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Review Article

Determination Of Selective COX-2 Inhibitors By Analytical And Bioanalytical Methods : A Review

Vinay V. Sarode*[1], Sadhana P. Gautam[2], Shweta V. Rane[3], Sapan K. Shah[4]

[1]*Research Scholar, Department of Pharmacology, VYWS, Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha, Maharashtra, India.*
[2]*Assistant Professor, Department of Pharmacology, VYWS, Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha, Maharashtra, India.*
[3]*Research Scholar, Department of Pharmaceutical Chemistry, Priyadarshini J. L. College of Pharmacy, Hingna, Nagpur-440016, Maharashtra, India.*
[4]*Assistant Professor, Department of Pharmaceutical Chemistry, Priyadarshini J. L. College of Pharmacy, Hingna, Nagpur-440016, Maharashtra, India.*

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ABSTRACT

NSAIDs, or non-steroidal anti-inflammatory medicines, suppress the inflammatory mediator enzyme cyclooxygenase (COX) in order to reduce inflammation. The development of newer NSAIDs, such as celecoxib, rofecoxib, etoricoxib, lumaricoxib, and valdecoxib, is responsible for the discovery of COX-2-specific inhibitors, or coxibs. Their usage is limited to the treatment of rheumatoid arthritis, an inflammatory illness characterized by inflammation of the joint lining, which leads to pain, edema, stiffness, joint degeneration, and loss of joint function. The deterioration of the cartilage that surrounds joints, particularly weight-bearing joints, is known as osteoarthritis and is treated with selective COX-2 inhibitors. This analysis's primary goal is to provide both qualitative and quantitative information about selective COX-2 inhibitors in pharmaceutical and biological formulations. In this review article, we have summarized UV/Vis spectroscopy, high-performance liquid chromatography (HPLC), High-performance thin-layer chromatography (HPTLC), Liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), and ultra performance liquid chromatography (UPLC) etc. Based methods for estimation of Selective COX-2 inhibitors. In addition to that, we have discussed the bioanalytical methods for Selective COX-2 inhibitors analysis. In conclusion, this review article will help to research scholars for further method development for drug estimation in pharmaceutical dosage

***Corresponding Author:** Vinay V. Sarode
Address: *Research Scholar, Department of Pharmacology, VYWS, Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha, Maharashtra, India.*
Email ✉: vinaysarode99@gmail.com

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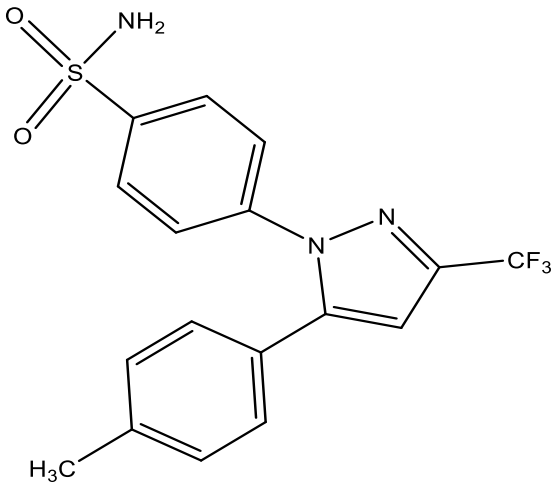
forms and biological fluids.

INTRODUCTION

In clinical practice, non-steroidal anti-inflammatory medications (NSAIDs) are frequently used to treat pain, inflammation, and fever. Because NSAIDs inhibit the cyclooxygenase (COX) enzyme, they impede prostaglandin synthesis, which accounts for their pharmacological actions. In humans, the enzyme cyclooxygenase (COX) comes in two forms: COX-1 and COX-2. COX-1 is necessary for numerous physiological housekeeping processes, including platelet aggregation, renal homeostasis maintenance, and gastric mucosa protection. Prostaglandins, which mediate reactions to pathologic processes like pain, fever, and inflammation, are synthesized by COX-2.(53) COX is inhibited by NSAIDS. Nevertheless, despite their advantageous benefits, they often conflict with the body's defenses against stomach lining deterioration and platelet dysfunction. As a result, many patients may find that their toxicity-related symptoms are unacceptable. The invention of more recent medications known as COX-2-specific inhibitors (coxibs), such as celecoxib, rofecoxib, etoricoxib, lumaricoxib, and valdecoxib, was made possible by this. They maintain the integrity of the stomach lining or platelet control while inhibiting inflammatory disorders. Selective COX-2 inhibitors are as effective as nonsteroidal anti-inflammatory drugs (NSAIDs), but they have a far better safety record, making it acceptable to use them to treat both acute and chronic pain, with or without inflammatory disorders. It is used to treat the signs and symptoms of osteoarthritis and rheumatoid arthritis. An autoimmune condition called rheumatoid arthritis damages and destroys joints by inflaming the lining of the joints, causing pain, stiffness, swelling, and loss of joint function. The substance that cushions joints wears down over time, usually in weight-bearing joints, and this leads to osteoarthritis.(22)

CELECOXIB:

A specific inhibitor of cyclooxygenase-2 (COX-2) is celecoxib. This medication is licensed to treat the inflammation-related signs and symptoms of osteoarthritis and rheumatoid arthritis. Celecoxib predominantly inhibits COX-2 but not COX-1 in humans at therapeutic levels. Celecoxib has a better safety profile as compared to traditional non-steroidal anti-inflammatory medicines (NSAIDs), which block both cyclooxygenases.First of all Clinical research has shown that celecoxib effectively reduces edema, discomfort, and sensitivity in the joints while also lowering the risk of stomach ulcers. Furthermore, new research has shown that COX-2 inhibitors reduce the growth of colon polyps.(2) The chemical name of celecoxib is (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl] benzenesulfonamide).(1)



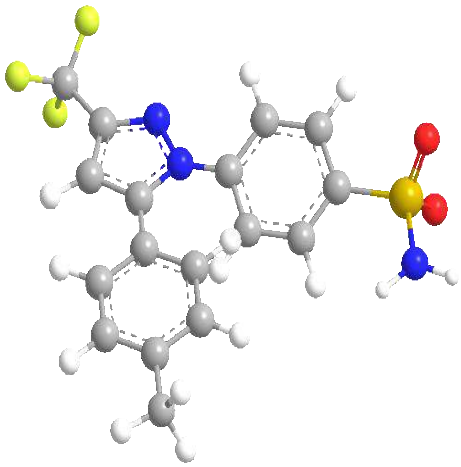
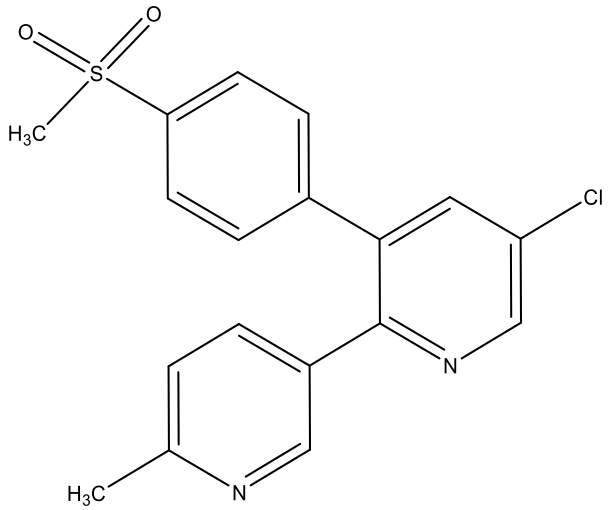


Figure 1: Chemical Structure of Celecoxib

ETORICOXIB:

In the group of nonsteroidal anti-inflammatory drugs (NSAIDs) the newest addition of etoricoxib takes place known as selective cyclooxygenase-2 inhibitors. The chemical name of etoricoxib is {5-chloro-3-(4-methanesulfonylphenyl)-6-methyl-[2,3]-bipyridinyl}. In 38 countries worldwide in Europe, Latin America and the Asia Pacific region ETX has been launched. The new drug application (NDA) has submitted a for ARCOXIA (etoricoxib) to the U.S. Food and Drug Administration (USFDA) by Merck & Co. Inc., for the treatment of osteoarthritis, rheumatoid arthritis, chronic low back pain, acute pain, dysmenorrheal, acute gouty arthritis and ankylosing spondylitis.(54)



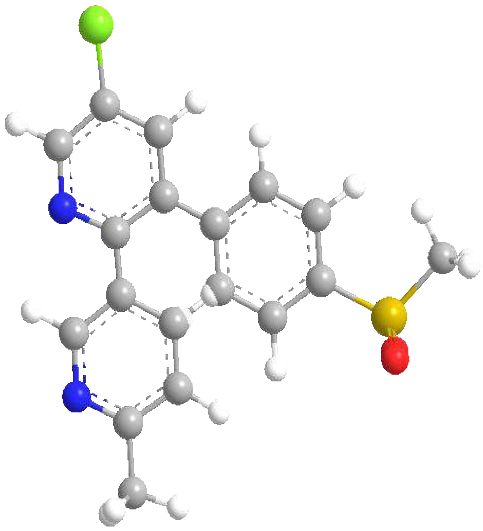


Figure 2: Chemical Structure of Etoricoxib

VALDECOXIB:

Valdecoxib is a diaryl substituted isoxazole with the trade name Vx2 (Novartis). The molecular weight of valdecoxib is 314.36. The chemical name of VDX is 4-(5-methyl- 3-phenyl-4-isoxazolyl)benzene sulphonamide. It is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties which is use for the treatment of osteoarthritis and Rheumatoid arthritis. Even chronic administration of valdecoxib would not increase the risk of cardiac arrhythmia associated with QT prolongation to patients for the treatment of osteoarthritis and rheumatoid arthritis like disease. Valdecoxib is official only in the martindale extra pharmacopoeia.(103) Valdecoxib was immediately banned by Government decision (GSR NO- 510E) from 28-07-2005 after evidence showed its prolonged used leads to increased risk of heart attacks and stroke.(162)

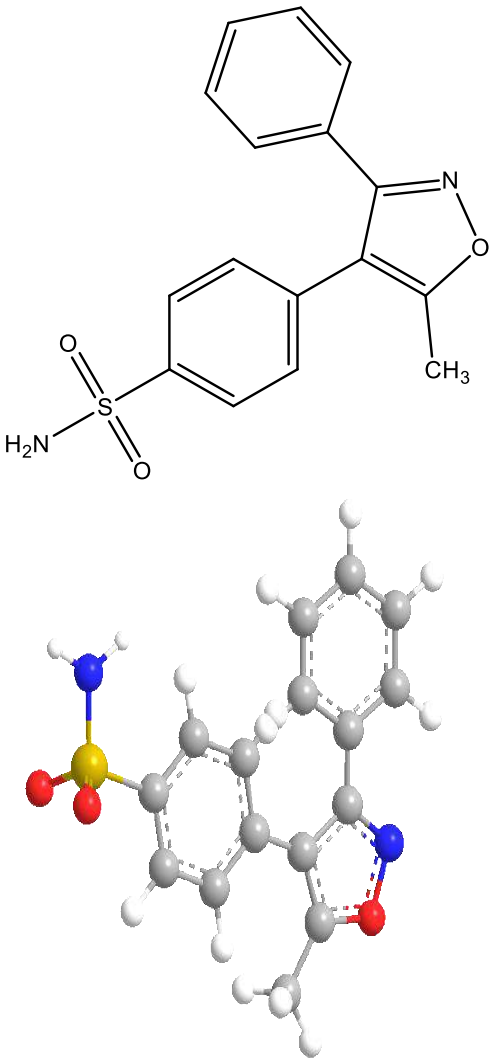


Figure 3: Chemical Structure of Valdecoxib

PARECOXIB:

Parecoxib is a prodrug of valdecoxib. It is a selective cyclooxygenase 2 (COX 2) inhibitor. Parecoxib administered intramuscularly or intravenously in the body.(131) Parecoxib has little or no effect on platelet function. PRX have longer duration of action and it reduced gastrointestinal risk which is considered advantageous in the postoperative repair. Parecoxib can be rapidly hydrolysed into its valdecoxib which is a active metabolite of PRX, and valdecoxib further metabolized by cytochrome P450 enzymes (CYP) into hydroxylated valdecoxib (OH-VX) as the major metabolite. However, the overdosing valdecoxib have been reported for renal safety and high risk of cardiovascular events of concerns. Therefore, it is necessary to monitor the parecoxib and its metabolites concentration in blood in order to control the concentration of valdecoxib in a reasonable range.(132)

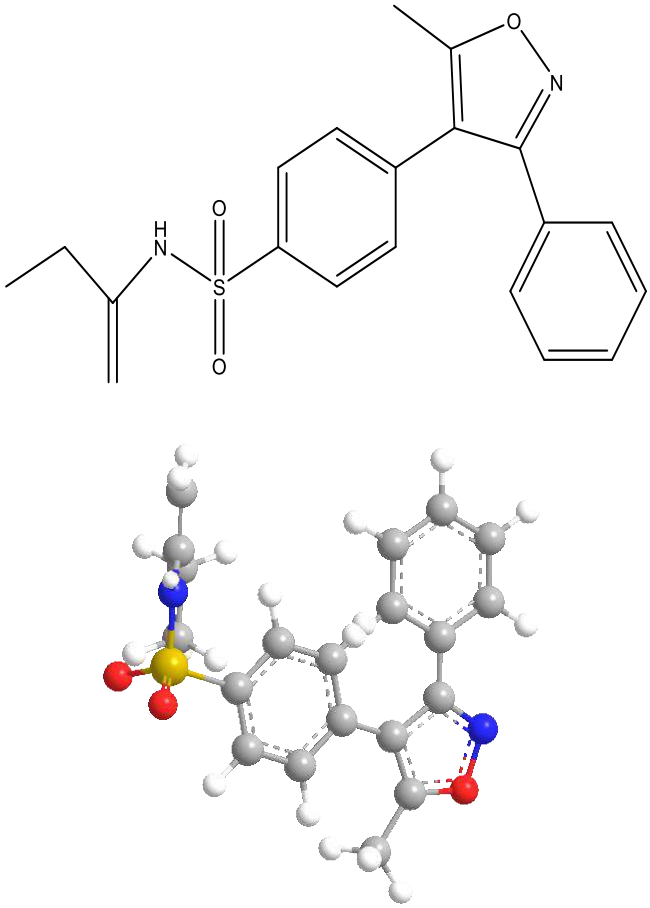


Figure 4: Chemical Structure of Parecoxib

ROFECOXIB:

Rofecoxib belongs to the class of nonsteroidal anti-inflammatory drug (NSAID) called as selective cyclooxygenase-2 inhibitor (COX-2), which gives anti-inflammatory, analgesic, and antipyretic effects. RFX is used for osteoarthritis symptoms, dysmenorrhea, and acute pain.(136) Rofecoxib is chemically known as 4-[4-(methyl-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone.(138) The rofecoxib was voluntarily withdrawn from the global markets because it increased risk of coronary thrombosis and cerebrovascular risk after its chronic use (about 18 months). However, for research purposes comprising characterization

studies, preparation of new formulations, and also in clinical studies rofecoxib is currently used. According to Biopharmaceutics Classification System (low solubility and high permeability) RFX is a Class II compound and it has a long half-life (t1/2 = 17 h). Therefore, In the formulation studies of controlled release dosage forms, and also in new drug delivery systems it is used as a model drug.(136) Rofecoxib was immediately banned by Government decision (GSR NO-810E) from 13-12-2004 after evidence showed its prolonged used leads to increased risk of heart attacks.(162)

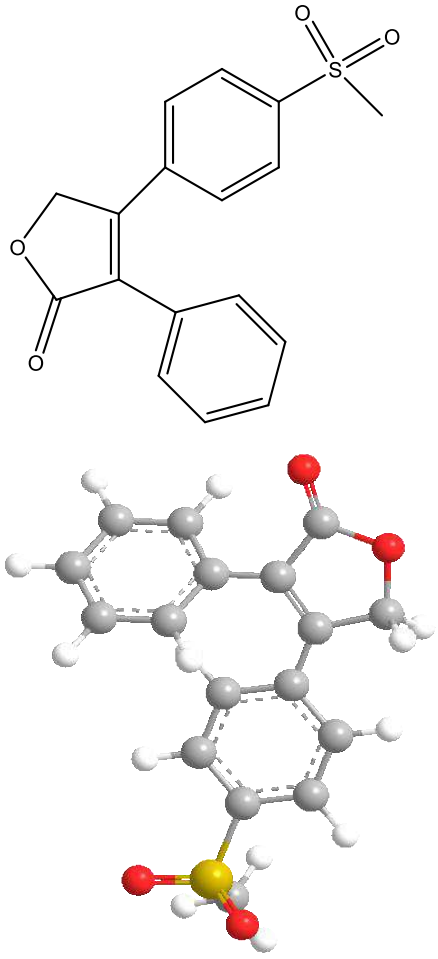


Figure 5: Chemical Structure of Rofecoxib

LUMIRACOXIB:

Lumaricoxib is a selective cyclooxygenase-2 inhibitor developed for the symptomatic treatment of osteoarthritis and acute pain. Lumiracoxib chemically known as 2-[(2-fluoro-6-chlorophenyl)amino]-5-methyl benzeneacetic acid.(157) The molecular weight of LMX is 294 Da. Lumaricoxib is chemically differ from the other COX-2 inhibitors that it lacks a sulfur-containing moiety and possesses a carboxylic group that confers weakly acidic properties (pKa 4.7). It was recently withdrawn from the market in some countries, however it could be available in others.(161)

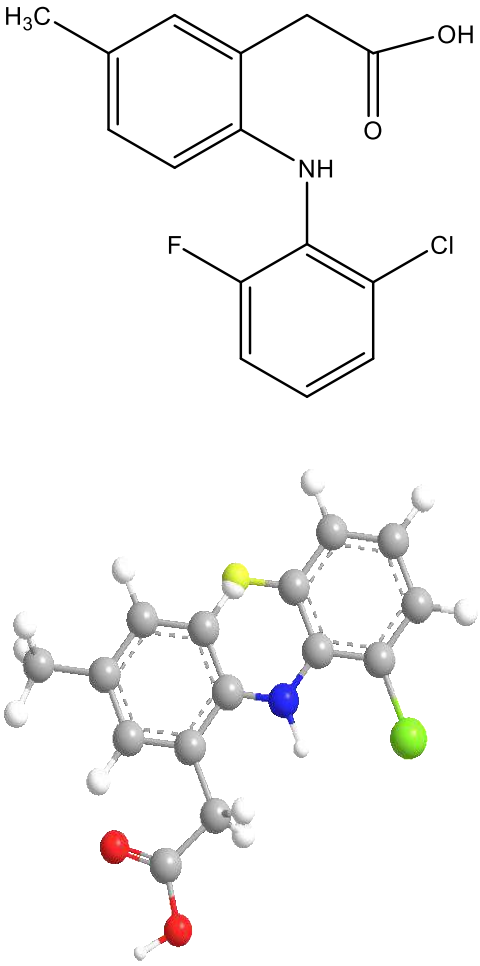


Figure 6: Chemical Structure of Lumiracoxib

Analytical techniques used for determination of Selctive COX-2 inhibitors:

For the determination of Selective COX-2 inhibitors in bulk and pharmaceutical formulations, an exhaustive literature search found numerous analytical techniques such as UV/Visible Spectrophotometry, HPLC, HPTLC, UPLC, LC-MS/MS, and bioanalytical approaches. Figure 7 shows different analytical methods

implemented for the estimation of Selective COX-2 inhibitors

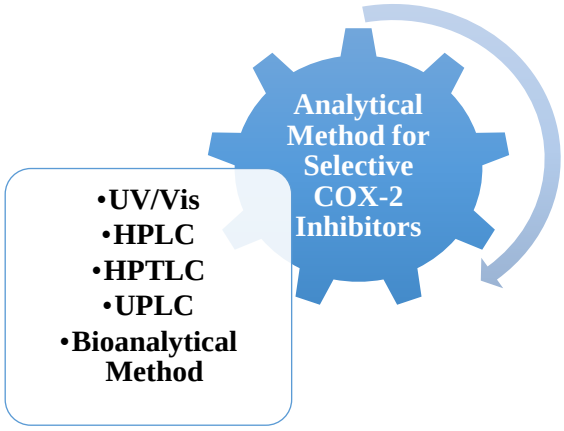


Figure 7: Analytical methods of Selective COX-2 Inhibitors

CELECOXIB:

Bio-analytical method for CXB

Bio-analysis is a sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems. The summary of the reported bioanalytical methods is shown in Table 1.

Table 1: Bioanalytical determination of CXB

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref
1	CXB	Human plasma	HPLC	Nova Pak C8 column	215 nm	SC-236	1
2	CXB	Human plasma	HPLC	Zorbax Eclipse Extend C18 column	***	Dimethyl - Celecoxib	2
3	CXB	Human plasma and breast milk	HPLC	C18 column	254 nm	***	3
4	CXB	Human plasma	HPLC	Monolithic silica column	254 nm	Mefenamic acid	4
5	CXB	Human plasma	HPLC	Nucleosil CN column	260 nm	Flutamide	5
6	CXB	Rat plasma	HPLC	C18 analytical column	254 nm	Ibuprofen	6
7	CXB	Rat plasma	HPLC	C18 reverse phase column	254 nm	Ketoprofen	7
8	CXB	Human plasma	HPLC	C18 µ-Bondapak HPLC column	260 nm	Flutamide	8
9	CXB	Human plasma	HPLC	Nucleosil-NO column	260 nm	***	9
10	CXB	Human serum	HPLC	Prontosil C AQ column	240 nm	Demethylated analogue	10
11	CXB	Human serum	HPLC	C18 Wakosil column	250 nm	Tolbutamide	11

12	CXB	Human plasma	HPLC	Knauer C18 column	250 nm	***	12
13	CXB	Skin samples	HPLC	C18 column	251 nm	Caffeine	13
14	CBX	Human urine	HPLC	Spherigel C18 column	255 nm	***	14
15	CXB	Human plasma	HPLC	Nucleosil C8 guard column	260 nm	Rofecoxib	15
16	REP, CXB	Male Sprague-Dawley rats	HPLC	Reversed C18 column	240 nm	Ketoconazole	16
17	RFX, CXB	Human plasma	HPLC	Zorbax SB-CN analytical column	254 nm	4-*n*-pentyl-phenyl-acetic acid	17
18	DTX, CXB	Rat plasma	HPLC	Reversed-phase C18 µ-Bondapack column	230 nm	Paclitaxel	18
19	IBU, DIC, CXB	Human urine	HPLC	MZ ODS-C18 column	330 nm	***	19
20	DIC, RFX, NIF, CXB	Human serum	HPLC	C18 bonded silica column	261 nm, 288 nm, 282 nm, 254 nm	***	20
21	CXB, OH-CXB, COOH-CXB	Human plasma	HPLC	C18 reverse phase column	254 nm	Phenacetin	21
22	ETX, SCA, VDX, KPF, NMS, CXB	Human plasma	HPLC	Kromasil KR 100-5C18 column	235 nm	DRF-4367	22
23	CXB	Human plasma	LC-MS	Shim Pack GLC-CN, C column	***	Sulindac	23
24	CXB	Rat blood	UPLC-MS/MS	Phenomenex Aqua C18	254nm	1-(4-sulfamoylphenyl)-5-(*p*-tolyl)-1*H*-pyrazole-3-carboxylic acid	24
25	CXB	Rat and human liver microsomes	UPLC-MS/MS	UPLC BEH C18 column	***	Carbamazepine	25

26	ETX, CXB	Serum and synovial fluid of inflammatory arthritis patients	UPLC/ICPMS	Acquity C18 BEH	***	***	26
27	CBX, DEZ, DEX	Beagle plasma	UPLC-MS/MS	UPLC BEH C18 column	***	Midazolam	27

***** Not Provided**

UV-Visible spectroscopy method for CXB

The spectrophotometric methods have been accounted for the determination of CXB. The details of Spectrophotometry determination of basic principle, sample matrix, lambda max, solvent linearity range and the correlation coefficient are summarized in Table 2.

Table 2: Spectrophotometric methods used for determination of CXB

Sr. No.	Drug	Matrix	Solvent	Lambda Max (nm)	Linearity (µg/mL)	Correlation coefficient (R2)	Ref.
1	CXB	Capsule	Either ethanol or acetonitrile	272 nm	0–3 mg/L	Ethanol = 0.995 Acetonitrile = 0.999	28
2	CXB	Capsule	Methanol	270 nm	10 to 50 µg/ml	0.9965	29
3	CXB	In pure form and In solid dosage form	High pure water, methanol, acetonitrile	251 nm	1–20 µg/ml	0.9999	30
4	AMD and CXB	In Pharmaceutical Formulation	Ethanol	364.3nm and 286.7nm	0.5 to 10 µg/ml and 5 to 40 µg/ml	0.9992 and 0.9990	31
5	CXB and AMD	Tablets	Methanol	250 nm And 290 nm	15–40 µg/ml and 3–8 µg/ml	0.9992 and 0.9991	32
6	AMD, CXB and RMP	Pharmaceutical combined dosage forms	Methanol	361 nm, 253nm and 222 nm	5–60 µg/ml, 5–30 µg/ml, and 5–110 µg/ml	0.9998, 0.9998 and 1	33
7	AMD and CXB	Pure and pharmaceutical Formulation	Ethanol	334.2 nm and 254.2 nm	1–6 µg/ml and 5–40 µg/ml	0.9994 and 0.9999	34

***** Not Provided**

Liquid-Chromatography-Mass Spectroscopy methods (LC-MS) for CXB:

In recent years, the combination of LC/MS has gained a lot of attention for the analysis of interest analytes in complex samples with improved performance. In brief, after a thorough examination, LC/MS interfaces are divided into two categories namely interfaces for indirect and direct input of column effluent. A mechanical mechanism is employed to transmit the column effluent to the MS vacuum at an indirect introduction interface. A classic example of an indirect introduction type of interface is the transportation system. In the case of the direct introduction system, the column effluent flows directly into the mass spectrometric vacuum system via a tube. Mainly, the most straightforward method of linking LC and MS appears to be the direct introduction.33 In this section, we have discussed the LC-MS methods for the determination of CXB in a dosage form Table 3.

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

Sr. No	Drug	Matrix	Stationary Phase	Mobile Phase	Internal Standard	Linearity (ng/mL)	Ref.
1	CXB	***	Symmetry C18 analytical column	5.0 mm ammonium acetate-acetonitrile in the ratio of 30:70 (v/v)	***	0.06 to 3.0 ppm	36
2	CXB	Bulk and formulations using a chiral column	Chiralcel OD column	Hexane: Ethanol (94:06 v:v)	***	0.25–0.75 mg:ml	37

***** Not Provided**

HPLC method for CXB

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision, and accuracy are attainable only if wide-ranging system suitability tests are carried before the HPLC analysis. For this reason, the expense to be paid for the high specificity, precision, and accuracy is also high. The summary of the reported HPLC methods is shown in Table 4.

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

Sr. No.	Drug name	Column	Mobile phase	Lambda max (nm)	Linearity (µg/mL)	Retention time (min)	Flow rate (mL/min)	Detector	Ref.
1	CXB	Inertsil ODS-3 column	Acetonitrile : water (55:45 v/v)	242 nm	0.25 to 1.0 µg/ml	16.55 min	1.0 ml/min	SPD-M10AVP photodiode array detector	38
2	CXB	Column L11	Buffer, Methanol and Acetonitrile	215nm	25-120 µg/ml	23.501 min	1.3 ml/min	VWD detector	39

			(60: 30: 10v/v/v)						
3	CXB	Reversed-phase C-18 column	Buffer and acetonitrile (40:60)	254 nm	1 to 150 mg/ml	10.9 min	1 ml/min	Photo-diode array detector	40
4	CXB	Reversed-phase C-18 column	Methanol and water (85:15)	251 nm	2 to 50 mg/ml	4.965 min	0.8 ml/min	Ultraviolet (UV)-visible detector	41
5	CXB	Reversed-phase C-18 column	Methanol and water (75:25 % v/v)	250 nm	0.27–80 µg/ml	4.8 ± 0.01 min	1.25 ml/min	UV–visible detector	42
6	AMD and CXB	Zorbax C18	Sodium phosphate buffer (ph. 5.6) : acetonitrile : methanol in a ratio 30:55:15 (v/v)	239 nm	5–30 µg/ml and 50–500 µg/ml	1.72±0.02 min 3.38±0.023 min	1.2 ml/min	UV detector	43
7	CUR and CXB	RP C18 XDB column	Water (1% acetic acid)-Acetonitrile	254 nm	1- 20 µg/ml and 0.1-2 µg/ml	***	1.50 ml/min	UV/Vis detector	44
8	AMD and CXB	C18 reversed phase column (Thermos ODS Hypersil	Acetonitrile: potassium phosphate Buffer 60:40 (v/v)	360 nm and 265 nm	0.017 and 0.0167 µg/ml	4.41min and 7.30 min	1 ml/min	UV detector	45
9	AMD and CXB	Reversed-phase C-18 column	MEOH + Water (70 : 30 v/v)	235 nm	1-5 µg/ml and 20-100 µg/ml	3.953 min and 6.587 min.	1 ml/min	UV Detector	46
10	ATV-Ca and CXB	Cosmosil-C18 column	Acetonitrile: ammonium acetate buffer: methanol (50 : 25 : 25 v/v/v)	277nm	100-500µg/ml	6.195 min and 3.989min	1.0ml/min	UV/Vis detector	47
11	CXB and AMD	Kromasil C18 column	Methanol and potassium dihydrogen phosphate	253 nm	10-60 µg/ml and 1-6 µg/ml	2.89 min and 5.89 min	1.2 ml/min	UV Detector	48

			70 : 30% v/v						
12	CXB and DIN	Inertsil ODS 3V L1 column	Methanol and acetonitrile; 50 : 50, v/v	255 nm	10-40 µg/ml and 5-20 µg/ml	7.42 min and 13.96 min	1.0ml/min	Photodiode array detector	49
13	AMD and CXB	Florosil C18 analytical column	Acetonitrile-Water (80:20 v/v)	250 nm	2-12 µg/ml and 50-300 µg/ml	1.98 min and 3.18 min	1.0ml/min	UV/Vis detector	50

HPTLC method for CXB

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 CXB in a single and combined dosage form

Sr. No.	Drug	Stationary Phase	Mobile Phase	Detection	Linearity	Ref.
1	CXB	Silica gel 60F254	N-hexane–ethyl acetate, 60 + 40 (v/v)	262 nm	200 and 2000 ng/spot	51
2	AMD and CXB	Pre-coated silica gel aluminum Plate 60 F254	Toluene : ammonia : methanol : acetonitrile (6.6:0.12:1.5:2 v/v/v/v)	240 nm	0.3-2 µg/spot 0.3-3.4 µg/spot	52

ETORICOXIB:

Bio-analytical method for ETX

Bio-analysis is a sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems. The summary of the reported bioanalytical methods is shown in Table 6.

Table 6: Bioanalytical determination of ETX

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref
1	ETX	Human plasma	HPLC	Hypersil BDS, C18 column	235 nm	Valdecoxib in acetonitrile	53
2	ETX	Human plasma	HPLC	Waters symmetry® C18 column	284 nm	Zaleplon	54

3	ETX	Human plasma	HPLC	Waters symmetry® C18 column	284 nm	Rofecoxib	55
4	ETX	Rat Plasma	HPLC	Novapak-C8 column	245 nm	Flurbiprofen	56
5	ETX	Human plasma	LC-APCI/MS/MS	Luna C18 column	***	Antipyrin	57
6	ETX	Human plasma	LC–MS–MS	Narrow bore RP C column	***	Phenazone	58
7	ETX	Human plasma	LC-MS/MS	Thermo Hypurity, C18 column	***	Etoricoxib D3	59
8	ETX	Spiked Human plasma	LC-MS/MS	C18 analytical column	234 nm	Piroxicam	60
9	ETX and VDX	Human plasma	RP-HPLC	Nucleosil C8 guard column	***	TO FIND IT	61
10	ETX, SCA, VDX, KPF, NMS, CXB	Human plasma	HPLC	Kromasil KR 100-5C18 column	235 nm	DRF-4367	62
11	ETX	Human plasma	UPLC-MS/MS	ACQUITY UPLC HSS T3 column	***	Etoricoxib-d3	63
12	RLZ and ETX	Rat plasma and brain tissue	LC-MS/MS	ACQUITY UPLC BEH C18 column	***	Etoricoxib D4	64

***** Not Provided**

UV-Visible spectroscopy method for ETX

The spectrophotometric methods have been accounted for the determination of ETX. The details of Spectrophotometry determination of basic principle, sample matrix, lambda max, solvent linearity range and the correlation coefficient are summarized in Table 7.

Table 7: Spectrophotometric methods used for determination of ETX

Sr. No.	Drug	Matrix	Solvent	Lambda Max (nm)	Linearity (µg/mL)	Correlation coefficient (R2)	Ref.
1	ETX	Bulk and tablet Formulation	0.1N HCl	233 nm	2-24 µg/ml	0.9996	65
2	ETX	Tablet dosage form	0.1 N HCl	271.6 nm	1-25µg/ml	0.9981	66

3	ETX	Bulk and Tablet Formulation	Methanol	234nm	1 to 11 µg/ml	0.9986	67
4	ETX	Pharmaceutical formulations	0.1 M HCl	233 nm	0.1–0.5 µg/ml	0.997	68
5	ETX and DRT	Combined tablet dosage form	Methanol	274nm and 351 nm	4.5-22.5 µg/ml and 4-20 µg/ml	***	69
6	ETX and THC	Bulk and combined tablet dosage form	0.1N HCl	240 nm and 260 nm	2.5–30 µg/ml	0.9999	70

***** Not Provided**

Liquid-Chromatography-Mass Spectroscopy methods (LC-MS) for ETX:

In recent years, the combination of LC/MS has gained a lot of attention for the analysis of interest analytes in complex samples with improved performance. In brief, after a thorough examination, LC/MS interfaces are divided into two categories namely interfaces for indirect and direct input of column effluent. A mechanical mechanism is employed to transmit the column effluent to the MS vacuum at an indirect introduction interface. A classic example of an indirect introduction type of interface is the transportation system. In the case of the direct introduction system, the column effluent flows directly into the mass spectrometric vacuum system via a tube. Mainly, the most straightforward method of linking LC and MS appears to be the direct introduction. In this section, we have discussed the LC-MS methods for the determination of ETX in a dosage form Table 8.

Table 8. Summary of LC-MS methods for the determination of ETX in a dosage form

Sr. No	Drug	Matrix	Stationary Phase	Mobile Phase	Internal Standard	Linearity (µg/mL)	Ref.
1	ETX	Pharmaceutical dosage forms	Synergi fusion C18 column	0.01M phosphoric acid – acetonitrile (62 + 38, v/v)	Piroxicam	0.02–150 µg/ml	71

HPLC method for ETX

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision, and accuracy are attainable only if wide-ranging system suitability tests are carried before the HPLC analysis. For this reason, the expense to be paid for the high specificity, precision, and accuracy is also high. The summary of the reported HPLC methods is shown in Table 9.

Table 9: Summary of HPLC methods for the determination of ETX in a single and combined dosage form

Sr. No	Drug name	Column	Mobile phase	Lambda max (nm)	Linearity (µg/mL)	Retention time (min)	Flow rate (mL/min)	Detector	Ref.

1	ETX	Hyper ODS 2 C18 column	Methanol	233 nm	20-55 µg/ml	3.28 min	1 ml/min	UV-Visible	72
2	ETX	Reverse phase C18 column	Acetonitrile : Ammonium Acetate buffer (50:50)	235 nm	20-75 µg/ml	5.337 min	1 ml/min	UV-Visible	73
3	ETX	Inertsil ODS-4 column	0.01M sodium perchlorate monohydrate and acetonitrile (48:52 v/v)	235 nm	34.44-63.96 µg/ml	4.299 min	1.5 ml/min	UV detector	74
4	ETX	Reverse phase C18 column	Methanol: phosphate buffer (90:10 v/v)	235 nm	10-200 µg/ml	3.428 min	1ml/min	UV detector	75
5	ETX	Kromasil 100, RP-C18 Column	Acetonitrile : methanol : 10mm potassium dihydrogen phosphate (35:35:30 v/v)	234 nm	25 to 400 ng/injection	***	1 ml/min	UV/VIS detector	76
6	ETX	Phenomenex ODS 2 C18 column	Methanol : 10mM Potassium Dihydrogen Phosphate (75:25 % v/v)	287 nm	4.99–99.70 µg/ml	3.2 min	0.8 ml/min	UV detector	77
7	ETX	BDS-Hypersil C-8 column	Water : acetonitrile : methanol (50 : 25 :25 v/v/v)	284 nm	5 -50 µg/ml	4.8 min	1.25 ml/min	UV detector	78
8	ETX	ODS Hypersil C18 column	Acetonitrile: water (55:45 v/v)	269 nm	10 to 60 µg/ml	5.03 min	0.9ml/min	UV/VIS detector	79

9	ETX	Hypersil ODS C-18 column	Acetonitrile and potassium dihydrogen phosphate buffer (46:54 % v/v)	280 nm	0.5-85.0 µg/ml	3.083 min	1.2 ml/min	UV detector	80
10	ETX	Zorbax SB CN column	Disodium hydrogen orthophosphate (0.02 M) : acetonitrile (60:40)	235 nm	***	11.510 min	0.8 ml / min	***	81
11	THC and ETX	BDS Hypersil C18 column	Acetonitrile : Buffer (75 :25)	220nm	***	3.97 min and 7.46 min	1.5 ml/min	***	82
12	THC and ETX	Zorbax C-18 analytical column	Methanol and water (60:40)	283 nm	2 to 20 µg/ml and 10 to 200 µg/ml	3.523 min and 9.627 min	0.7 ml/min	UV detector	83
13	PCT and ETX	Kromasil C18 column	Buffer : Acetonitrile	220 nm	48 to 146 µg/ml and 6 to 19 µg/ml	8.34 min and 18.45 min	1.0 ml/min	UV-VIS detector	84
14	THC and ETX	BDS Hypersil C-18 column	Trifluoroacetic acid buffer and acetonitrile (75:25, v/v)	220 nm	2 to 16 ppm and 20 to 160 ppm	3.1 min and 6.6 min	1.5 ml/min	UV detector	85
15	PCT and ETX	Phenomenex Luna C18 column	Methanol : water (70:30 v/v)	235 nm	5-30 µg/ml	3.07 min and 5.72 min	1.0 ml/min	UV detector	86
16	PGBN and ETX	Thermo C18 column	Orthophosphoric acid (0.1%) : methanol (60:40 v/v)	236 nm	37.5 to 112.5 µg/ml and 30 to 90 µg/ml	2.636 min and 5.607 min	1.0 ml/min	Waters photodiode detector	87
17	THC and ETX	Hypersil BDS C18 column	Phosphate buffer(ph-3.4) and acetonitrile (35:65 v/v)	260nm	2.5-15 µg/ml and 5.0-30 µg/ml	2.83 min And 6.92min	1.0 ml/min	UV detector	88

18	PGBN and ETX	Hypersil ODS, C18 column	Methanol: acetonitrile: phosphate buffer (ph 5) (40:20:20)	215 nm	12.5–37.5 µg/ml and 150–450 µg/ml	3.523 min and 4.702 min	1.0 ml/min	UV-VIS detector	89
19	ETX and PCT	Hypersil ODS, C18 column	0.05 M sodium dihydrogen phosphate buffer : acetonitrile (35:65 v/v)	235nm	50-150% of the working standard solution concentration	1.889 min and 2.460 min	1.0 ml/min	UV-VIS detector	90
20	KPF, ETX and DIC	C18 column	50% Cetrimide and 50% acetonitrile for KPF and ETX 30% Cetrimide and 70% acetonitrile for DIC	254 nm, 234 nm, and 254 nm	0.03- 0.50 mg/ml , 0.007-0.11 mg/ml and 0.016 - 0.250 mg/ml	9.41 min, 7.34 min, and 6.66 min	1.0 ml/min	UV detector	91
21	PCT and ETX	Inertsil ODS, C8-3 column	Methanol: acetonitrile: phosphate buffer (40:20:40 v/v)	242 nm	50 to 150 µg/ml and 6-18µg/ml	3.27min, 6.12 min	1.0 ml/min	***	92
22	THC and ETX	Inertsil C18 column	Acetonitrile: ph 3 phosphate buffer (70:30% v/v)	254nm	25-125 µg/ml and 15-75 µg/ml	2.325 min and 4.296 min	1.0 ml/min	UV detector	93
23	ETX and PCT	PURITAS ™ EXIMIUS C18 analytical column	Acetonitrile and 0.1 percent acetic acid in water (70:30V/V)	235nm	20-120ppm and 20-200ppm	4.2 min and 2.1 min	1.0 ml/min	PDA detector	94
24	ETX and PCT	Phenomenex® C18 column	Acetonitrile, methanol	236 nm	8.3-41.5 µg/ml and 1-5 µg/ml	5.472 min, 7.650 min	1.0 ml/min	UV detector	95

			and water 60:15:25 (v/v/v)						
25	TOP and ETX	Eclips plus C18 column	0.035M triethylamine and acetonitrile (70:30 v/v)	290nm	5-15 µg/ml	2.826 min and 7.566 min	1.0 ml/min	PDA detector	96
26	PGBN and ETX	Ascentis C18 column	Acetonitrile and 0.01N potassium dihydrogen phosphate (50: 50)	228nm	***	2.313 min and 2.840 min	0.8 ml/min	PDA detector	97

***** Not Provided**

HPTLC method for ETX

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 10.

Table 10: Summary of HPTLC methods for the determination of ETX in a single and combined dosage form

Sr. No.	Drug	Stationary Phase	Mobile Phase	Detection	Linearity	Ref.
1	ETX	Precoated silica gel $60F_{254}$	Chloroform: methanol: toluene (4:2:4 v/v)	289 nm	100 to 600 ng/spot	98
2	ETX	Precoated silica gel $60F_{254}$	Toluene–1,4-dioxane–methanol 8.5:1.0:0.5 (v/v)	235 nm	100 to 1500 ng/spot	99
3	PCT and ETX	Precoated silica gel $60F_{254}$	Toluene: ethylacetate: methanol in the ratio of 6: 4: 1 (v/v/v)	263 nm	60-360 ng/spot 50-300 ng/spot	100
4	ETX and THC	Precoated silica gel $60F_{254}$	Ethyl acetate–methanol (8 + 2, v/v)	290 nm	50–250 and 100–500 ng/band	101

UPLC methods for ETX

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. Sanjay Shesha Shetgar1*, Ramadevi Dharmasoth2, Bandlamudi Mallikarjuna Rao3,

Basavaiah Keloth4 established 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 µm,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 a Acquity Tunable UV detector at a flow rate of 0.3 ml/minute. The linearity of the calibration curve ranged from 1–6 µg/ml of Thiocolchicoside and 15–90µg/ml of Etoricoxib and the regression coefficient (r2) was 0.999 for both Etoricoxib and Thiocolchicoside drugs.(102)

VALDECOXIB:

Bio-analytical method for VDX

Bio-analysis is a sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems. The summary of the reported bioanalytical methods is shown in Table 11.

Table 11: Bioanalytical determination of VDX

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref
1	VDX	Human plasma	HPLC	ODS C18 column	244 nm	Nimesulide	103
2	VDX	Human plasma	HPLC	ODS-AQ column	210 nm	Rofecoxib	104
3	VDX	Human plasma	HPLC	C18 column	240 nm	Celecoxib	105
4	VDX	Human plasma	HPLC	Cosmosil C18 column	239 nm	Rofecoxib	106
5	PRX and VDX	Canine plasma	HPLC	Luna C18 ODS2 analytical columns	265 nm and 375 nm	Celecoxib, Rofecoxib	B5
6	PRX and VDX	Rat plasma	UPLC-MS/MS	ACQUITY UPLC BEH C18 reversed phase column	***	Celecoxib	107
7	PRX and VDX	Beagles' plasma	UPLC-MS/MS	Acquity UPLC BEH C18 column	***	Celecoxib	108
8	PRX and VDX	Rat plasma	UPLC-MS/MS	Kinetex C18 column	***	Ketoprofen	109
9	PRX and VDX	Beagle plasma	UPLC-MS/MS	Acquity UPLC BEH C18 column	***	Celecoxib	110

10	ETX, SCA, VDX, KPF, NMS, CXB	Human plasma	HPLC	Kromasil KR 100-5C18 column	235 nm	DRF-4367	111

***** Not Provided**

UV-Visible spectroscopy method for VDX

The spectrophotometric methods have been accounted for the determination of VDX. The details of Spectrophotometry determination of basic principle, sample matrix, lambda max, solvent linearity range and the correlation coefficient are summarized in Table 12.

Table 12: Spectrophotometric methods used for determination of VDX

Sr. No.	Drug	Matrix	Solvent	Lambda Max (nm)	Linearity (µg/mL)	Correlation coefficient (R2)	Ref.
1	VDX	Pure form and Tablet	0.1N Sodium Hydroxide	243 nm	3-15 µg/mL	0.9998	112
2	VDX	Pure and pharmaceutical dosage forms	1 M sodium hydroxide	610 nm	5-25 mg/ml	0.9999	113
3	VDX and TNZ	Combined tablet dosage form	Methanol	237 nm and 289.5 nm	5-30 µg/mL And 0.5-3.0 µg/mL	0.9999 and 0.9997	114
4	VDX and TZN	Mixture	Methanol:0.1 mhcl (1:1)	243 nm and 228 nm	5-30 µg/ml and 2-20 µg/ml	***	115
5	VDX and PCT	Combined tablet dosage form	0.1 N NaOH	244 nm and 257 nm	1-6 µg/ml and 5-30 µg/ml	1.0	116

***** Not Provided**

Liquid-Chromatography-Mass Spectroscopy methods (LC-MS) for VDX:

In recent years, the combination of LC/MS has gained a lot of attention for the analysis of interest analytes in complex samples with improved performance. In brief, after a thorough examination, LC/MS interfaces are divided into two categories namely interfaces for indirect and direct input of column effluent. A mechanical mechanism is employed to transmit the column effluent to the MS vacuum at an indirect introduction interface. A classic example of an indirect introduction type of interface is the transportation system. In the case of the direct introduction system, the column effluent flows directly into the mass spectrometric vacuum system via a tube. Mainly, the most straightforward method of linking LC and MS appears to be the direct introduction.33 In this section, we have discussed the LC-MS methods for the determination of VDX in a dosage form Table 13.

Table 13. Summary of LC-MS methods for the determination of VDX in a dosage form

Sr. No	Drug	Matrix	Stationary Phase	Mobile Phase	Internal Standard	Linearity (ng/mL)	Ref.
1	VDX	Bulk drug	Agilent Zorbax SB-CN	0.01M potassium dihydrogen ortho phosphate : acetonitrile 80:20 (v/v)	***	25 to 150 µg/ml	117

HPLC method for VDX

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision, and accuracy are attainable only if wide-ranging system suitability tests are carried before the HPLC analysis. For this reason, the expense to be paid for the high specificity, precision, and accuracy is also high. The summary of the reported HPLC methods is shown in Table 14.

Table 14: Summary of HPLC methods for the determination of VDX in a single and combined dosage form

Sr. No.	Drug name	Column	Mobile phase	Lambda max(nm)	Linearity (µg/mL)	Retention time (min)	Flow rate (mL/min)	Detector
1	VDX	Synergi fusion C18 column	Water : acetonitrile (52:48, v/v)	210 nm	0.05-150 µg/ml	5.51 min	1.0 ml/min	PDA detector
2	PCT and VDX	Luna C-18 column	Methanol: phosphate buffer ph. 3.5 (60:40 v/v)	242 nm	25-150 µg/ml and 1-6 µg/ml	3.01min and 8.51 min	1.0 ml/min	***
3	TNZ and VDX	Hypersil C-18 column	Ammonium acetate buffer (0.1 M): methanol: acetonitrile 50:30:20 v/v	232 nm	1-100 µg/ml	3.2 min and 4.5 min	1 ml/min	UV detector
4	VDX	Phenomenex Luna C18 column	20mm nah2po4, methanol and Tetrahydrofuran 60:30:10 (v/v)	240 nm	***	19.436 min	1.0 ml/min	UV detector
5	VDX	Xterratm RP18 column	0.01M ammonium acetate in water and Acetonitrile 50 : 50 (v/v)	220 nm	***	6.89 min	1ml/min	UV detector
6	VDX	Phenomenex Luna C18 column	Acetonitrile : 0.5% triethylamine (50:50 v/v)	240 nm	0.1-0.5 µg/ml and 1.0-3.0 µg/ml	8.95 min and 10.34 min	1ml/min	***

7	TNZ and VDX	Hypersil BDS C-18 column	0.3% triethylamine and acetonitrile 70:30 v/v	***	***	3.15 min and 10.92 min	***	***
8	TNZ and VDX	Luna C18 column	Acetonitrile: phosphate buffer pH 3.5 (50:50 v/v)	227 nm	0.4-2.0 µg/ml and 4-20 µg/ml	4.43 min and 16.60 min	0.5 ml/min	***
9	TNZ and VDX	C18 Intersil column	Acetonitrile : 0.02M phosphate buffer (ph 3.5) (60:40 v/v)	240 nm	0-20 µg/ml And 0-100 µg/ml	2.16 min and 4.21 min	1.5 ml/min	***

***** Not Provided**

HPTLC method for VDX

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 15.

Table 15: Summary of HPTLC methods for the determination of VDX in a single and combined dosage form

Sr. No.	Drug	Stationary Phase	Mobile Phase	Detection	Linearity	Ref.
1	VDX	Precoated silica gel aluminum plates 60 GF_{254}	Toluene : acetone : ammonia (5%) 7:5:1 v/v/v	236 nm	200–1000 ng/µL	127
2	VDX and PCT	Pre coated silica gel 60 GF_{254} TLC plate	Chloroform: isopropyl alcohol: glacial acetic acid (9.5:1:0.2 v/v/v)	250 nm	0.1 to 0.5 µg/spot 2.5 to 12.5 µg/spot	128

PARECOXIB:

Bio-analytical method for PRX

Bio-analysis is a sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems. The summary of the reported bioanalytical methods is shown in Table 16.

Table 16: Bioanalytical determination of PRX

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref
1	PRX and VDX	Canine plasma	HPLC	C18 ODS2	265 nm	Celecoxib, Rofecoxib	130

				analytical column			
2	PRX	Human plasma	RP-HPLC	CLC C18 column	200 nm	Ibuprofen	131
3	PRX, VDX and OH-VDX	Mouse plasma	LC–MS/MS	Extend-C18 HPLC column	***	Piperaquine	132
4	PRX and VDX	Beagle Plasma	UPLC-MS/MS	Acquity UPLC BEH C18 column	***	Celecoxib	133
5	PRX and VDX	Rat plasma	UPLC–MS/MS	Kinetex C18 column	***	Ketoprofen	134

***** Not Provided**

ROFECOXIB:

Bio-analytical method for RFX

Bio-analysis is a sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems. The summary of the reported bioanalytical methods is shown in Table 17.

Table 17: Bioanalytical determination of RFX

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref
1	RFX	Human serum	HPLC	Novapak-C18 analytical column	254 nm	Diazepam	135
2	RFX	Bovine serum albumin microsphere	HPLC	C18 column	272 nm	***	136
3	RFX	Rat and Human Plasma	HPLC	C18 analytical column	272 nm	Ketoprofen	137
4	RFX	Bulk Drug, Tablets and Human Plasma	HPLC	Spherisorb ODSI column	244 nm	Etodolac	138
5	RFX	Human Plasma	HPLC	BDS-Hypersil C-18 analytical column	250 nm	Not mention name only structure is given	139
6	RFX and CXB	Human plasma	HPLC	Zorbax SB-CN	254 nm	4-*n*-pentyl-phenyl-acetic acid	140

				analytical column			
7	DIC, RFX, NIF, CXB	Human serum	HPLC	C18 bonded silica column	261 nm, 288 nm, 282 nm, 254 nm	***	141
8	RFX	Human plasma	HPLC-MS	Nucleosil C-8 guard column	***	Celecoxib	142

***** Not Provided**

UV-Visible spectroscopy method for RFX

The spectrophotometric methods have been accounted for the determination of RFX. The details of Spectrophotometry determination of basic principle, sample matrix, lambda max, solvent linearity range and the correlation coefficient are summarized in Table 18.

Table 18: Spectrophotometric methods used for determination of RFX

Sr. No.	Drug	Matrix	Solvent	Lambda Max (nm)	Linearity (µg/mL)	Correlation coefficient (R2)	Ref.
1	RFX and MSPC	Individual dosage form	Methanol	282 nm and 331 nm	10-50 ng/ml 2-10 ng/ml	0.9990 0.9996	143

Liquid-Chromatography-Mass Spectroscopy methods (LC-MS) for RFX:

In recent years, the combination of LC/MS has gained a lot of attention for the analysis of interest analytes in complex samples with improved performance. In brief, after a thorough examination, LC/MS interfaces are divided into two categories namely interfaces for indirect and direct input of column effluent. A mechanical mechanism is employed to transmit the column effluent to the MS vacuum at an indirect introduction interface. A classic example of an indirect introduction type of interface is the transportation system. In the case of the direct introduction system, the column effluent flows directly into the mass spectrometric vacuum system via a tube. Mainly, the most straightforward method of linking LC and MS appears to be the direct introduction.33 In this section, we have discussed the LC-MS methods for the determination of RFX in a dosage form Table 19.

Table 19. Summary of LC-MS methods for the determination of RFX in a dosage form

Sr. No	Drug	Matrix	Stationary Phase	Mobile Phase	Internal Standard	Linearity (µg/mL)	Ref.
1	RFX	***	Shimpak ods C18 column	Acetonitrile/0.05% phosphoric acid (35:65)	***	2–36 µg/ml	144
2	RFX	Bulk and pharmaceutical dosage forms	Symmetry *C*18 analytical Column	Acetonitrile–water (50:50, v/v)	Chlorophenyl methyl sulphone	125 to 500 µg/ml	145
3	TZN and RFX	Tablets	Spherisorb ODS column	Triethylamine : acetonitrile 55:45% (v/v)	Nimesulide	0.1–0.5 µg/ml 1.2–6.0 µg/ml	146

***** Not Provided**

HPLC method for RFX

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision, and accuracy are attainable only if wide-ranging system suitability tests are carried before the HPLC analysis. For this reason, the expense to be paid for the high specificity, precision, and accuracy is also high. The summary of the reported HPLC methods is shown in Table 20.

Table 20: Summary of HPLC methods for the determination of RFX in a single and combined dosage form

Sr. No	Drug name	Column	Mobile phase	Lambda max (nm)	Linearity (µg/mL)	Retentio Time (min)	Flow rate (mL/min)	Detector	Ref.
1	RFX	C18 analytical column	Water: Acetonitrile (55:45 v/v)	366 nm	10-60 µg/ml	7.5 to 8 min	1 ml/min	UV-Vis spectroph otometer	147
2	RFX	Apollo C18 analytical column	Methanol and water (45:55 % v/v)	260 nm	24-120 mg/ml	2.379 ±0.02 min	0.8 ml/min	UV spectroph otometer	148
3	RFX	ODS C-18 column	Methanol : Water (50:50)	230 nm	2-40 µg/ml	7.79–8.00 min	1 ml/min	UV-Vis Detector	149
4	RFX and TNZ	Luna C-18 column	Methanol : Phosphate Buffer (55:45 v/v)	240 nm	7.5-17.5 µg/ml and 0.6-1.4 µg/ml	4.53 min and 5.92 min	1 ml/min	UV-Vis Detector	150
5	RFX and TNZ	Wakosil C-18 column	Acetonitrile : phosphate buffer (50:50 v/v)	240 nm	50-200 µg/ml and 10-80 µg/ml	4.9 min and 12.2 min	0.5 ml/min	UV-Vis Detector	151
6	PCT and RFX	Hypersil C-18 column	20mM phosphate buffer : Acetonitrile (55:45 v/v)	254 nm	7-13 µg/ml and 0.35-0.65 µg/ml	2.61 min and 10.49 min	1 ml/min	UV-Vis Detector	152
7	TNZ and RFX	Kromasil C-18 column	Phosphate buffer ph. 5.5 and methanol (45:55 v/v)	235 nm	10–200_g/ml and 100–2000_g/ml	3.199 min and 7.109 min	1 ml/min	UV detector	153

HPTLC method for RFX

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 21.

Table 21: Summary of HPTLC methods for the determination of RFX in a single and combined dosage form

Sr. No.	Drug	Stationary Phase	Mobile Phase	Detection	Linearity	Ref.
1	RFX and TZN	Precoated with silica gel 60F254 on aluminum sheets	Toluene: ethyl acetate: methanol: triethyl amine 6:3:0.5:0.1 (v/v/v/v)	235 nm	3.75 to 11.25 µg/spot 0.30 to 0.90 µg/spot	154
2	TZN and RFX	Merck HPTLC aluminum sheets of silica gel 60 F254	Toluene : methanol : acetone (7.5:2.5:1.0, v/v/v)	311 nm	10–100 ng/spot 100–1500 ng/spot	155
3	TZN and RFX	Precoated silica Gel G 60 F254 TLC plate	N- butyl acetate: formic acid: chloroform (6:4:2 v/v/v)	315 nm	2-10 mg/spot 16-80 mg/spot	156

LUMIRACOXIB:

Bio-analytical method for LMX

Bio-analysis is a sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems. The summary of the reported bioanalytical methods is shown in Table 22.

Table 22: Bioanalytical determination of LMX

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref
1	LMX	Human Plasma	HPLC	Nucleosil C8 reversed-phase column	270 nm	Niflumic acid	157
2	LMX	Rat plasma	UHPLC–MS/MS	ACQUITY BEH C18 column	***	Diclofenac	158

***** Not Provided**

UV-Visible spectroscopy method for LMX

The spectrophotometric methods have been accounted for the determination of LMX. The developed UV spectroscopy method is validated and therefore could be further used for quantitative analysis of lumiracoxib. Moreira, T.S., Pierre, M.B.R. , Fraga, C.A.M. , Sousa, VP established development and validation of HPLC and UV spectrophotometric methods for the determination of lumiracoxib in tablets. The UV method was performed with ethanol as a solvent with the 2-30 □g/ml linearity. The UV method based on absorbance at 275 nm and the correlation coefficient (r2) is 0.999.(159)

Liquid-Chromatography-Mass Spectroscopy methods (LC-MS) for LMX:

In recent years, the combination of LC/MS has gained a lot of attention for the analysis of interest analytes in complex samples with improved performance. In brief, after a thorough examination, LC/MS interfaces are divided into two categories namely interfaces for indirect and direct input of column effluent. A mechanical mechanism is employed to transmit the column effluent to the MS vacuum at an indirect introduction interface. A classic example of an indirect introduction type of interface is the transportation system. In the case of the direct introduction system, the column effluent flows directly into the mass spectrometric vacuum system via a tube. Mainly, the most straightforward method of linking LC and MS appears to be the direct introduction. In this section, we have discussed the LC-MS methods for the determination of LMX in a dosage form Table 23.

Table 23. Summary of LC-MS methods for the determination of LMX in a dosage form

Sr. No	Drug	Matrix	Stationary Phase	Mobile Phase	Internal Standard	Linearity (µg/mL)	Ref.
1	LMX	Pharmaceutical formulations	Synergi Fusion C18 column	Phosphoric acid – acetonitrile (40:60 v/v)	Nimesulide	5–150 µg/ml	160
2	LMX	Pharmaceutical formulations	Synergi fusion C18 column	phosphoric acid : acetonitrile (40:60 v/v)	***	10–100 µg/mL	161

***** Not Provided**

HPLC method for LMX

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision, and accuracy are attainable only if wide-ranging system suitability tests are carried before the HPLC analysis. For this reason, the expense to be paid for the high specificity, precision, and accuracy is also high. The developed HPLC method is validated and therefore could be further used for quantitative analysis of lumiracoxib. Moreira, T.S., Pierre, M.B.R. , Fraga, C.A.M. , Sousa, VP established development and validation of HPLC and UV spectrophotometric methods for the determination of lumiracoxib in tablets. The HPLC method was performed on the chromatographic column was packed with propylsulfonic acid bonded with silica gel by using 10 mM phosphate buffer (pH 7.4) - water – acetonitrile (10 : 40 : 50, v/v/v) as a mobile phase at flow rate 1.0 ml/min. The linearity of the drug is 2-30 □g/ml and the detection of drug at 278 nm by using UV detector.(159)

CONCLUSION

The present review article provides comprehensive data of various analytical and bioanalytical methods developed for Selective COX-2 Inhibitors alone and in combinations. For analysis purpose, different analytical methods have been reported that includes HPLC, HPTLC, UPLC, UV spectroscopy, etc. The method along with their details concerning the mobile phase, stationary phase, retention time, etc., have been summarized in tabular form that will more helpful for the researchers. In the future, enlisted data can be used for the development of analytical methods bio-analysis of Selective COX-2 inhibitors in pharmaceutical and biological formulations. Finally, it presents an opportunity for greater information on what has already been done and what new methods and changes can be developed to get a better estimation of Selective COX-2 inhibitors.

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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. TLC - Thin layer chromatography
7. RP - Reverse phase
8. nm - Nanometer
9. µg/mL - Micro gram per Milliliter
10. PDA - Photo diode array
11. CXB – Celecoxib
12. ETX – Etoricoxib
13. VDX – Valdecoxib
14. PRX – Parecoxib
15. RFX – Rofecoxib
16. LMX – Lamiracoxib
17. REP – Repaglinide
18. DTX – Docetaxel
19. IBU – Ibuprofen
20. DIC – Diclofenac
21. NIF – Niflumic Acid
22. OH-CXB – Hydroxycelecoxib
23. COOH-CXB – Carboxycelecoxib
24. SCA – Salicylic acid
25. KPF – Ketoprofen
26. NMS – Nimesulide
27. DEZ – Dezocine
28. DEX – Dexmedetomidine
29. AMD – Amlodipine
30. CUR – Curcumin
31. ATV-Ca – Atorvastatin calcium
32. RMP – Ramipril
33. PCT – Paracetamol
34. RLZ – Riluzole
35. THC – Thiocholchicoside
36. PGBN – Pregabalin
37. TOP – Tolperisone
38. DRT – Drotraverine
39. TNZ – Tizanidine
40. OH-VDX – Hydroxylated valdecoxib
41. MSPC – Mosapride Citrate

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