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COST EFFECTIVE ISOCRATIC RP-HPLC METHOD FOR SIMULTANEOUS DETERMINATION OF ETORICOXIB AND PARACETAMOL IN PURE AND IN TABLET FORMULATION

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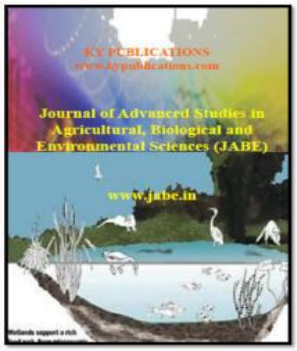

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ABSTRACT

The present paper describes the development and validation of a cost effective isocratic RP-HPLC method for simultaneous determination of etoricoxib and Paracetamol in pure and in tablet formulation as per ICH Norms. The chromatographic separations of the two drugs were analyzed on a Hypersil BDS C18 (250 x 4.6 mm i.d., 5µm particle size) column with mobile phase composed of 0.05 M sodium dihydrogen phosphate buffer (1% TEA, edjusted pH 3.2 with o-phosphoric acid): acetonitrile (35:65 v/v) at an injection volume of 20µl, flow rate of 1.0mL min^{-1} and UV detection was carried out at 235nm. Separation of both analytes was completed within 3 min. Calibration curves were linear with coefficient correlation between 0.9999 over a concentration range of 1000 to 3000µg/mL of etoricoxib and 1200 to 3600µg/mL for Paracetamol. The proposed RP-HPLC method was validated by determining its accuracy, precision and system suitability.

KEYWORDS: Etoricoxib, Paractamol and RP-HPLC.

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INTRODUCTION

Etoricoxib[1-3] is 5-chloro- 2-(6-methylpyridin-3-yl)-3-(4-methylsulfonylphenyl) pyridine belongs to the group of nonsteroidal anti-inflammatory drugs (NSAIDs) known as selective Cox-2 inhibitor. This drug is used for treatment in rheumatoid arthritis, osteoarthritis and pain. Paracetamol[4-7] is chemically 4-hydroxyacetanilide, is a centrally and peripherally acting non-opioid analgesic and antipyretic..

Different formulations of etoricoxib and Paracetamol are available in local pharmacy for clinical practice. In the present investigation tablet formulation (Tro P) containing 500 mg of Paracetamol and 60mg of Etoricoxib has been used in the assay of etoricoxib and Paracetamol with the developed RP-HPLC method.

A survey of literature revealed that few HPLC methods are reported for the simultaneous determination of Etoricoxib and Paracetamol in dosage forms [8-13]. However, the reported methods for simultaneous determination of Paracetamol and etoricoxib in combine dosage form suffered from draw backs in terms of long retention times and cost effectiveness and this made the author to develop and validate a new RP-HPLC method for the assay of etoricoxib and Paracetamol in dosage forms. The present work describes the development and validation of a simple, precise and accurate isocratic RP-HPLC method for simultaneous estimation of etoricoxib and Paracetamol in pure and in combine dosage forms.

EXPERIMENTAL

INSTRUMENTATION: Chromatography was performed on Shimadzu (Shimadzu Corporation, Kyoto, Japan) chromatographic system equipped with Shimadzu LC-20AT pump and Shimadzu SPD-20AV absorbance

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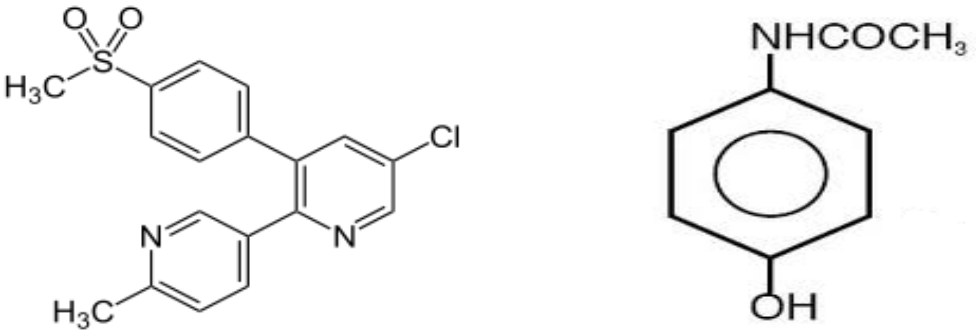
detector. Samples were injected through a Rheodyne 7725 injector valve with fixed loop at 20 µl. Data acquisition and integration was

performed using Empower2 software. HPLC separation of both the analytes was performed at room temperature on a Hypersil BDS C18 (250 x 4.6 mm i.d., 5µm particle size) column with mobile phase composed of 0.05 M sodium dihydrogen phosphate buffer (1% TEA, adjusted pH 3.2 with o-phosphoric acid): acetonitrile (35:65 v/v) at an injection volume of 20µl, flow rate of 1.0mL.min-1 and UV detection was carried out at 235nm.. Shimazdu electronic weighing balance, model BL 220 H was used for weighing the samples. Elico pH meter (Hyderabad, India) LI 120 model was used for pH measurements.



ETORICOXIB **PARACETAMOL**

Figure.1.MOLECULAR STRUCTURE OF ETORICOXIB AND PARACETAMOL

CHEMICALS AND REAGENTS: Milli-Q water, Acetonitrile (HPLC Grade), Orthophosphoric acid (GR Grade), sodium dihydrogen phosphate monohydrate (GR Grade),Triethylamine(GR Grade) was obtained from Qualigens Ltd., Mumbai. Pure Paracetamol in dosage forms was provided as gift sample by Micro Lab Pvt. Ltd. Bangalore and pure etoricoxib and was provided as gift sample by Kurekem Rishab Healthcare Pvt Ltd. Combined dosage form Tro-P (60 mg of Etoricoxib and and 500 mg of Paracetamol), was procured from local pharmacy. All dilutions were performed in standard class-A, volumetric glassware.

MOBILE PHASE PREPARATION: 350 ml of the phosphate buffer was mixed with 650ml of acetonitrile. The solution was degassed in an ultrasonic water bath for 5 minutes and filtered through 0.45µm filter under vacuum.

DILUENT PREPARATION: The same mobile phase was used as diluent in the present assay.

PREPARATION OF STOCK & WORKING STANDARD SOLUTIONS: The stock solution (1.0mg/ml) was prepared by weighing accurately 100mg of pure etoricoxib and PARACETAMOL and transferred into a clean and dry 100 ml volumetric flask. About 70 ml of diluent was added and sonicated. The volume was made unto the mark with the same diluent. From the above prepared stock solution pipette out suitable aliquots and transferred into a clean and dry 10ml volumetric flask, the diluent was added up to the mark to get final concentration of 1000-3000µg/ml of pure etoricoxib and 1200-3600µg/ml of PARACETAMOL respectively.

PREPARATION OF SAMPLE SOLUTION: Twenty tablets (TRO-P 60/500mg,strength 60mg of Etoricoxib and and 500 mg of Paracetamol, Kurekem Rishab Healthcare Pvt Ltd) procured from local pharmacy were weighed, and then powdered. A sample of the powdered tablets, equivalent to 100mg of the active ingredient, was mixed with 30 ml of diluent in 100 ml volumetric flask. The mixture was allowed to stand for 1 hr with intermittent sonication to ensure complete solubility of the drug, and then filtered through a 0.45µm membrane filter, followed by adding the same solvent upto 100ml to obtain a stock solution of 1000µg/ml. From above prepared stock solution pipette out aliquots of the above solution and transferred into a clean and different dry 10ml volumetric flasks, the diluent was added up to the mark 10ml to get final concentration of 1000-3000µg/ml of etoricoxib and 1200-3600µg/ml of PARACETAMOL respectively. 20µL volumes of these standard and sample solutions were injected five times and the peak areas were recorded. The mean and percentage relative standard deviation were calculated from the peak areas.

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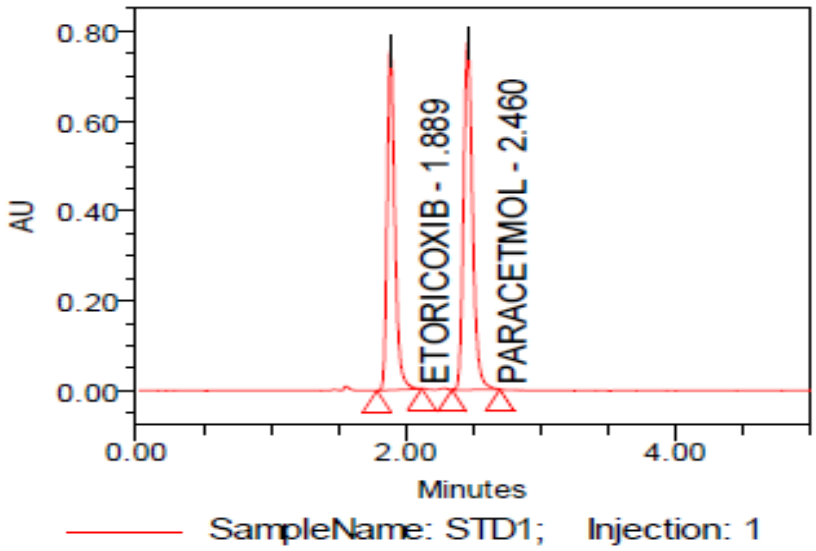

Figure. 2: TYPICAL HPLC CHROMATOGRAM SHOWING THE PEAKS OF ETORICOXIB AND PARACETAMOL

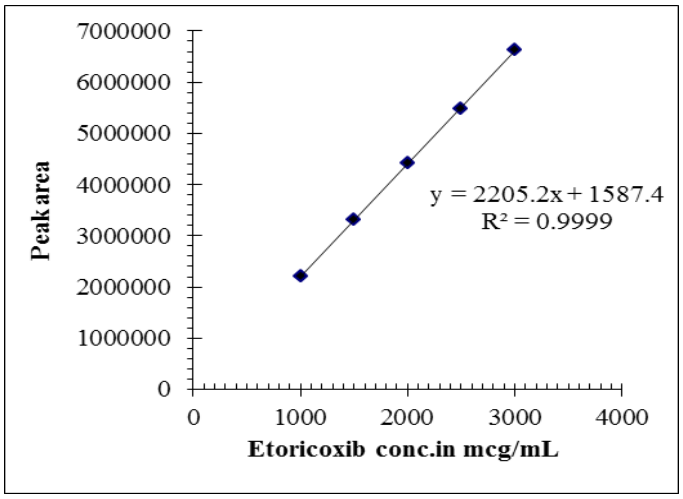

Figure.3.a. LINEARITY CURVE FOR ETORICOXIB

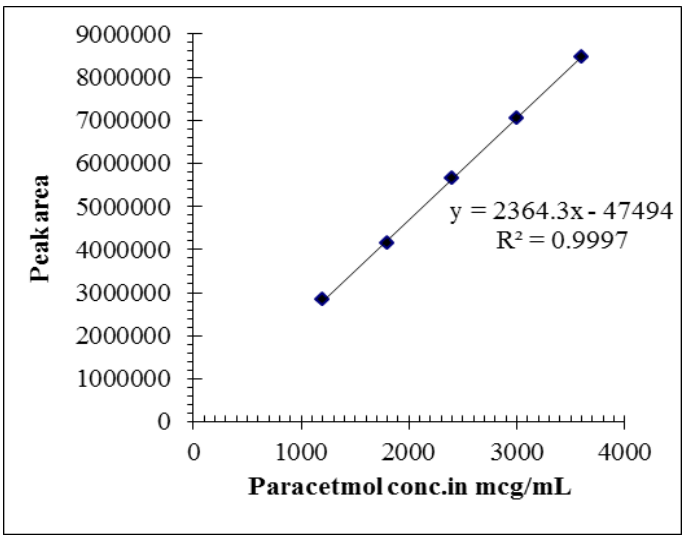

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Figure.3.b.LINEARITY CURVE FOR PARACETAMOL

RESULTS AND DISCUSSIONS

A.METHOD DEVELOPMENT AND OPTIMIZATION: The analytical conditions for the proposed method were selected, basing on the chemical nature of etoricoxib and Paracetamol.

Initial spectroscopic analysis of compounds showed that etoricoxib and Paracetamol showed a maximum UV absorbance (λmax) at 233.2nm, 238nm respectively. Therefore, the chromatographic detection was performed at 235nm using a photo diode array detector as both the compounds showed good response at this wave length. The development trials of each component were carried, by keeping them in various extreme conditions.

In order to effect the simultaneous elution of etoricoxib and Paracetamol peaks under isocratic conditions, the mixtures of acetonitrile and phosphate buffer in different combinations at various flow rates were assayed. The mixture of acetonitrile: 0.05 M phosphate buffer (1% TEA, pH 3.2 adjusted with ophosphoric acid) (65:35 v/v) at 1.0 ml min^{-1} flow rate, proved to be better than the other mixtures and flow rates for the separation, since the chromatographic peaks were better defined, resolved and free from tailing. The chromatogram for simultaneous estimation of etoricoxib and Paracetamol standard by using the aforementioned mobile phase from 20µL of the proposed method is represented in Fig.2. As shown in Figure.2, the retention times were 1.189min. for etoricoxib, 2.460min.for Paracetamol and the system suitability results of the proposed RP-HPLC method are presented in Table.2.

B.METHOD VALIDATION: The analytical characteristics used in this method validation were accuracy, precision, linearity, limit of detection, limit of quantification and robustness.

1.SYSTEM SUITABILITY: A system suitability test of the chromatographic system was performed before each validation run. Five replicate injections of standard preparation were injected and asymmetry, theoretical plate and % RSD of peak area were determined for same. Acceptance criteria for system suitability, asymmetry not more than 2.0, theoretical plate not less than 2000 and % RSD of peak area not more then 2.0, were full fill during each validation parameter as shown in Table.2.

2.LINEARITY OF DETECTOR RESPONSE: The linearity of the present proposed RP-HPLC method was determined by preparing a standard stock solution from which working solutions were prepared by diluting appropriately to yield solutions containing 50, 75, 100, 125 and 150% of the working standard solution concentration. 10µL of each of these solutions was injected into the column along with the above said mobile phase and then analyzed in triplicate and the peak areas obtained for each analyte compound plotted against concentration Fig.2.a&b. The data so obtained from the linearity determination experiments was subjected to linear regression analysis and the equations were $y = 2205.2 x + 1587.4$, $R^2 = 0.9999$ for etoricoxib and $y = 2364.3 x + 47494$, $R^2 = 0.9997$ for PARACETAMOL respectively. Correlation coefficient (R^2) values of both the studied drugs were greater than 0.9999 indicating a strong correlation exists between the concentrations of the analytes and the peak areas and therefore the proposed RP-HPLC method could be applied in the assay of the two analytes in routine quality control labs. The summary of the linearity analysis results obtained is shown in Table.3.a&b.

3. SENSITIVITY: a)Limit of detection: The limit of detection (LOD) is the lowest amount of analyte in a sample that can be detected but not necessarily quantified using an analytical technique under specified experimental conditions. The LOD was established by signal over noise (S/N) method where 6 injection of blank (mobile phase) were injected and the mean peak height was determined and the results obtained are summarized in Table.3.a&b respectively.

b)Limit of quantitation: The limit of quantitation (LOQ) is the lowest amount of analyte in a sample that can be determined with acceptable precision under specified experimental conditions. The degree of precision considered to be acceptable for purposes of LOQ determination from peak areas of six injections (n = 6) is CV

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(coefficient of variance) less than 20% and at a signal to noise ratio of 10:1. The results of LOQ obtained for are summarized in Table.3.a&b.

4. PRECISION: Reproducibility is assessed by means of inter-laboratory trials but this was not done during the course of this study. The inter-day precision of the developed RP-HPLC method was determined by running six replicate injections of a freshly prepared standard solution after every three day interval. Fresh mobile phase was prepared for each day of analysis. The component peak areas obtained were calculated to determine the inter-day precision of the method and the results obtained are summarized in Table.4. The coefficient of variation in both cases was below 2% indicating that the method was precise.

5. ACCURACY: The accuracy for the developed method was determined by spiking the finished commercial products with working standards of compounds under study. The difference between spiked sample result and the unspiked sample resulted was calculated as percentage of the known added spike concentration. The standards were added to the samples at 3 concentrations 50, 100 and 150% of the assay concentrations and injected in triplicate and the chromatograms were recorded and the % recovery results were reported in Table.5.a&b.

6. ROBUSTNESS: Robustness of the present RP-HPLC method was determined from the degree of variation observed in peak areas and retention times from the same working standard solution analyzed while adjusting each of the liquid chromatographic factors indicated (that include the variations in column temperature and mobile phase composition). Six replicate injections of the same working standard solution were run after having adjusted a single chromatographic parameter and coefficient of variation of peak areas of component peaks calculated. The degree of variation observed was then used to infer the method's robustness.

The change in flow rate and temperature unaffected the elution of etoricoxib and Paracetamol. Changing each of the two chromatographic factors had no effect on the peak areas and the coefficient of variance in all cases was below 2.0% (Table.6). The resolution of all the compounds remained unaffected by variation of these factors.

7. DETERMINATION OF TADALAFIL IN TABLETS. The validated RP-HPLC method was applied to the determination of etoricoxib and PARACETAMOL in tablets. 20µl of sample solution of etoricoxib and PARACETAMOL was injected into the injector of liquid chromatograph. The retention time was found to be 1.912 min. for etoricoxib and 2.473min. for Paracetamol. The amount of etoricoxib and Paracetamol present per tablet was calculated by comparing the peak area of the sample solution with that of the standard solution. The data are presented in Table 7.

TABLE: 1:OPTIMIZED CHROMATOGRAPHIC CONDITIONS

Parameters	RP- HPLC
Elution	Isocratic
Mobile phase	KH_2PO_4 buffer (pH 4.0) and Acetonitrile (35:65v/v)
Column	Hypersil,$BDSC_{18}$(250 x 4.6 mm) column
Flow rate	1.0 $mL.min^{-1}$
Detection	UV at 235nm
Injection volume	20µL
Temperature	Ambient
Retention time	1.889 min. for etoricoxib and 2.460 min. for PARACETAMOL
Run time	3 minutes

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TABLE:.2:SYSTEM SUITABILITY PARAMETERS FOR ETORICOXIB AND PARACETAMOL BY THE PROPOSED METHOD

NAME OF THE COMPOUND	RETENTION TIME	THEORETICAL PLATES	TAILING FACTOR	USP RESOLUTION
ETORICOXIB	1.889	4671	1.14	-
PARACETAMOL	2.460	3245	1.74	4.14

TABLE: 3.a: LINEARITY STUDIES FOR ETORICOXIB BY THE PROPOSED METHOD

LINEARITY STUDY FOR ETORICOXIB		
% LEVEL (APPROX.)	**CONC. µg/mL**	**AREA**
50	1000	2204508
75	1500.00	3315112
100	2000.00	4418619
125	2500	5492653
150	3000	6628635
Slope		2205.16
Intercept		1587.4
RSQ(r^2)		0.9999
LOD (µg/mL)		0.0075
LOQ (µg/mL)		0.025

TABLE: 3.b:LINEARITY STUDIES FOR PARACETAMOL BY THE PROPOSED METHOD

LINEARITY STUDY FOR PARACETAMOL		
% LEVEL (APPROX.)	**CONC. µg/mL**	**AREA**
50	1200	2829953
75	1800	4239236
100	2400	5649443
125	3000	7056630
150	3600.00	8469585
Slope		2364.28
Intercept		-47494
RSQ(r^2)		0.9996
LOD (µg/mL)		0.0184
LOQ (µg/mL)		0.0618

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TABLE:.4::METHOD PRECISION (INTER AND INTRADAY) STUDIES FOR ETORICOXIB AND PARACETAMOL BY THE PROPOSED METHOD

METHOD PRECISION BY PROPOSED METHOD		
FOR ETORICOXIB METHOD PRECISION (INTER & INTRA DAY)		**FOR PARACETAMOL METHOD PRECISION (INTER & INTRA DAY)**
Set-1	4416852	5643562
Set-2	4414992	5644336
Set-3	4411891	5642624
Set-4	4416117	5647978
Set-5	4415773	5644366
Set-6	4418450	5646346
Over All Avg.	4415679	5644869
Over All Std Dev.	2194.23	1956.159
Over All %RSD	0.049	0.0346

TABLE:5(a):RECOVERY STUDIES FOR ETORICOXIB BY THE PROPOSED METHOD

ETORICOXIB						
Spiked Level	**Sample Weight**	**Sample Area**	**µg/ml added**	**µg/ml found**	**% Recovery**	**% Mean**
50%	674.85	2203569	991.000	988.25	99.72	
50%	674.85	2206780	991.000	989.69	99.86	99.79 [%RSD 0.0566]
50%	674.85	2203927	991.000	988.41	99.73	
50%	674.85	2202229	991.000	987.65	99.82	
50%	674.85	2205956	991.000	989.32	99.83	
50%	674.85	2205014	991.000	988.90	99.78	
100%	1349.70	4415764	1982.000	1980.38	99.91	99.89 [%RSD 0.015]
100%	1349.70	4414427	1982.000	1979.78	99.88	
100%	1349.70	4415226	1982.000	1980.13	99.90	
150%	2024.60	6624519	2973.073	2970.95	99.92	
150%	2024.60	6624623	2973.073	2971.00	99.93	
150%	2024.60	6621244	2973.073	2969.49	99.88	99.91 [%RSD 0.028]
150%	2024.60	6628448	2973.073	2972.72	99.96	
150%	2024.60	6623817	2973.073	2970.64	99.92	
150%	2024.60	6622003	2973.073	2969.83	99.89	

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TABLE:5(b): RECOVERY STUDIES FOR PARACETAMOL BY THE PROPOSED METHOD

PARACETAMOL						
Spiked Level	Sample Weight	Sample Area	µg/ml added	µg/ml found	% Recovery	% Mean
50%	424.33	2829909	1196.400	1200.57	100	
50%	424.33	2825406	1196.400	1198.66	100	
50%	424.33	2826615	1196.400	1199.17	100	100
50%	424.33	2826905	1196.400	1199.29	100	[%RSD 1.00]
50%	424.33	2825731	1196.400	1198.79	100	
50%	424.33	2826388	1196.400	1199.07	100	
100%	848.65	5648536	2392.800	2396.35	100	
100%	848.65	5649510	2392.800	2396.76	100	100
100%	848.65	5648558	2392.800	2396.36	100	[%RSD 1.00]
150%	1273.00	8468437	3589.289	3592.67	100	
150%	1273.00	8465703	3589.289	3591.51	100	
150%	1273.00	8469250	3589.289	3593.01	100	100
150%	1273.00	8465826	3589.289	3591.56	100	[%RSD 1.00]
150%	1273.00	8466447	3589.289	3591.82	100	
150%	1273.00	8466099	3589.289	3591.67	100	

TABLE.6.: RECOVERY STUDIES OF THE PROPOSED RP-HPLC METHOD

ROBUST CONDITIONS		**ETORICOXIB**		**PARACETAMOL**	
		Rt	**PEAK AREA**	**Rt**	**PEAK AREA**
FLOW RATE	**0.8 ml/min**	2.79	4315764	2.01	28123678
	1.2 ml/min	2.56	4556427	2.56	29707905
TEMP	**40°C**	2.80	4361564	1.94	30653678
	45°C	2.86	4567237	2.12	29543205

TABLE:7:ANALYSIS OF MARKETED TABLETS OF ETORICOXIB AND PARACETAMOL[TRO-P] BY THE PROPOSED METHOD

DRUG	**LABALCLAIM**	**QUANTITYFOUND***	**%ASSAY**
ETORICOXIB	**60mg**	**59.97**	**99.95**
PARACETAMOL	**500mg**	**499.95**	**99.99**

*Average of six determinations

CONCLUSIONS

A fast simple, reliable, precise and robust isocratic reverse phase HPLC method with UV detection was developed for the simultaneous determination of etoricoxib and PARACETAMOL. The optimized conditions for the separation of etoricoxib and PARACETAMOL were: Hypersil,BDS C18 (250 mm × 4.6 mm i.d. 5 µm) column, mobile phase: KH2PO4 buffer(pH 3.2) and acetonitrile (35:65% v/v);ambient temperature maintained; Flow rate 1.0ml/min: Detection at 235nm and injection of 20µl.

The method was validated for precision, specificity, accuracy and linearity. The precision of the method was shown through adequate repeatability or intraday precision (CV ≤ 2) and intraday precision (CV ≤ 2). The run time was very short (less than 3mins) which can allow rapid quantification of many samples in routine and quality control analysis of tablets. The method also demonstrated adequate linearity over the rage of 50-150%. The % recoveries of each added working standard for all compounds were within the specified guidelines (ICH) of 100% which showed that the method was accurate. The developed RP-HPLC method also showed adequate robustness to small variations in Flow rate, column temperature representing the proposed RP-HPLC method a good procedure for the assay of etoricoxib and PARACETAMOL in pure and dosage forms as it is simple, versatile reference method and could be also satisfactory for biological fluids due to its high separation power.

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