible spectrophotometer	Methanol	407 & 416 nm	2
3	Bulk and tablet	Systronic 2101 UV-Visible spectrophotometer	2 M Sodium Benzoate solution	282 nm	23
4	Tablet	Shimadzu 1800 UV-Visible spectrophotometer	0.1 M HCl	233 nm	24
5	Tablet	V570 UV-Visible spectrophotometer	Methanol	284 nm	25
6	Bulk and tablet	UV-Visible spectrophotometer	0.1 M NaOH	284 nm	26
7	Tablet	UV-Visible spectrophotometer Shimadzu 1800	0.1 N HCl solution for Method 1 NaCH3COO buffer of pH 7 for method 2 and phosphate buffer pH for method 3	Method1=234 method2=225.6 method3=234.4	27
8	Tablet	UV-Visible spectrophotometer Shimadzu 1800	Methanol	248	28
9	Tablet	UV-Visible spectrophotometer Shimadzu 1800	Methanol	235	29

4 Analytical method development by HPLC

Thimmaraju *et al.* developed a very simple, accurate and reliable reverse phase HPLC method and also validation was done for the estimation of etoricoxib in various pharmaceutical dosage forms. The excipients in tablet dosage forms were found to not affect the quantification of active drugs using the proposed process. Reverse-phase chromatography was used on a Shimadzu HPLC with a detector of 10 AT and a C18 Column 250 X 4.6 mm of ODShypersiland a flow pump with constant flow. Acetonitrile: (0.05M) KH2PO4 buffer (50:50) used as a mobile phase. The detection was monitored at 283 nm. Interday and

intraday precision were calculated and were observed in an acceptable range. The method which is used by RP-HPLC is sensitive, reproducible, and specific for the estimation of etoricoxib in various pharmaceutical dosage forms [31]. Haque *et al.* developed the method for the estimation of etoricoxib by the reverse phase HPLC method in pharmaceutical drugs where the chromatographic determination is determined on the C18 column. The details for the method have been summarised in Table 3 [32-36].

Table 3: *Analytical method development using HPLC method*

Sr No	Sample	Stationary phase/column	Mobile phase	Wavelength (nm)	Flow rate (ml/min)	RT(min)	Reference
1	Tablet & bulk	ODS C-18 250 x 4.6 mm,Hypersil	acetonitrile: (0.05M) Potassium dihydrogen phosphate buffer (50:50)	283	1.8	3.083	31
2	Tablet	C18 column (250 × 4.6 mm. 5µm	acetonitrile : Ammonium Acetate buffer	235	1	5.337	32
3	Tablet	ODS Hypersil C-18 (250 x 4.6 mm., 5µm)	acetonitrile and potassium dihydrogen phosphate buffer (pH 4.2) (46:54 % v/v)	280	1.2	3.083	33
4	Tablet	(ODS) octadecylsilane C18	Methanol &phoshpahte buffer pH 6 (70:30)v/v	215	0.8	5.98	34
5	Tablet and bulk	ODS Hypersil 2 C18 (size 4.6mmx250mm, particle size 5 µm	Methanol	233	1	3.28	35
6	FDC tablet (Etoricoxib + Thiocolchicoside)	lichrosphere RP-select B column (250x4.6mm) partical size 5 µm	1 ml TFA in 2 litermilli-Q water: Acetonitrile (75:25 v/v)	258	1.5	Etoricoxib =8.62 Thiocolchicoside= 3.37	36
7	Tablet	ODS Hypersil C18 (size 4.6mmx200mm, particle size 5 µm	Methanol & Phosphate buffer pH 6 (70:30 v/v)	215	0.8	5.98	37

5 Analytical Method Development Using HPTLC Method

Shah NJ *et al.* studied and developed a suitable, sensitive validation method by using the HPTLC method for the analysis of etoricoxib and Dhaneshwar SR *et al.* developed the method by HPTLC techniques for the determination of etoricoxib and paracetamol which is summarised in table 4 [38, 39].

Table 4: *Analytical method development using HPTLC method*

Sr No	Method	Sample	Stationary phase/column	Mobile phase	Wavelength (nm)	Reference
1	HPTLC	Bulk	Silica gel pre-coated 60F254	Chloroform:methanol:toluene (4:2:4 v/v/v)	289	38
2.	HPTLC	Bulk and tablet	Aluminium plates coated with silica	Methanol:toluene:ethyl acetate (1:6:4 v/v/v)	263	39

6 Bioanalytical Method Development

Ramakrishna NV *et al.* studied the liquid chromatographic method by using ultraviolet spectroscopy for the analysis of etoricoxib in plasma obtained from humans by using liquid-liquid extraction. SPE means solid-phase extraction and HPLC with photochemical cyclization and fluorescence detector was used for the detection purpose along with a structural counterpart as internal standards are employed to quantify drugs from urine and plasma collected from humans. Matthews *et al.* determined the limit of quantification and it was 5 ng/ml. Rose *et al.*. identified a liquid chromatography/tandem mass spectrometry (LC-MS/MS) method for determining Etoricoxib in human plasma using atmospheric pressure chemical ionization (APCI). Brum Junior L *et al.* studied and developed the LC-Tandem mass spectroscopy method and its validation for the analysis of drugs in plasma collected from the human body and in the pharmaceutical dosage form. Werner U *et al.* studied the method development for the combination of the drug etoricoxib and valdecoxib from the plasma collected from the human body. The method developed was LCMS. In this study, researches had connected the RP-HPLC method with mass spectroscopy. Many researchers have made efforts for the development of the bioanalytical method for etoricoxib. Some of the examples have summarized in Table 5 [41-45].

Table 5: *Bioanalytical method development using various methods*

Sr No	Method	Sample/ dosage form	Stationary phase/column	Mobile phase	Wavelength (nm)	Flow rate min/ml	Retention time (min)	Reference
1	HPLC-UV	Human plasma	C18 column, waters symmetry, (5µm, 250× 4.6 mm)	Water: acetonitrile (58:42 v/v)	284	1.2	7.8	41
2.	LC-MS/MS	Tablet, human plasma	Column of C18, Phenomenex Luna (50mm x 3.0mm, 3µm)	Water: acetonitrile (5:95 v/v)& 1 % acetic acid	-	-	0.79	42

3	LC-APCI/MS/MS	Human plasma	C18, Phenomenex Luna (50mm x 3.0mm, 3µm)	Water: acetonitrile (5:95 v/v) & 1 % acetic acid	-	-	0.75	43
4	HPLC-MS/MS	Human plasma	Hypersil, C8 (50mm x 3.0mm, 3µm)	Acitonitrile and ammonium ethanoate (35:65 v/v)	-	-	2.1	44
5	LC-MS/MS	Rat plasma	Waters ACQUITY UPLC BEH C_{18} column (2.1 × 50mm, 1.7 µm particle size	Ammonium acetate buffer pH 9.2 & Methanol (30:70 v/v)	-	0.2	1.1	45

7 Conclusion

This review has been emphasized mainly on the different analytical and bioanalytical methods used for the estimation of the etoricoxib in various medicinal drugs as well as in the bulk form of the drugs. Different dosage forms are containing a combination of etoricoxib. The researchers have made their efforts for the development of analytical and bioanalytical methods which include, UV spectrophotometry, LC, HPLC, HPTLC, RP-HPLC, TLC and also other hyphenated methods. Hyphenated techniques include LC-MS/MS, HPLC-MS/MS, LC-APCI/MS/MS, etc. all the analytical methods developed are very sensitive, reliable, reproducible, precise and having a higher level of automation and sample throughput. The literature survey is done to collect the information of different analytical instrumental methods. Such data would get beneficial to develop a novel analytical method.

8 Competing Interests

Authors report no conflict of interest concerning this review article.

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