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Development and Validation of a Stability Indicating Reverse Phase HPLC Method for Simultaneous Determination of Etodolac and Paracetamol in Its Tablet Dosage Formulation

Mithlesh Rajput[1], Hinna Hamid[2], Manjeet Aggarwal[3], Rakesh Kumar Khandal[4]*

Department of Drugs and Pharma, Shriram Institute for Industrial Research, Delhi, India[1]

Department of Chemistry, Jamia Hamdard, New Delhi, India[2]

The National Institute of Food Technology Entrepreneurship and Management, Sonipat, Haryana, India[3]

Uttar Pradesh Technical University, IET Campus, Sitapur Road, Lucknow, Uttar Pradesh, India[4]

ABSTRACT: A simple, sensitive, accurate, HPLC-UV method has been developed for the simultaneous determination of etodolac and paracetamol in presence of their degradation products in tablet combined dosage formulation. Chromatographic separation was achieved successfully by using phenomenex C18 column (150 mm x 4.6 mm, i.d. 5 m particale size) with an optimized mobile phase of ACN:H_2O:H_3PO_4 in the ratio of 500:500:0.25 (v/v/v) pH 3.0 with triethyamine. The mobile phase was run at a flow rate of 1 ml / minute under isocratic conditions with injection volume 10µl and the quantification of etodolac and paracetamol was carried out by UV detector at 274 nm based on peak area maeasurment. The reliability and performance of the proposed method were statistically validated with respect to system suitability, linearity, accuracy, precision (inter-day and intra-day), specificity, and robustness, limit of detection and limit of quantification. The method was found to be linear in the wide working range of 2 to 80µg/ml and 2.5-100µg/ml for both the analyte of interest with correlation coefficient 0.999 and 0.999 for etodolac and paracetamol respectively.

The proposed method proved to be selective and suitable for indicating stability study for both etodolac and paracetamol in presence of any degradation product formed under different forced stress conditions (acidic, alkaline, oxidation, thermal and photolytic). The proposed validated method was successfully applied to the analysis of etodolac and paracetamol in their combined dosage form and thus can be routinely used for the simultaneous determination of etodolac and paracetamol when present in combined formulation.

KEYWORDS: Etodolac, Paracetamol, UV-HPLC, Stability indicating method.

I. INTRODUCTION

Etodolac is chemically (R, S) -2- (1, 8-Diethyl-4, 9-dihydro-3H-pyrano [3, 4-b] indol-1-yl) acetic acid. Its molecular weight and formula are $C_{17}H_{21}NO_3$ and 287.35g/mol respectively [1]. Etodolac works by reducing the levels of prostaglandins, responsible for pain, fever and tenderness that occur with inflammation. Etodolac blocks the enzyme that makes prostaglandins (cyclooxygenase) thereby resulting into lower concentrations of prostaglandins. As a consequence, inflammation, pain and fever are reduced [2] [3].Various methods have been reported for determination of etodolac drug formulations and in biological samples. Reported methods are based on spectrophotometry method [4] [5] HPLC with UV detection [6], HPLC with mass spectrometric detection [7] for the determination of etodolac.

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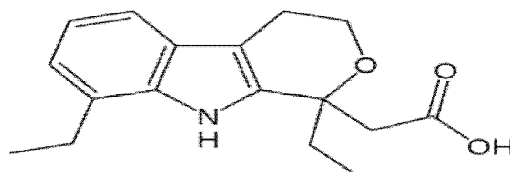

Figure 1: Chemical Structure of Etodolac

Paracetamol chemically is 4-hydroxyphenylacetanilide and its structure is given in figure 2. Its molecular formula is $C_8H_9NO_2$ and molecular weights are 151.16 g/mol [8]. It is classified as a mild analgesic and is most commonly used for the relief of headache and other minor aches and pains such as post-surgical pain, providing palliative care in advanced cancer patients. It is a major ingredient in numerous cold and flu remedies in combination with opioid analgesics [9]

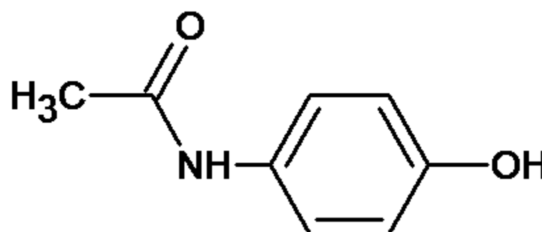

Figure 2: Structure of paracetamol

There are various other publications also which describe various analytical methods for the determination of paracetamol either present alone or in combination with certain other active pharmaceutical ingredients in different formulations and biological fluids. The reported analytical techniques are based on the use of spectrophotometry [10] [11] [12], High performance liquid chromatography (HPLC) [13] [14] [15], Tandem liquid chromatography mass spectroscopy (LC-MS/MS) [16] [17] [18]. There are various methods have been reported for simultaneous determination of etodolac and paracetamol using spectrophotometery [19] [20] [21], High performance thin layer liquid chromatography (HPTLC) [22] [23] and HPLC [24] [25]. To the best of our knowledge there is no Stability indicating HPLC method is available for simultaneous quantification of etodolac and paracetamol in its combined dosage formulation. The International conference on harmonization guidelines requires that stress testing be carried out to elucidate the inherent stability of active pharmaceutical ingredient. Stability is the most important criteria in pharmaceutical formulation. The drug which is free from its degraded product is safe and effective for patients. With this background a study has been undertaken to develop a stability indicating reverse phase HPLC method for simultaneous quantification of etodolac and paracetamol in the presence of its degradation products in tablet combined dosage formulation.

II. MATERIALS & METHODS

Chemical and reagents:

Etodolac (Make:Fluka), Paracetamol (Make:Fluka), Marketed formulation of tablet containing 400 mg etodolac and 500 mg paracetamol (Make:orthokind), Acetonitrile (HPLC-grade, Make:Rankem),Water (HPLC-grade, Make:Rankem), Methanol (HPLC-grade, Make:Spectrochem), Orthophosphoric acid (AR-grade, Make:Rankem), Hydrochloric acid, (AR-grade, Make:Rankem), Sodium hydroxide pellets (AR-grade, Make:Rankem) and Hydrogen peroxide solution (AR-grade, Make:Rankem).

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Instrumentation:

Table 1: HPLC Conditions

Instrument Make	:	The Agilent technologies HPLC system, model: LC-1100 consisting of quaternary pump, a photo-diode array
Data acquisition and data processing system	:	EZ chrome Elite enterprises
Diluent	:	Mobile phase
Wavelength	:	274 nm
Injected volume	:	10µl
Column	:	Phenomenex C18 column (150 mm x 4.6mm i. d., 5 µm particle size).
Flow rate	:	1.0 ml/min
Diluent	:	Mobile phase was used as diluent

Methods:

(A) Preparation of Mobile Phase: The mobile phase was prepared by mixing of acetonitrile, water and orthophosphoric acid in the ratio of 500:500:0.25 (v/v/v). The pH of the mobile phase was set to 3.0 by using triethylmine. Mobile phase was filtered through a 0.45µm nylon membrane filter.

(B) Standard solution preparation:

Solution –A: Etodolac standard stock solution containing 400 µg/ml was prepared in a 100 ml volumetric flask taking 40.7 mg of etodolac in 20 ml of mobile phase in the flask. This solution was shaken for 10 minutes and made to volume with mobile phase (final concentration is of 400.7 µg/ml).

Solution –B: Paracetamol stock solution containing 500 µg/ml was prepared in a 100 ml volumetric flask taking 50.7 mg of paracetamol in 20 ml of mobile phase in the flask. This solution was shaken for 10 minutes and made to volume with mobile phase (final concentration is of 500.7 µg/ml).

Solution –C: 10 ml of each of solution A and solution B were pipetted in 100 ml volumetric flask and made to the volume using mobile phase. This gave combined standard working solution of etodolac and paracetamol each having concentration of 40µg/ml of etodolac and 50 µg/ml of paracetamol respectively. 10 µL of the standard solution C was injected in to the HPLC.

(C) Sample analysis:

Twenty tablets of sample were weighed in order to calculate average weight of the tablet and then finely powdered. An accurate weight of the powder equivalent to 40 mg of etodolac and 50 mg of paracetamol was weighed and transferred to 100 ml volumetric flask to which 20 ml of diluents was added. This solution was shaken and sonicated for 15 minutes, and made to volume with diluent to 100 ml (sample stock solution). A 10 ml aliquot of this solution was further accurately pipette into 100 ml volumetric flask and diluted to volume with mobile phase. This gave combined test solution of etodolac and paracetamol each having concentration of approximately 40 µg/ml of etodolac and 50 µg/ml of paracetamol respectively.

(D) Forced degradation study of the sample was carried out under following conditions:

a) Acidic conditions: To study the effect of acidic degradation 5 ml of sample stock solution was taken into 50 ml empty volumetric flask and 5 ml 0.1M HCl solution to this flask and heating on a water bath at temperature 60^0C for approximately six hours. This solution was left to reach ambient temperature, neutralized to pH 7 by addition of 5 ml of 0.1 M NaOH, further diluted to 100 ml with diluent. The final concentration of this resulted test solution was 40 µg/ml of etodolac and 50 µg/ml of paracetamol respectively.

b) Alkaline conditions: To study the effect of basic degradation 5 ml of sample stock solution was taken into 50 ml empty volumetric flask and 5 ml 0.1M NaOH solution to this flask and heating on water bath at a temperature 60^0C

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for approximately six hours. This solution was left to reach ambient temperature, neutralized to pH 7 by addition of 5 ml of 0.1 M HCL, further diluted to 100 ml with diluents. The final concentration of this resulted test solution is 40 µg/ml of etodolac and 50 µg/ml of paracetamol respectively

c) **Oxidative condition : :** Oxidative degradation study was performed by refluxing the 5 ml of sample stock solution with 10 % hydrogen peroxide at 60^0 C for 1 hr. Solution was allowed to cool at room temperature and further diluted with dilutent to 50 ml. The final concentration of this resulted test solution was 40 µg/ml of etodolac and 50 µg/ml of paracetamol respectively.

d) **Thermal condition:** Thermal degradation was performed by exposing the intact tablet formulations at 80 °C for 72 hours. Then tablets were crushed in order to obtain fine powder and weight equivalent to 40 mg of etodolac and 50 mg of paracetamol was taken in to 100 ml of volumetric flask. 10 ml of diluent was added in to flask and sonicated for 15 minutes and further diluted with diluents this sample solution gave final concentration of 400 µg/ml and 500 µg/ml etodolac and paracetamol. This sample was further diluted to obtain final concentration of 40 µg/ml and 50 µg/ml etodolac and paracetamol.

e) **Photolytic condition:** Photolytic degradation was performed by exposing the intact tablet formulations to UV –light for 48 hours and these tablets were crushed in order to obtain fine powder. Then the weight equivalent to 40 mg of etodolac was weighed and taken into 100 ml of volumetric flask. 10 ml of diluent was added into flask and sonicated for 15 minutes and then further diluted with diluents this solution gave final concentration of 400 µg/ml and 500 µg/ml etodolac and paracetamol. This sample was further diluted to obtain final concentration of 40 µg/ml and 50 µg/ml etodolac and paracetamol. The sample solution and degradation sample solution was then filtered through syringe using 0.45 mm membrane filter. 10µL of this sample solution was injected in to the HPLC. Calculation was based on the peak area ratio in the standard chromatogram and peak area in test chromatogram

III. CALCULATIONS

Prototype calculation for one set of Etodolac

Assay (%) =	AT / AS	X	W1 / 100	X	10 / `100	X	100 / W2	X	100 / 10	X	P / 100	X	AW / LC	X	100	=	Result %

Whereas,
AT = Average area of etodolac obtained in test preparation
AS = Average area of etodolac obtained in standard preparation
W1 = Weight taken of etodolac reference standard (mg)
W2 = Weight taken of etodolac sample (mg)
AW = Average weight of tablets (mg)
LC = Label claim (mg)
P = Potency of etodolac reference standard (%)

Prototype calculation for paracetamol

Assay (%) =	AT / AS	X	W1 / 100	X	10 / `100	X	100 / W2	X	100 / 10	X	P / 100	X	AW / LC	X	100	=	Result %

Whereas,
AT = Average area of paracetamol obtained in test preparation
AS = Average area of paracetamol obtained in standard preparation
W1 = Weight taken of paracetamol reference standard (mg)
W2 = Weight taken of paracetamol sample (mg)

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AW = Average weight of tablets (mg)
LC = Label claim (mg)
P = Potency of paracetamol reference standard (%)

IV. METHOD VALIDATION

Specificity and Selectivity: The specificity of the method was checked by injecting blank solution and sample Solution There was no interference from blank on the retention time of analyte peak. To prove this method a stability indicating, force degradation study was also performed.

Linearity: The method showed linear in the concentration range of 2 µg/ml to 80 µg/ml and 2.5-100 µg/ml for etodolac and paracetamol respectively. The correlation coefficient was found 0.999 for the drugs. The results are shown in table 2-3.

Precision: The method precision and intermediated precession were calculated. The results were within the limits**.** The results of the method precision and intermediate precision were shown in table 4-5.

Accuracy: The accuracy of the method was determined by adding known amount of etodolac and paracetamol corresponding to three concentration levels of 50%, 100%, and 200% of analytes concentration. The accuracy was calculated by amount of analytes added and amount of analytes found. This gives the percentage of analyte recovered by the assay method. Based on our results that the method is highly accurate. The accuracy results are shown in table6-7.

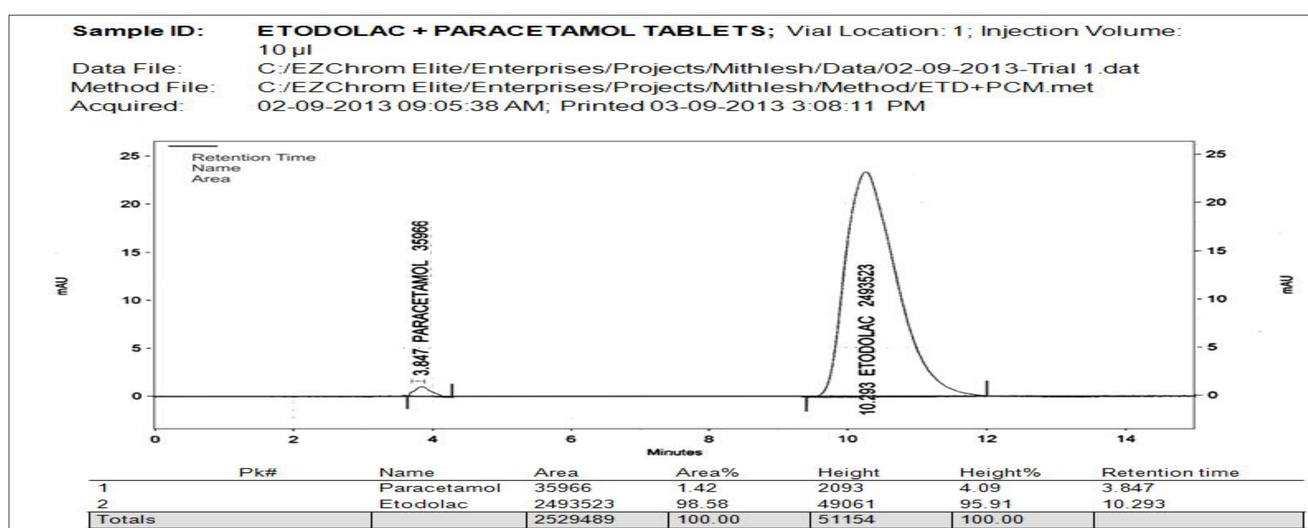
Robustness of the method: Changing with the flow rate (±0.1mL/min), and mobile phase composition. No change in assay result % was observed. The results of the robustness results are shown in table 8.

LOD and LOQ: Limit of detection of method is 0.2 µg/ml and 0.25 µg/ml for etodolac and paracetamol respectively and limit of quantification is 0.4 µg/ml for etodolac and for paracetamol 0.5 µg/ml.

V. EXPERIMENTAL RESULTS

In the present work, an analytical method is based on LC method using UV detector, the analytical conditions were selected, keeping in mind the different chemical nature of etodolac and paracetamol. The development trials were performed by using original standard preparation with different mobile phases. Trial 3 is final mobile phase for validation study.

Figure 3: Chromatogram of trial I (mobile phase –methanol: water 20:80 V/V)



Pk#	Name	Area	Area%	Height	Height%	Retention time
1	Paracetamol	35966	1.42	2093	4.09	3.847
2	Etodolac	2493523	98.58	49061	95.91	10.293
Totals		2529489	100.00	51154	100.00	

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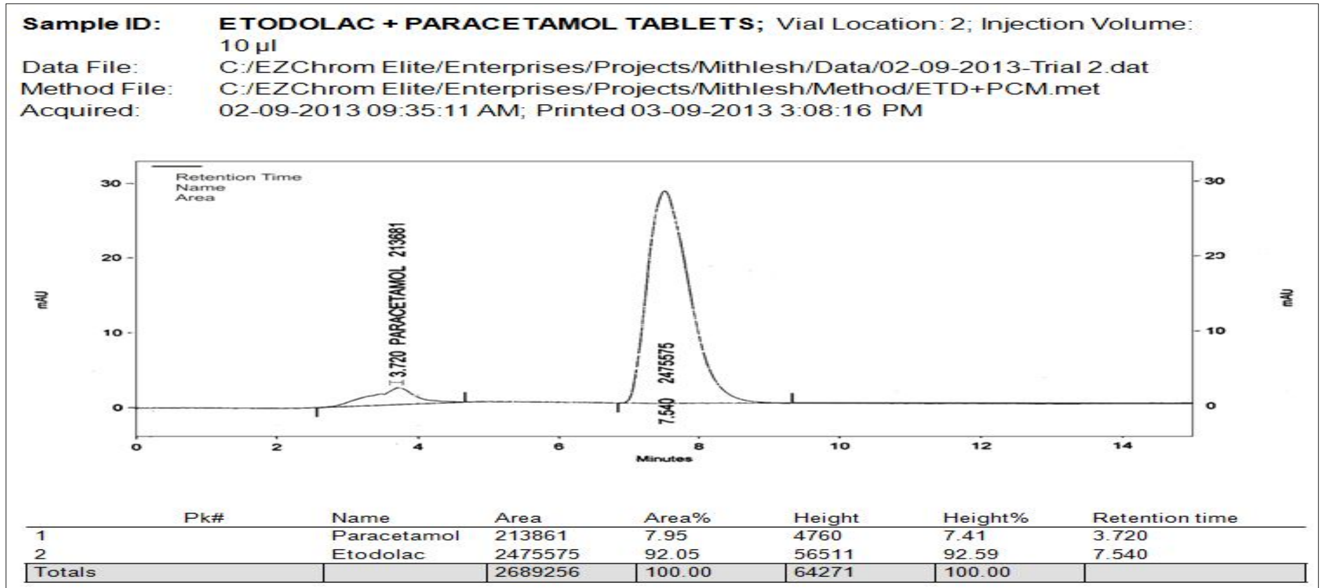
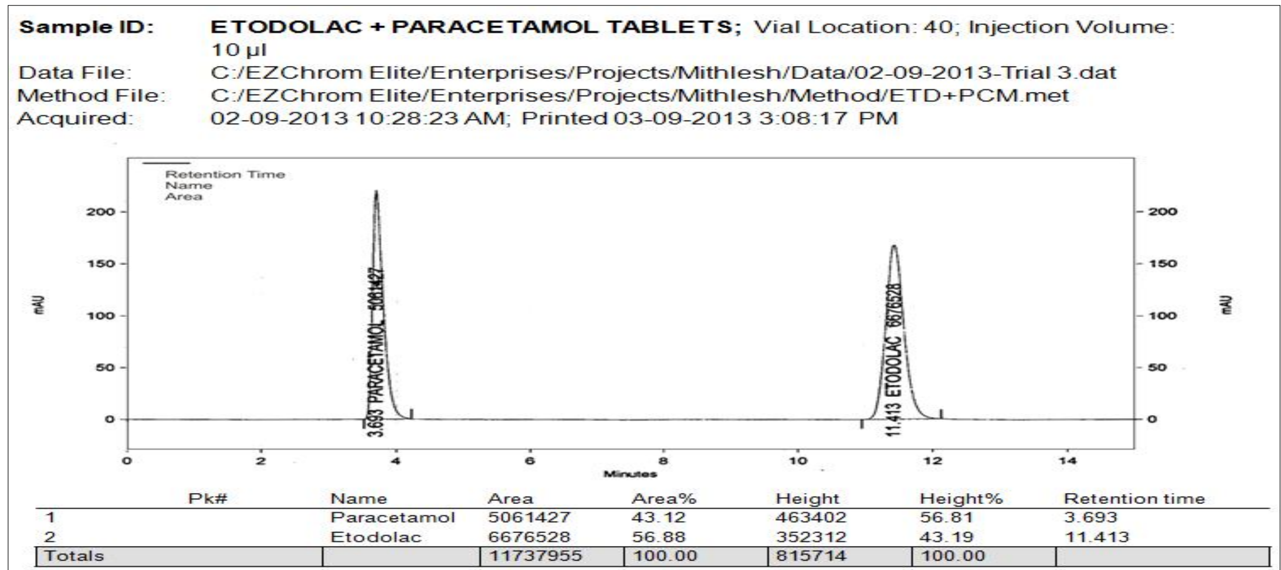
Figure 4: Chromatogram of trail II (mobile phase –methanol: acetonitrile: water 30:50:20 v/v/v)



Pk#	Name	Area	Area%	Height	Height%	Retention time
1	Paracetamol	213861	7.95	4760	7.41	3.720
2	Etodolac	2475575	92.05	56511	92.59	7.540
Totals		2689256	100.00	64271	100.00	

Figure 5: Chromatogram of Trial III (acetonitrile: water: orthophosphoric acid 50:50:0.25 v/v/v)



Pk#	Name	Area	Area%	Height	Height%	Retention time
1	Paracetamol	5061427	43.12	463402	56.81	3.693
2	Etodolac	6676528	56.88	352312	43.19	11.413
Totals		11737955	100.00	815714	100.00	

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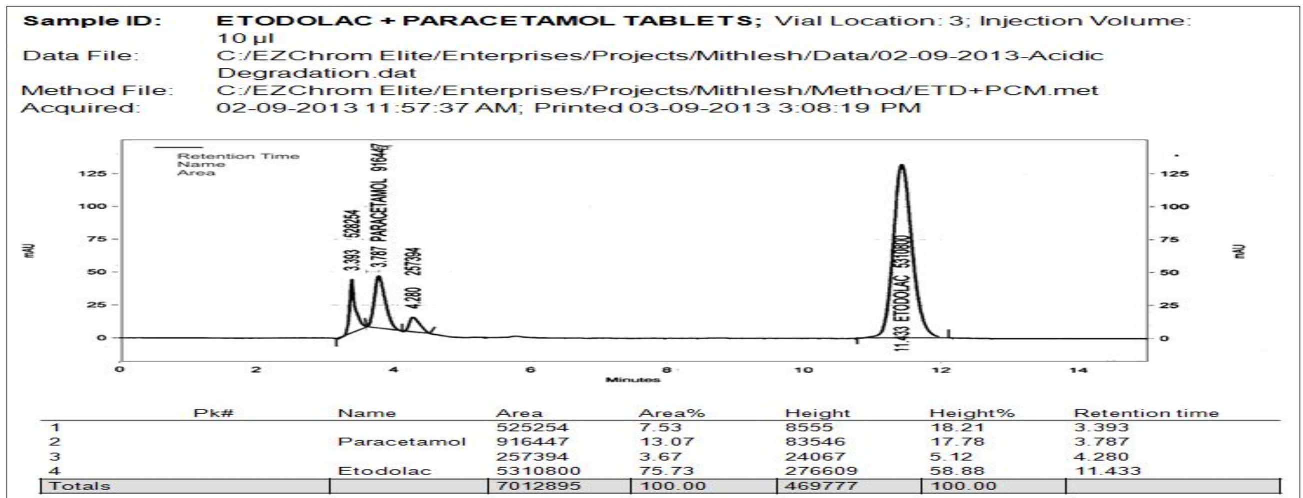
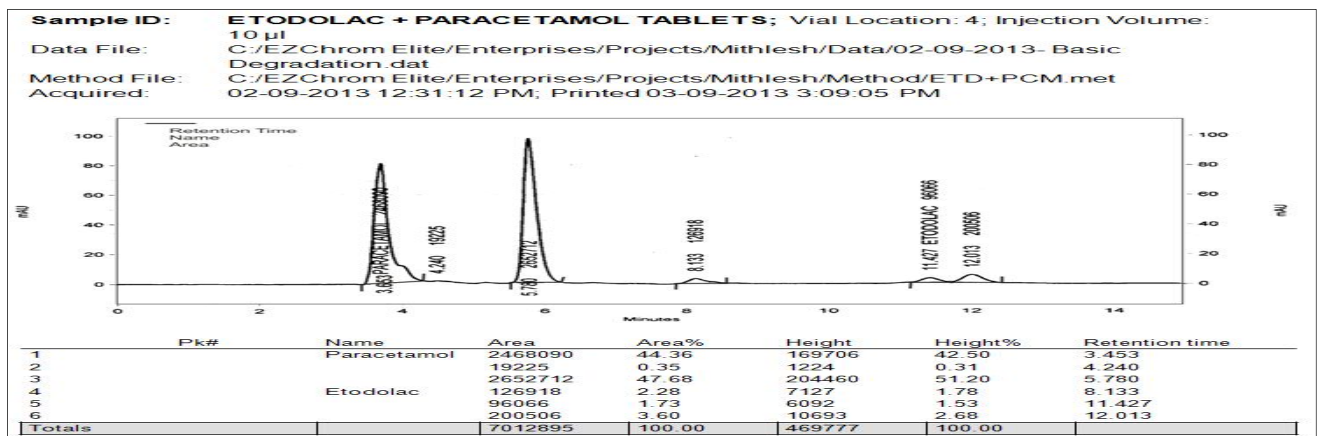
Figure 6: Chromatogram of Acidic degradation.



Sample ID: ETODOLAC + PARACETAMOL TABLETS; Vial Location: 3; Injection Volume: 10 µl
Data File: C:/EZChrom Elite/Enterprises/Projects/Mithlesh/Data/02-09-2013-Acidic Degradation.dat
Method File: C:/EZChrom Elite/Enterprises/Projects/Mithlesh/Method/ETD+PCM.met
Acquired: 02-09-2013 11:57:37 AM; Printed 03-09-2013 3:08:19 PM

Pk#	Name	Area	Area%	Height	Height%	Retention time
1		525254	7.53	8555	18.21	3.393
2	Paracetamol	916447	13.07	83546	17.78	3.787
3		257394	3.67	24067	5.12	4.280
4	Etodolac	5310800	75.73	276609	58.88	11.433
Totals		7012895	100.00	469777	100.00	



Sample ID: ETODOLAC + PARACETAMOL TABLETS; Vial Location: 4; Injection Volume: 10 µl
Data File: C:/EZChrom Elite/Enterprises/Projects/Mithlesh/Data/02-09-2013- Basic Degradation.dat
Method File: C:/EZChrom Elite/Enterprises/Projects/Mithlesh/Method/ETD+PCM.met
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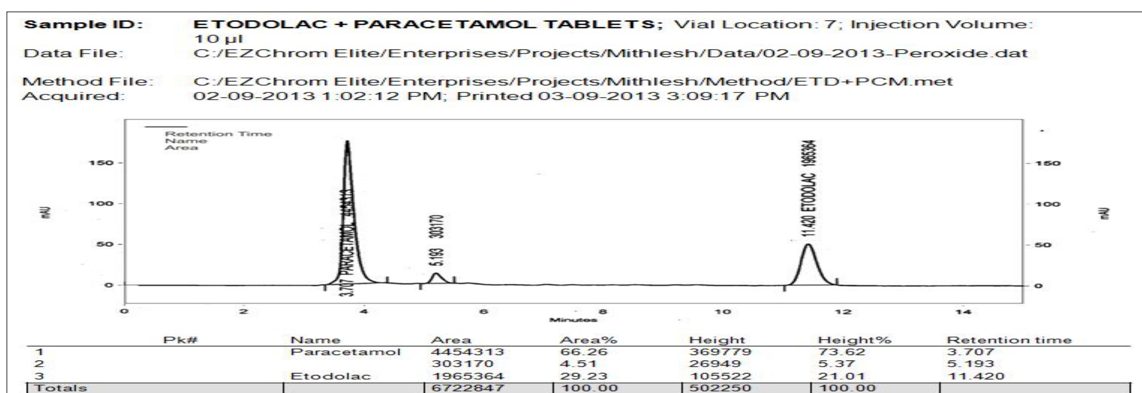
Pk#	Name	Area	Area%	Height	Height%	Retention time
1	Paracetamol	2468090	44.36	169706	42.50	3.453
2		19225	0.35	1224	0.31	4.240
3		2652712	47.68	204460	51.20	5.780
4	Etodolac	126918	2.28	7127	1.78	8.133
5		96066	1.73	6092	1.53	11.427
6		200506	3.60	10693	2.68	12.013
Totals		7012895	100.00	469777	100.00	

Figure 7: Chromatogram of basic degradation study



Sample ID: ETODOLAC + PARACETAMOL TABLETS; Vial Location: 7; Injection Volume: 10 µl
Data File: C:/EZChrom Elite/Enterprises/Projects/Mithlesh/Data/02-09-2013-Peroxide.dat
Method File: C:/EZChrom Elite/Enterprises/Projects/Mithlesh/Method/ETD+PCM.met
Acquired: 02-09-2013 1:02:12 PM; Printed 03-09-2013 3:09:17 PM

Pk#	Name	Area	Area%	Height	Height%	Retention time
1	Paracetamol	4454313	66.26	369779	73.62	3.707
2		303170	4.51	26949	5.37	5.193
3	Etodolac	1965364	29.23	105522	21.01	11.420
Totals		6722847	100.00	502250	100.00	

Figure 8: Chromatogram of peroxide degradation study (Oxidative condition)

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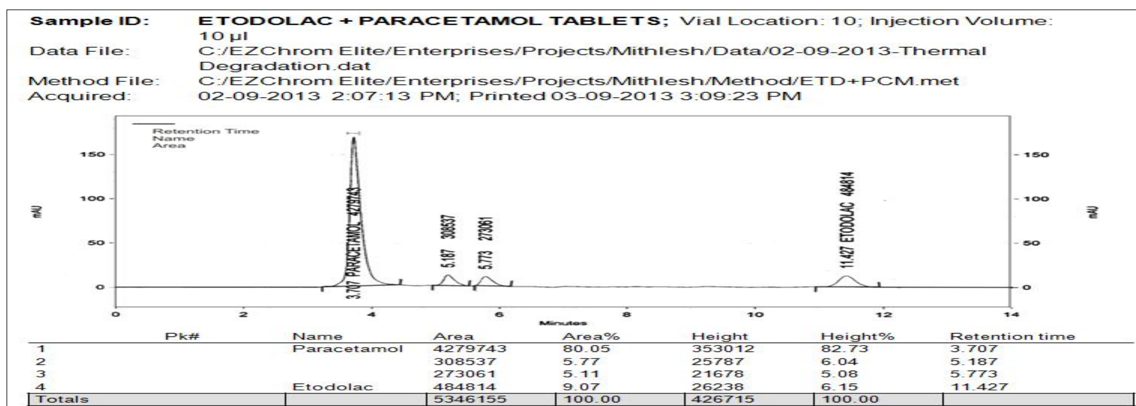

Figure 9: Chromatogram of thermal degradation.

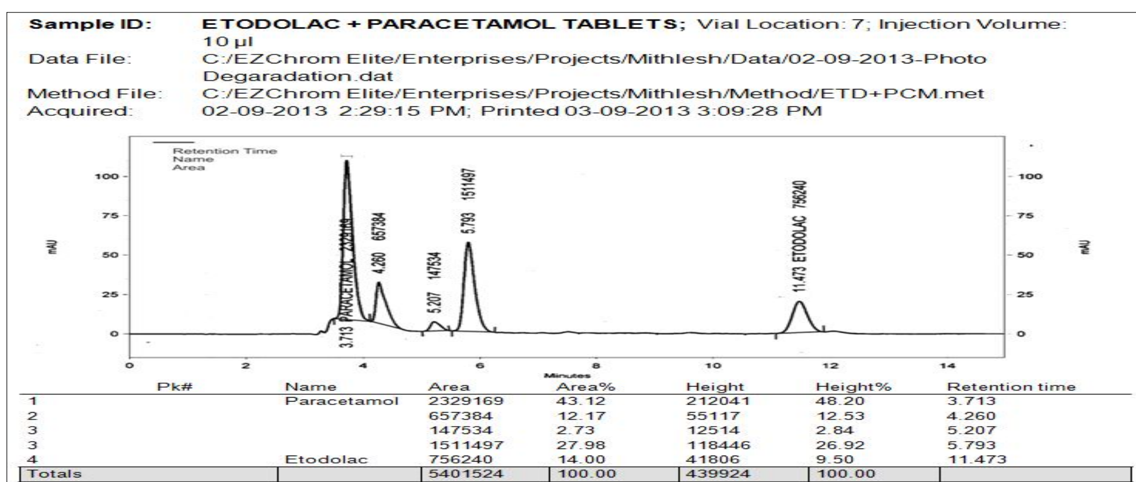

Figure 10: Chromatogram of photo degradation.

During the force degradation study different peaks were generated but this proposed method can easily separate the peaks of etodolac and paracetamol along with its degraded impurities.

Table 2: Linearity table for etodolac.

Conc. level (µg/ml)	Vol of line stock sol	Diluted (ml)	Final conc. (mg/ml)	Mean area
2	0.5	100	0.002	326799.5
4	1	100	0.004	655505.5
10	2.5	100	0.010	1693216.5
20	5	100	0.020	3349736
40	10	100	0.040	6730491
60	7.5	50	0.060	10329067
80	10	50	0.080	13255387

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	Slope	2E+0.8X
	Intercept	10700
	Correlation co-efficient	0.999

Figure 11: Regression analysis chart for linearity study of etodolac

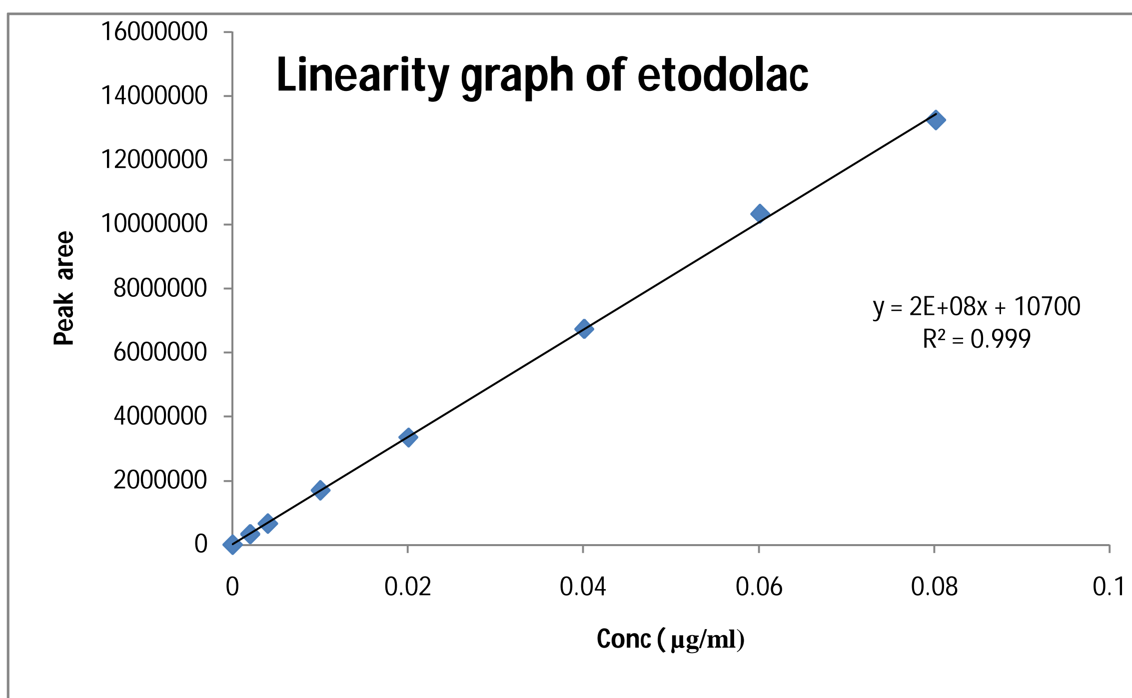

Table 3: Linearity of paracetamol

Conc. level (µg/ml)	Vol of line stock sol	Diluted (ml)	Final conc. (mg/ml)	Mean area
2.5	0.5	100	0.0025	255563
5	1	100	0.0050	494380
12.5	2.5	100	0.0125	1366736
25	5	100	0.0251	2573722
50	10	100	0.0501	5205646
75	7.5	50	0.0752	7859638
100	10	50	0.1002	9989130
			Slope	1E+08X
			Intercept	43916
			Correlation coefficient	0.999

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Figure 12: Regression analysis chart for linearity study of paracetamol

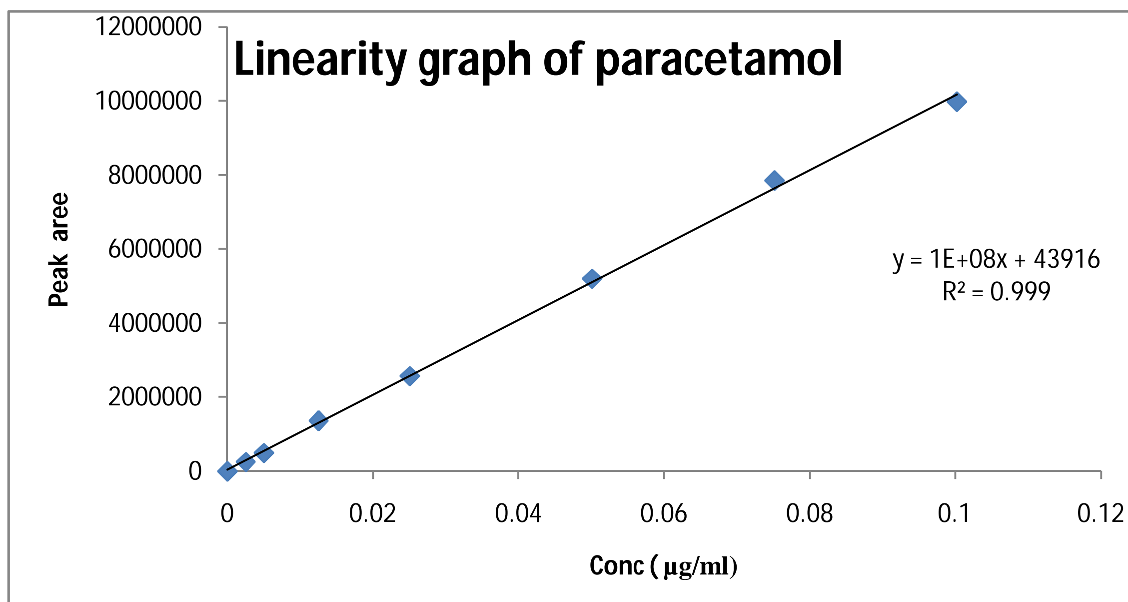

Table 4: Results of precision studies for etodolac

Set No	Assay (%)	Mean assay (%)	Steve	%RSD
1	100.75	100.53	0.448	0.446
2	100.16			
3	100.12			
4	100.39			
5	100.45			
6	101.32			
1	101.55	100.27	1.092	1.089
2	99.2			
3	99.12			
4	99.90			
5	101.58			
6	100.29			
Mean	100.40	Absolute difference between mean % assay values of Method precision and Intermediate precision= 0.5		
Steve	0.81			
% RSD	0.80			

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Table 5: Results of precision studies for paracetamol

Set No	Assay (%)	Mean assay (%)	Stdev	%RSD
1	99.49	99.9883	0.611	0.611
2	99.64			
3	99.80			
4	100.68			
5	99.48			
6	100.84			
1	100.66	101.03	0.508	0.503
2	101.58			
3	100.67			
4	101.77			
5	100.84			
6	100.66			
Mean	100.51	Absolute difference between mean % assay values of Method precision and Intermediate precision= 1		
Stdev	0.76			
% RSD	0.76			

Table 6: Summary of recovery study for etodolac at three different concentration levels

Recovery level	Set. No.	Value added concentration (mg/ml)	Value found concentration (mg/ml)	% Recovery	Mean % Recovery	Stdev	% R.S.D
50%	Set 1	0.02020	0.02037	100.86	100.37	1.113	1.108
	Set 2	0.02040	0.02064	101.17			
	Set 3	0.02040	0.02022	99.11			
100%	Set 1	0.04000	0.03990	99.76	99.08	0.786	0.793
	Set 2	0.04000	0.03970	99.26			
	Set 3	0.04080	0.04007	98.22			
150%	Set 1	0.06150	0.06251	101.64	100.32	1.141	1.138
	Set 2	0.06030	0.06010	99.67			
	Set 3	0.05970	0.05950	99.66			

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Table 7: Summary of recovery study for paracetamol at three different concentration levels

Recovery level	Set. No.	Value added concentration (mg/ml)	Value found concentration (mg/ml)	% Recovery	Mean % Recovery	Stdev	% R.S.D
50%	Set 1	0.02540	0.02567	101.08	100.36	0.760	0.758
	Set 2	0.02460	0.02449	99.57			
	Set 3	0.02500	0.02511	100.45			
100%	Set 1	0.05040	0.05067	100.53	100.07	0.494	0.494
	Set 2	0.05000	0.05004	100.07			
	Set 3	0.04920	0.04897	99.54			
150%	Set 1	0.07770	0.07849	101.01	100.587	0.531	0.527
	Set 2	0.07680	0.07679	99.99			
	Set 3	0.07680	0.07738	100.76			

Table 8: Robustness study for etodolac and paracetamol

Robust conditions	Etodolac			Paracetamol		
	Assay	Retention time	% Assay difference	Assay	Retention time	% Assay difference
0.9 ml/min	99.08	12.780	1.02	99.34	4.127	1.46
1.1 ml/min	99.22	10.43	0.88	99.89	3.367	0.91
Buffer: ACN (48:52 v/v)	99.64	11.762	0.46	100.56	3.931	0.24
Buffer :CAN (52: 48 v/v)	100.33	11.172	0.61	100.58	3.480	0.22

VI. CONCLUSION

The reverse phase HPLC has been developed and validated for simultaneous quantification of etodolac and paracetamol in its tablet formulation. Accuracy of the method was confirmed from the results obtained at different concentration levels. Reliability and precision of the proposed method was also confirmed from method precision and intraday studies. The results obtained from various validation studies conclude that the developed reverse phase HPLC method is simple, accurate, precise, selective and reliable for the simultaneous determination of assay of etodolac and paracetamol in their combined pharmaceutical dosage form. Significant advantage concluded from the study that reported method can not only separate paracetamol and etodolac but also peaks with its major degraded impurities generated during five different types of force degradation conditions. Thus, the proposed method can be used for the routine analysis, quality control check and for checking the quality of etodolac and paracetamol during stability in their preparation in combined dosage formulation

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