RP-HPLC Method Developed for the Estimation of Etodolac and Thiocolchicoside in Bulk and Combined Dosage Forms

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ABSTRACT

A new, simple, specific, sensitive, rapid, accurate and precise RP-HPLC method was developed for the estimation of Etodolac (ETO) and Thiocolchicoside (THIO) in bulk and combined pharmaceutical dosage forms. Etodolac (ETO) and Thiocolchicoside (THIO) was chromatographed on a Symmetry ODS C18 (4.6mm×250mm, 5µm) Column in a mobile phase consisting of Acetonitrile: Methanol: Acetate Buffer (25:20:55% v/v). The mobile phase was pumped at a flow rate of 1.0 ml/min with detection at 238 nm. The detector response was linear in the concentration of 200-600µg/ml 20-60µg/ml for Etodolac and Thiocolchicoside respectively. The intra and inter day variation was found to be less than 2%. The mean recovery of the drug from the solution was 99.98%. The developed method was validated for sensitivity, accuracy, precision, ruggedness and robustness. The % RSD results for precision and intermediate precision found less than 2.0%. The LOD and LOQ were found to be 0.86 and 1.18 µg/ml for Etodolac and 2.4 and 3.54µg/ml for Thiocolchicoside respectively. The proposed method is simple, fast, accurate, precise and reproducible hence; it can be applied for routine quality control analysis of Etodolac (ETO) and Thiocolchicoside (THIO) in bulk and combined pharmaceutical formulations.

KEYWORDS: Accuracy, Etodolac, Precision, RP-HPLC, Thiocolchicoside and Validation

INRODUCTION

Chromatography is a laboratory technique for the separation of a mixture. The mixture is dissolved in a fluid called the *mobile phase,* which carries it through a structure holding another material called the *stationary phase.* There are following variants of HPLC, depending upon the phase system (stationary) in the process: The normal Phase HPLC method separates analytes on the basis of polarity [1]. NP-HPLC uses polar stationary phase and non-polar mobile phase. Therefore, the stationary phase is usually silica and typical mobile phases are hexane, methylene chloride, chloroform, diethyl ether, and mixtures of these. Polar samples are thus retained on the polar surface of the column packing longer than less polar materials. In the Reverse Phase HPLC, the stationary phase is non polar (hydrophobic) in nature, while the mobile phase is a polar liquid, such as mixtures of water and methanol or acetonitrile [2]. It works on the principle of hydrophobic interactions hence the more non polar the material is, the longer it will be retained. Etodolac is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. Used for acute and long-term management of signs and symptoms of osteoarthritis and rheumatoid arthritis, as well as for the management of pain. It is a muscle relaxant with anti-inflammatory and analgesic effects. Thiocolchicoside is a skeletal muscle-relaxant drug used in the treatment of orthopedic, traumatic and rheumatologic disorders. It is indicated as an adjuvant drug in the treatment of painful muscle contractures and is indicated in acute spinal pathology, for adults and adolescents 16 years of age and older 15 [3].

The main aim of the research work was to develop and validate the reverse phase-high performance liquid chromatography method for the simultaneous estimation of Etodolac and Thiocolchicoside in bulk and combined pharmaceutical tablet dosage form.

The objective was to develop new simple, sensitive, accurate and economical analytical method for the simultaneous estimation of Etodolac (ETO) and Thiocolchicoside (THIO). To validate the proposed method in accordance with USP and ICH guidelines for the intended analytical application i.e., to apply the proposed method for analysis of the Etodolac (ETO) and Thiocolchicoside (THIO) in dosage form.

MATERIALS AND METHODS

Etodolac and Thiocolchicoside were obtained as a gift sample from lupin Ltd., Acetonitrile served as solvent mixture was also obtained from CDH, New Delhi. All other chemicals/reagents were of analytical grade and were used without further purification.

Preparation of standard solution:
Accurately weigh and transfer 10 mg of Etodolac and Thiocolchicoside working standard into a 10ml of clean dry volumetric flasks add about 7ml of Methanol and sonicate to dissolve and removal of air completely and make volume up to the mark with the same Methanol.

Further pipette 4ml of the above Etodolac and 0.4ml of Thiocolchicoside stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol [4].

Method of validation: The proposed method was validated for various parameters such as linearity and range, accuracy, precision, robustness, ruggedness, sensitivity and specificity according to ICH Q2 (R1) guideline and USP guidelines [5].

Method of Linearity and range: The linearity of an analytical procedure is its ability (within a given range) to obtain test result which are directly proportional to the concentration of an analyte in the sample. The range of an analytical procedure is the interval between the upper and lower concentration of an analyte in the sample for which it has been demonstrated that the analytical procedure has a suiTablelevel of precision, accuracy and linearity. The linearity of the analytical method was demonstrated over the concentration range investigated by triplicate analysis (n = 3) at a concentration range of 2-20 µg/ml. The absorbance obtained at respective concentration was recorded, and the graph is plotted as concentration (µg/ml) versus absorbance. The linear regression equation and the coefficient correlation were obtained from the UV probe software [6].

Method of Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. The accuracy of proposed method was determined on the basis of recovery study. Recovery study was carried out by spiking standard working solution to sample solution (formulation) at three different levels 50%, 100% and 150%. The percentage recovery was calculated as mean ± standard deviation [7].

Method of Precision: The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the homogeneous sample under the prescribed conditions. The precision of the method was demonstrated by intra-day and inter-day variation studies. In the intra-day precision study, three different solutions of same concentration were prepared and analysed in the same day (morning, noon and evening), whereas in the inter-day precision study, the solutions of same concentration were prepared and analysed, for three consecutive days, and the absorbance were recorded. All study was performed in triplicates. The result was indicated by calculating percentage RSD [8].

Method of Robustness: The robustness of an analytical procedure is a measure of its capacity remains unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage [9].

Method of Ruggedness: The ruggedness is a degree of reproducibility of test result under verification of condition like a different analyst, different instruments and different days [10].

Assay Procedure
Column is equilibrated for 30 min with mobile phase. 20 µl of diluent as blank was injected into the system and recorded the chromatogram for a run time of 30 min. 20 µl of standard preparation-1 was injected into the system and recorded the chromatogram for a run time of 30 min. 20 µl of standard preparation-2 was injected into the system and recorded the chromatogram for a run time of 30 min. Test is valid only when the match factor is in between 0.98 to 1.02. 20 µl of standard preparation-2 into the system was separately injected for four times and recorded each chromatogram for a run time of 30 min. Test is valid only when the five standard preparation-2 injections pass the system suitability [11].

RESULTS AND DISCUSSIONS

Table1: Results of System suitability data of etodolac

Sl. No.	Name	Rt	Peak Area	Height	USP plate Count	USP Tailing
1	Etodolac	2.247	76859	26321	7826	1.47
2	Etodolac	2.246	76958	26852	7894	1.48
3	Etodolac	2.248	77253	27852	7924	1.47
4	Etodolac	2.252	76985	27461	7842	1.48
5	Etodolac	2.248	77456	26989	7963	1.47
Mean			77102.2			
Std. Dev			245.7594			
% RSD			0.318745			

Acceptance Criteria:
➢ %RSD of five different sample solutions should not more than 2.
➢ The %RSD obtained is within the limit, hence the method is suitable.

Table2: Results of System suitability data of Thiocolchicoside

Sl. No.	Name	Rt	Peak Area	Height	USP plate Count	USP Tailing
1	Thiocolchicoside	5.452	9685784	685242	9685	1.64
2	Thiocolchicoside	5.484	9659452	685985	9725	1.65
3	Thiocolchicoside	5.491	9689568	684751	9624	1.64
4	Thiocolchicoside	5.482	9685972	685235	9638	1.65
5	Thiocolchicoside	5.491	9758645	689523	9784	1.64

Mean			9695884			
Std. Dev			37102.5			
% RSD			0.382662			

Acceptance Criteria:
➢ % RSD for sample should be NMT 2.
➢ The %RSD for the standard solution is below 1, which is within the limits hence method is precise.

Specificity
The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components.
Analytical method was tested for specificity to measure accurately quantitate Etodolac and Thiocolchicoside in drug product.
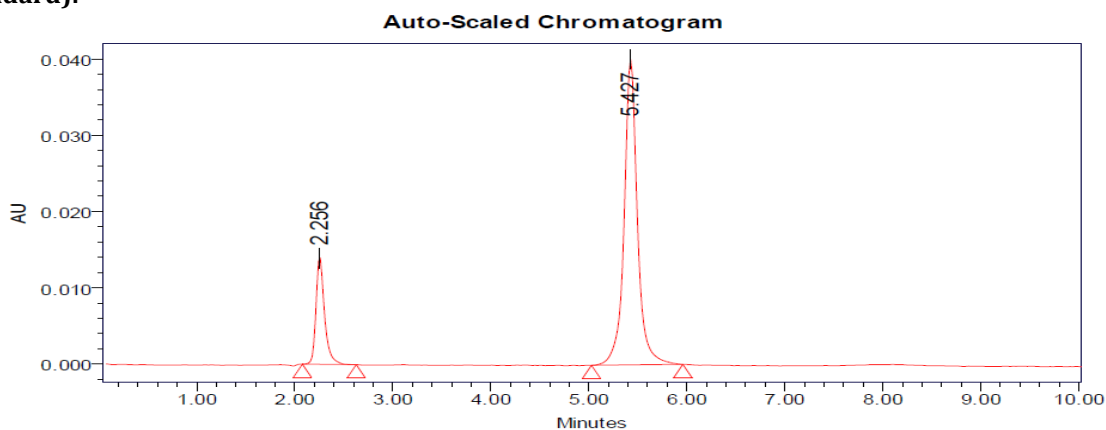
Assay (Standard):

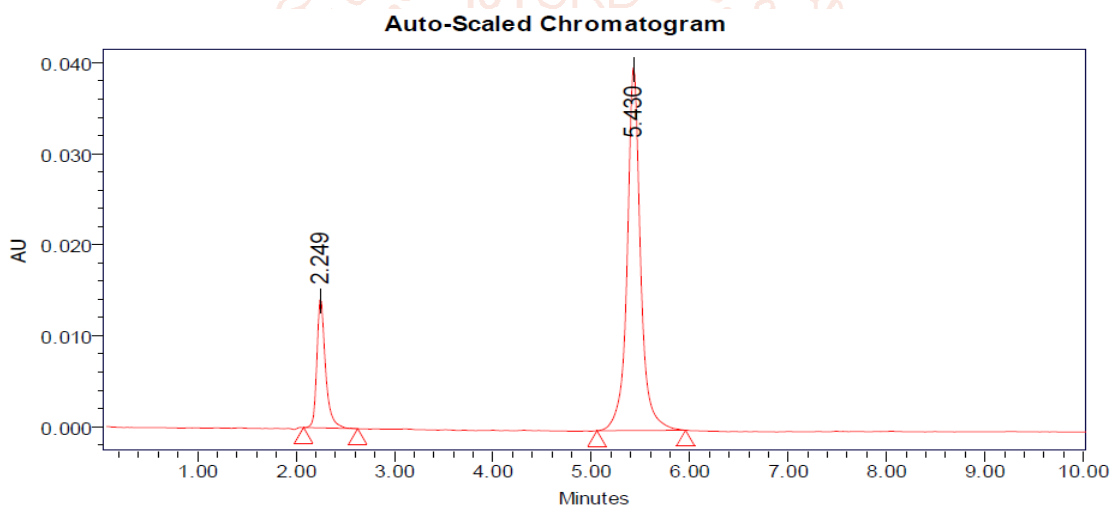**Fig.1: Chromatogram showing assay of standard injection -1**

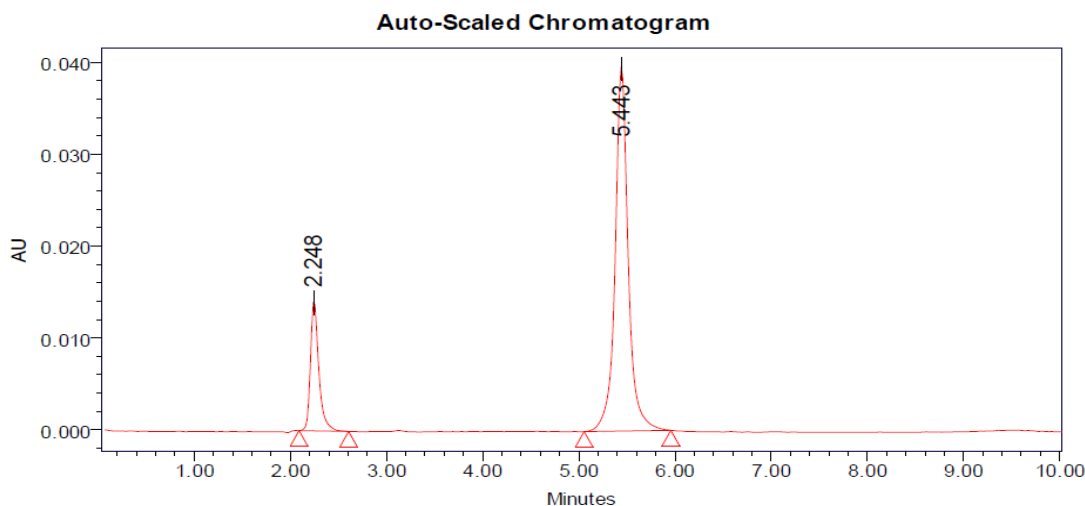**Fig.2: Chromatogram showing assay of standard injection -2**

Fig.3: Chromatogram showing assay of standard injection -3

Table3: Peak Results for Assay Standard

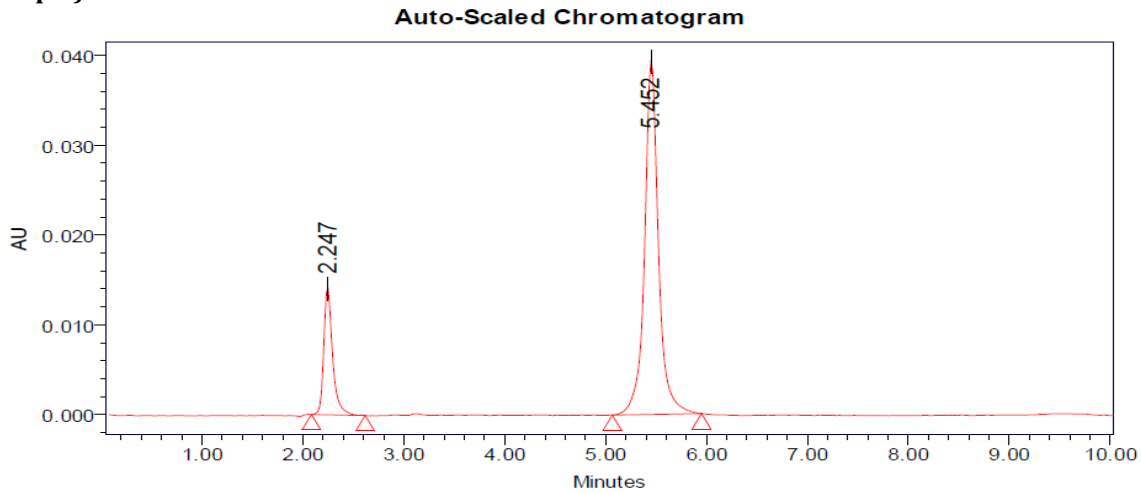| Sl. No.	Name	Rt	Area	Height	USP Resolution	USP Tailing	USP plate count	Injection
1	Etodolac	2.256	76859	26584		1.48	7856	1
2	Thiocolchicoside	5.427	9685463	9685475	6.54	1.65	9674	1
3	Etodolac	2.249	76982	26985		1.47	7826	2
4	Thiocolchicoside	5.430	9685642	9658647	6.55	1.66	9628	2
5	Etodolac	2.248	76259	26859		1.65	7926	3
6	Thiocolchicoside	5.443	9689235	9685692	6.56	1.48	9682	3

Assay (Sample):

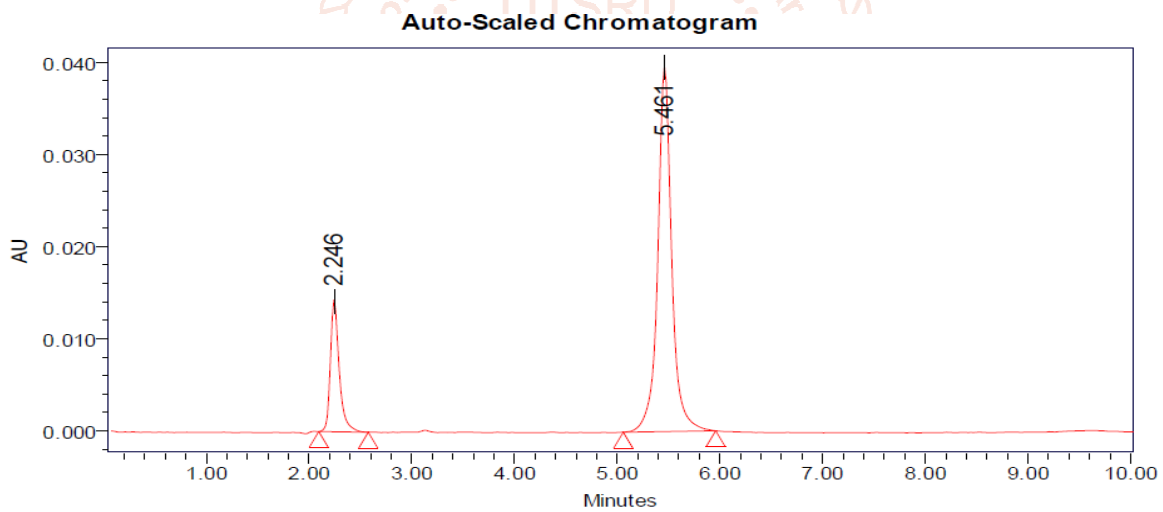**Fig.4: Chromatogram showing assay of sample injection-1**

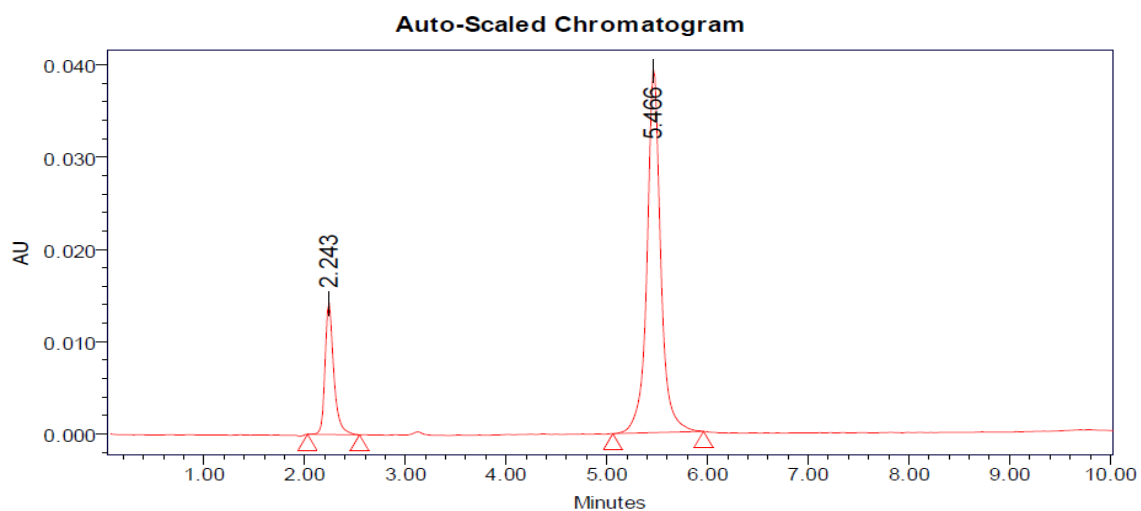

Fig.5: Chromatogram showing assay of sample injection-2

Fig.6: Chromatogram showing assay of sample injection-3

Table4: Peak Results for Assay Sample

Sl. No.	Name	Rt	Area	Height	USP Resolution	USP Tailing	USP plate count	Injection
1	Etodolac	2.247	77854	27856		1.49	7982	1
2	Thiocolchicoside	5.452	9785624	698652	6.56	1.67	9785	1
3	Etodolac	2.246	78469	28653		1.48	7926	2
4	Thiocolchicoside	5.461	9786542	698754	6.57	1.68	9768	2
5	Etodolac	2.243	77586	27856		1.49	7984	3
6	Thiocolchicoside	5.466	9853643	695647	6.56	1.67	9796	3

% ASSAY =

$$\frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

The % purity of Etodolac and Thiocolchicoside in pharmaceutical dosage form was found to be 99.98%.

Linearity

Fig.7: Chromatogram for linearity concentration-200μg/ml of Etodolac & 20μg/ml of Thiocolchicoside

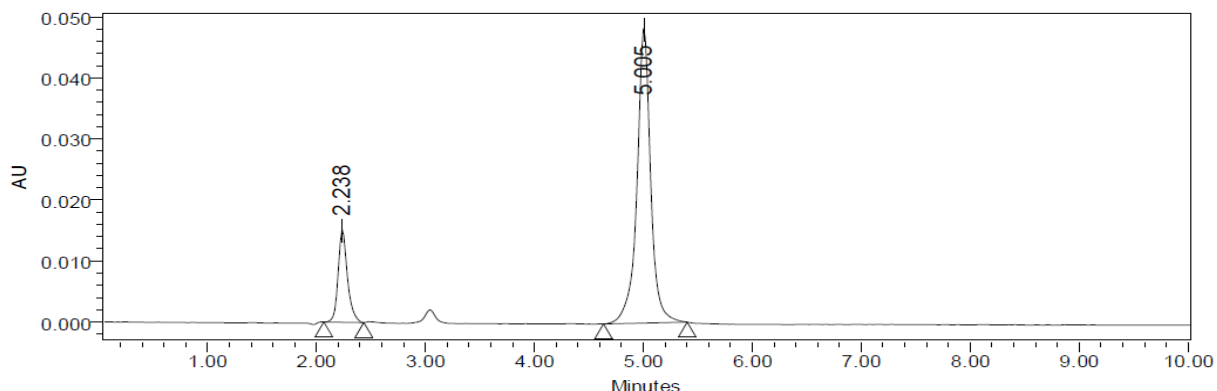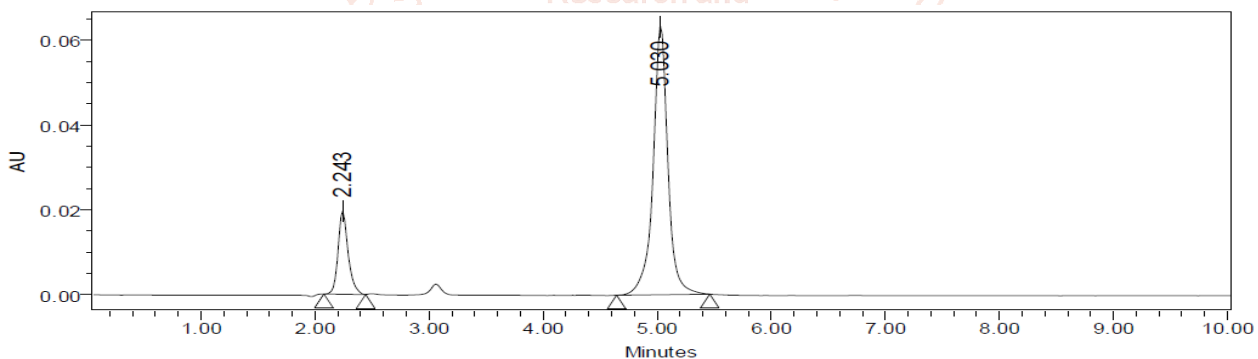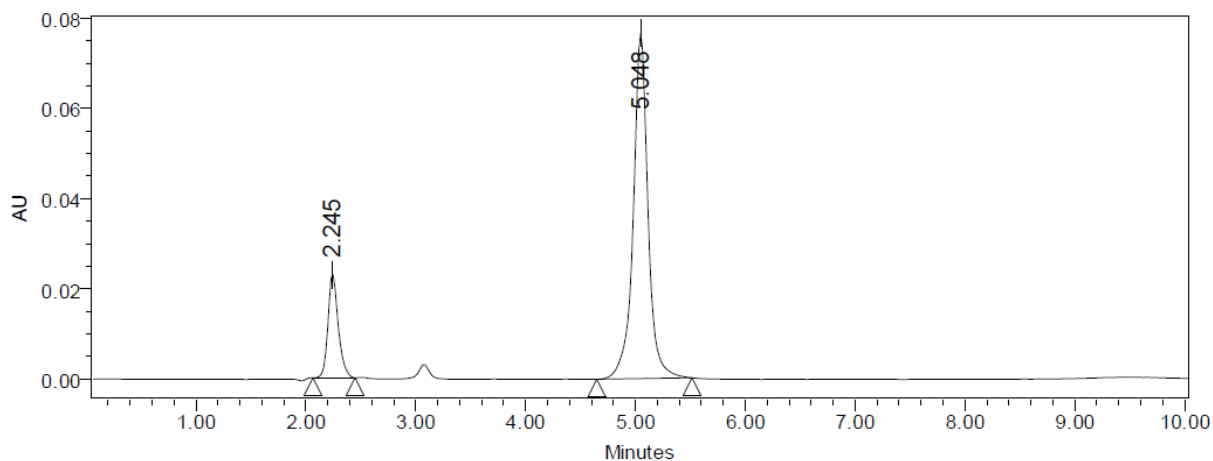**Fig.8: Chromatogram for linearity concentration-300 μg/ml of Etodolac& 30μg/ml of Thiocolchicoside**

Fig.9: Chromatogram for linearity concentration-400μg/ml of Etodolac& 40μg/ml of Thiocolchicoside
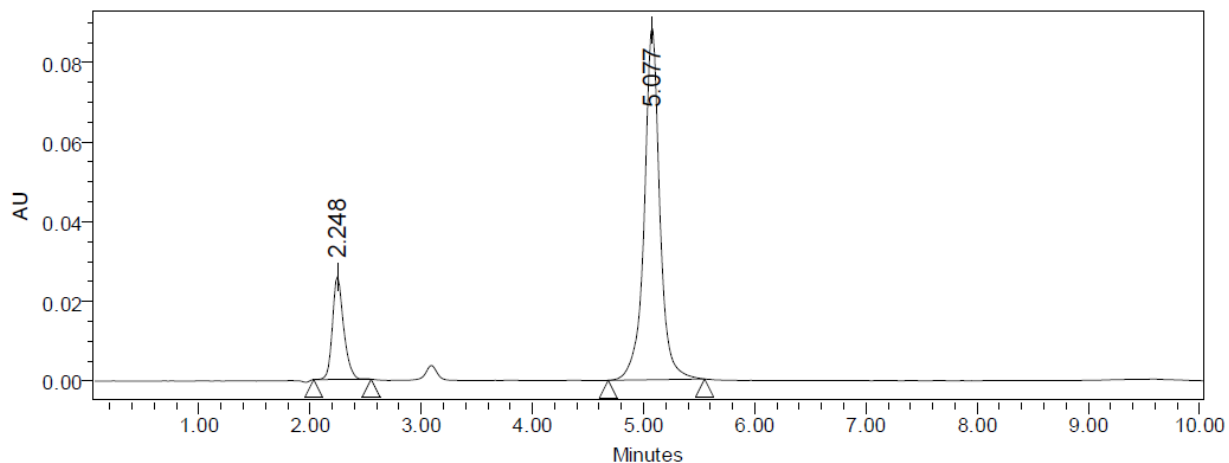
Fig.10: Chromatogram for linearity concentration-500 μg/ml of Etodolac & 50μg/ml of Thiocolchicoside
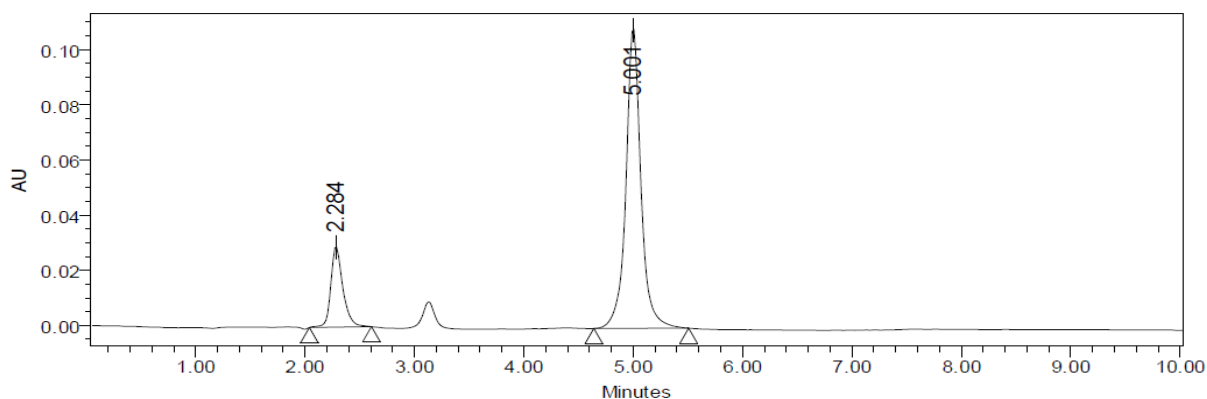
Fig.11: Chromatogram for linearity concentration-600μg/ml of Etodolac & 60μg/ml of Thiocolchicoside

Table5: Chromatographic data for linearity study of Etodolac

Concentration μg/ml	Average Peak Area
200	38697
300	57588
400	75864
500	93787
600	112566

Validation criteria: The response linearity is verified if the Correlation Coefficient is 0.99 or greater.

Table6: Chromatographic data for linearity study of Thiocolchicoside

Concentration μg/ml	Average Peak Area
20	5128242
30	7635873
40	9895684
50	12368475
60	14858247

Validation criteria: The response linearity is verified if the Correlation Coefficient is 0.99 or greater.

Precision:
The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Repeatability
Obtained Five (5) replicates of 100 % accuracy solution as per experimental conditions. Recorded the peak areas and calculated % RSD.

Fig.12: Chromatogram showing precision injection -1

Fig.13: Chromatogram showing precision injection -2
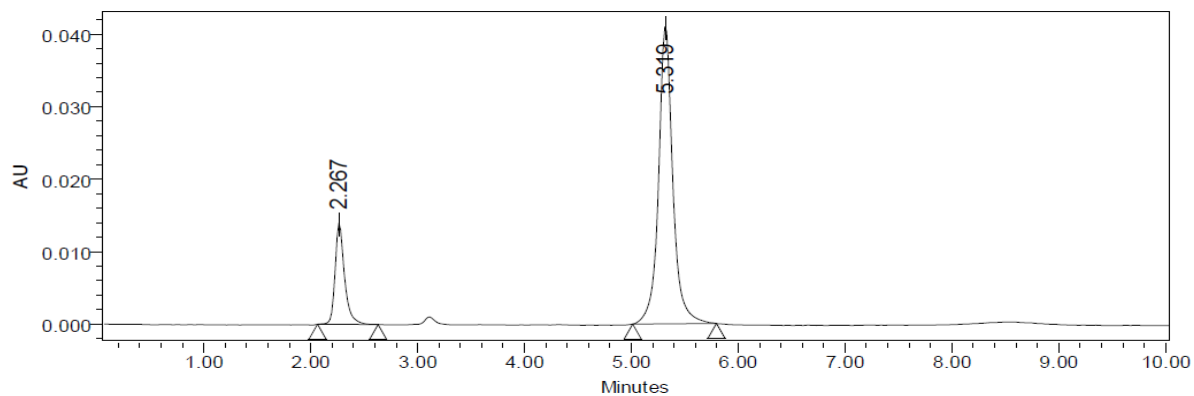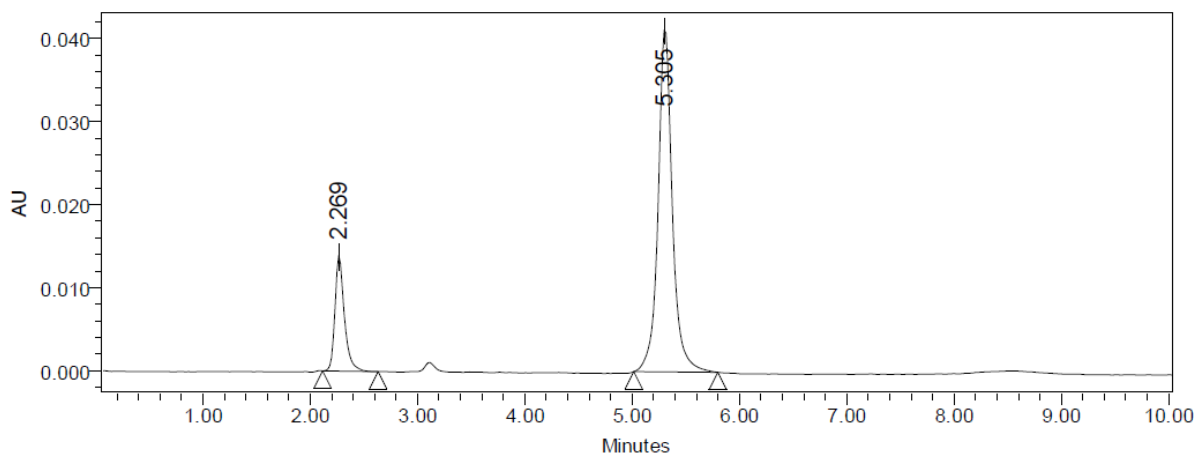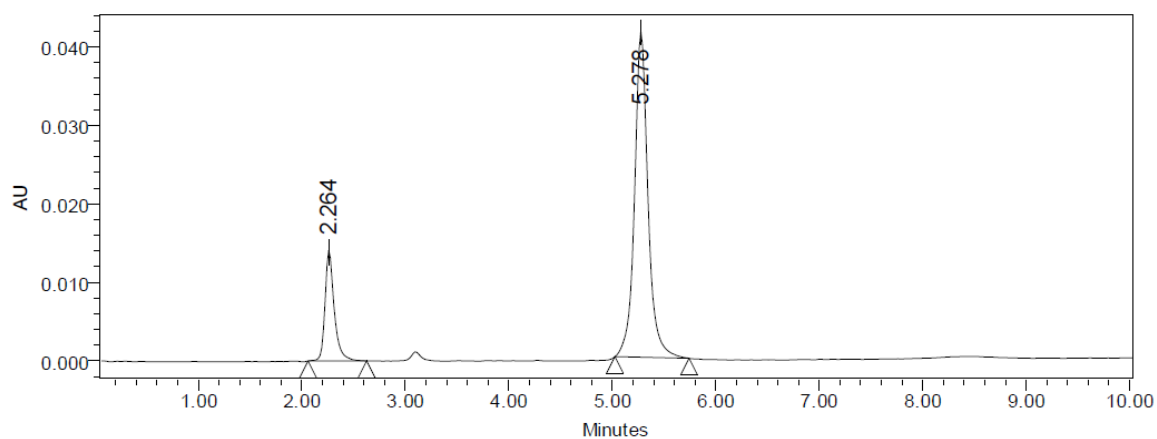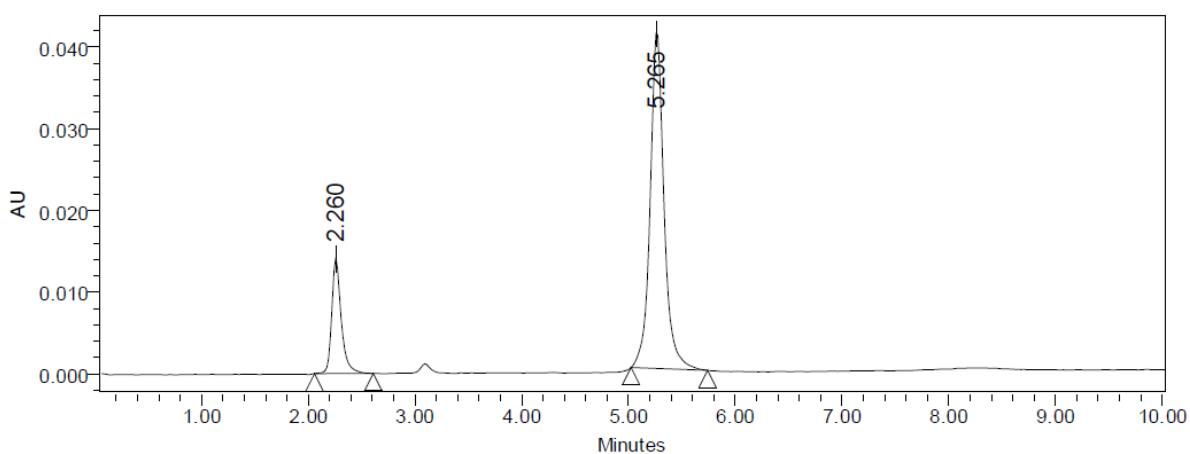

Fig.14: Chromatogram showing precision injection -3
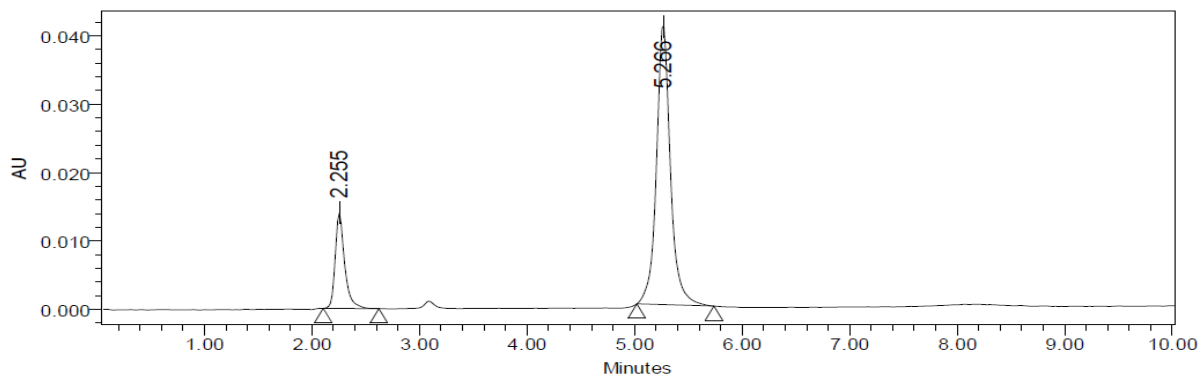

Fig.15: Chromatogram showing precision injection -4

Fig.16: Chromatogram showing precision injection -5

Table7: Results of Repeatability for Etodolac

Sl. No.	Name	Rt	Area	Height	USP plate count	USP Tailing
1	Etodolac	2.269	76869	27856	7859	1.48
2	Etodolac	2.255	76982	26985	7846	1.47
3	Etodolac	2.252	76845	26587	7824	1.46
4	Etodolac	2.267	76824	26534	7839	1.47
5	Etodolac	2.260	76826	26854	7856	1.48
Mean			76869.2			
Std. Dev			65.61021			
% RSD			0.085353			

Acceptance Criteria:

➤ %RSD for sample should be NMT 2.

➤ The %RSD for the standard solution is below 1, which is within the limits hence method is precise.

Table8: Results of Method Precision for Thiocolchicoside

Sl. No.	Name	Rt	Area	Height	USP Plate Count	USP Tailing
1	Thiocolchicoside	5.274	9685424	685985	9685	1.65
2	Thiocolchicoside	5.266	9685472	695564	9682	1.64
3	Thiocolchicoside	5.265	9653685	685447	9642	1.65
4	Thiocolchicoside	5.278	9685423	685246	9682	1.64
5	Thiocolchicoside	5.305	9685986	685423	9684	1.65
Avg			9679198			
Std. Dev			14264.18			
% RSD			0.147369			

Acceptance Criteria: % RSD for sample should be NMT 2, The %RSD for the standard solution is below 1, which is within the limits hence method is precise.

Intermediate precision:

Table9: Results of Intermediate Precision for Etodolac

Sl. No.	Name	Rt	Area	Height	USP Plate Count	USP Tailing
1	Etodolac	2.248	78548	28542	7985	1.50
2	Etodolac	2.245	78526	28462	7849	1.49
3	Etodolac	2.242	78564	28745	7952	1.50
4	Etodolac	2.239	78452	29652	7856	1.49
5	Etodolac	2.243	79685	28745	7854	1.51
6	Etodolac	2.246	79458	28695	7826	1.52
Mean			78872.17			
Std. Dev			547.7811			
% RSD			0.694518			

Acceptance Criteria: %RSD of six different sample solutions should not more than 2.

Table10: Results of Intermediate Precision for Thiocolchicoside

Sl. No.	Name	Rt	Area	Height	USP Plate Count	USP Tailing
1	Thiocolchicoside	5.284	9785642	698568	7985	1.48
2	Thiocolchicoside	5.293	9785685	698245	7962	1.49
3	Thiocolchicoside	5.306	9786634	693524	7984	1.48
4	Thiocolchicoside	5.319	9785425	698745	7936	1.49
5	Thiocolchicoside	5.346	9854682	693562	7964	1.48
6	Thiocolchicoside	5.352	9854826	693546	7925	1.49
Mean			9808816			
Std. Dev			35586.14			
% RSD			0.362798			

Acceptance Criteria: % RSD of six different sample solutions should not more than 2. The %RSD obtained is within the limit, hence the method is rugged.

Table11: Results of Intermediate precision Day 2 for Etodolac

Sl. No.	Name	Rt	Area	Height	USP Plate Count	USP Tailing
1	Etodolac	2.255	75986	25698	7785	1.46
2	Etodolac	2.260	75258	25364	7746	1.45
3	Etodolac	2.242	75462	24968	7796	1.46
4	Etodolac	2.245	75982	25876	7784	1.45
5	Etodolac	2.260	75934	25369	7692	1.45
6	Etodolac	2.255	74989	25478	7699	1.46
Mean			75601.83			
Std. Dev			427.9684			
% RSD			0.566082			

Acceptance Criteria: % RSD of six different sample solutions should not more than 2.

Table12: Results of Intermediate precision for Thiocolchicoside

Sl. No.	Name	Rt	Area	Height	USP plate count	USP Tailing
1	Thiocolchicoside	5.266	9586485	678542	9582	1.63
2	Thiocolchicoside	5.265	9575864	678526	9587	1.62
3	Thiocolchicoside	5.306	9586432	678594	9563	1.62
4	Thiocolchicoside	5.293	9584675	678556	9574	1.61
5	Thiocolchicoside	5.265	9536542	678595	9537	1.62
6	Thiocolchicoside	5.266	9568795	678542	9584	1.61
Mean			9573132			
Std. Dev			19253.75			
% RSD			0.201123			

Acceptance Criteria: % RSD of six different sample solutions should not more than 2.The %RSD obtained is within the limit, hence the method is rugged.

Accuracy:
Accuracy at different concentrations (50%, 100%, and 150%) was prepared and the % recovery was calculated.

Table13: Results of Accuracy for concentration-50%

Sl. No.	Name	Rt	Area	Height	USP Resolution	USP Tailing	USP plate count	Injection
1	Etodolac	2.251	38028	21658		1.56	6584	1
2	Thiocolchicoside	5.466	498937	485695	5.65		7658	1
3	Etodolac	2.251	38125	21364		1.58	6652	2
4	Thiocolchicoside	5.447	506856	478565	5.68		7754	2
5	Etodolac	2.252	38224	20989		1.58	6594	3
6	Thiocolchicoside	5.425	504567	478524	5.69		7699	3

Table14: Results of Accuracy for concentration-100%

Sl. No.	Name	Rt	Area	Height	USP Resolution	USP Tailing	USP plate count	Injection
1	Etodolac	2.261	75495	27856		1.48	7856	1
2	Thiocolchicoside	5.416	997564	686524	6.58	1.64	9682	1
3	Etodolac	2.261	75568	26989		1.49	7952	2
4	Thiocolchicoside	5.395	986472	698542	6.59	1.65	9726	2
5	Etodolac	2.267	75476	26854		1.49	7824	3
6	Thiocolchicoside	5.382	995243	685954	6.57	1.66	9668	3

Table15: Results of Accuracy for concentration-150%

Sl. No.	Name	Rt	Area	Height	USP Resolution	USP Tailing	USP plate count	Injection
1	Etodolac	2.271	112854	35264		1.52	8526	1
2	Thiocolchicoside	5.368	1492652	726582	8.65	1.78	9985	1
3	Etodolac	2.272	113235	36524		1.53	8624	2
4	Thiocolchicoside	5.354	1486584	736524	8.66	1.79	9936	2
5	Etodolac	2.273	112452	35628		1.52	8692	3
6	Thiocolchicoside	5.339	1495287	726598	8.65	1.78	9987	3

Table16: The Accuracy Results for Etodolac

% Concentration (at specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery	Mean Recovery
50%	38125.67	200	199.928	99.964%	99.97%
100%	75513	400	399.967	99.991%	

Table17: The accuracy results for Thiocolchicoside

% Concentration (at specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery	Mean Recovery
50%	503453.3	20	20.012	100.060%	
100%	993093	40	39.899	99.747%	100.02%
150%	1491508	60	60.143	100.238%	

Acceptance Criteria: The percentage recovery was found to be within the limit (98-102%).
The results obtained for recovery at 50%, 100%, 150% are within the limits. Hence method is accurate.

Limit of detection
The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.
LOD= 3.3 × σ / s

Where- σ = Standard deviation of the response, S = Slope of the calibration curve

Result:
Etodolac: =0.86μg/ml
Thiocolchicoside: =1.18μg/ml

Limit of quantitation
The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined.
LOQ=10×σ/S

Where- σ = Standard deviation of the response, S = Slope of the calibration curve

Result:
Etodolac: = 2.4μg/ml
Thiocolchicoside: = 3.54μg/ml

ROBUSTNESS
The robustness was performed for the flow rate variations from 0.9 ml/min to 1.1ml/min and mobile phase ratio variation from more organic phase to less organic phase ratio for Etodolac and Thiocolchicoside. The method is robust only in less flow condition and the method is robust even by change in the Mobile phase ±5%. The standard and samples of Etodolac and Thiocolchicoside were injected by changing the conditions of chromatography. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

Table18: Results for Robustness Etodolac:

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 1.0 mL/min	76856	2.264	7853	1.47
Less Flow rate of 0.9 mL/min	82658	2.505	8152	1.53
More Flow rate of 1.1 mL/min	74526	2.046	7526	1.42
Less organic phase	73652	2.505	7452	1.46
More organic phase	72584	2.046	7365	1.45

Acceptance Criteria: The tailing factor should be less than 2.0 and the number of theoretical plates (N) should be more than 2000.

Table19: Results for Robustness Thiocolchicoside:

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 1.0 mL/min	9658742	5.278	9625	1.64
Less Flow rate of 0.9 mL/min	9986958	5.599	9256	1.62
More Flow rate of 1.1 mL/min	9358475	4.576	9466	1.63
Less organic phase	9258746	5.599	9358	1.64
More organic phase	91587643	4.576	9562	1.61

Acceptance criteria: The tailing factor should be less than 2.0 and the number of theoretical plates (N) should be more than 2000.

CONCLUSION

In the present investigation, a simple, sensitive, precise and accurate RP-HPLC method was developed for the quantitative estimation of Etodolac (ETO) and Thiocolchicoside (THIO) in bulk drug and pharmaceutical dosage forms. This method was simple, since diluted samples are directly used without any preliminary chemical derivatisation or purification steps. Acetonitrile: Methanol: Acetate Buffer (25:20:55% v/v) was chosen as the mobile phase. The solvent system used in this method was economical. The % RSD values were within 2 and the method was found to be precise. The results expressed in Tables for RP-HPLC method was promising. The RP-HPLC method is more sensitive, accurate and precise compared to the Spectrophotometric methods. This method can be used for the routine determination of Etodolac (ETO) and Thiocolchicoside (THIO) in bulk drug and in Pharmaceutical dosage forms.

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