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Research Article

RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS DETERMINATION OF PREGABALIN AND ETORICOXIB IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT:
The simultaneous estimation of the Pregabalin and Etoricoxib in Tablet dosage form. Chromatogram was run through Agilent C18 150 mm (4.6 x 150mm, 5µm) Mobile phase containing Buffer 70% (Ammonium acetate) :40% Acetonitrile was pumped through column at a flow rate of 1 ml/min. Temperature was maintained at 30°C. Optimized wavelength selected was 234.0 nm. Retention time of Pregabalin and Etoricoxib were found to be 2.233 min and 2.712 min. %RSD of the Pregabalin and Etoricoxib were and found to be 0.5 and 0.5 respectively. %Recovery was obtained as 100.06% and 99.81% for Pregabalin and Etoricoxib respectively. LOD, LOQ values obtained from regression equations of Pregabalin and Etoricoxib were 0.03, 0.09 and 0.02, 0.06 respectively. Regression equation of Pregabalin is y = 33728x + 2248.7, and y = 37618x + 3978.9 of Etoricoxib.

Key Words: Pregabalin and Etoricoxib, Rp Hplc, Validation.

INTRODUCTION

Pregabalin is an antiepileptic drug that blocks pain by obstructing pain signals that proceed through the brain and damaged nerves. One type of non-steroidal anti-inflammatory medicine (NSAID) known as a COX-2 inhibitor is Etoricoxib. It works by blocking the release of certain chemical messengers that are responsible for pain and inflammation (redness and swelling).[1] Pregabalin is structurally similar to gamma-aminobutyric acid (GABA) - an inhibitory neurotransmitter.[2] It is chemically known as (3S)-3-(aminomethyl)-5-methylhexanoic acid.[3] It may be used to manage neuropathic pain, postherpetic neuralgia, and fibromyalgia among other conditions. Etoricoxib is a new COX-2 selective inhibitor. Current therapeutic indications are: treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, chronic low back pain, acute pain and gout. Etoricoxib reduces the production of prostaglandins (PGs) from arachidonic acid by selectively inhibiting isoform 2 of the cyclo-oxigenase enzyme (COX-2), just like any other COX-2 selective inhibitor.[4]

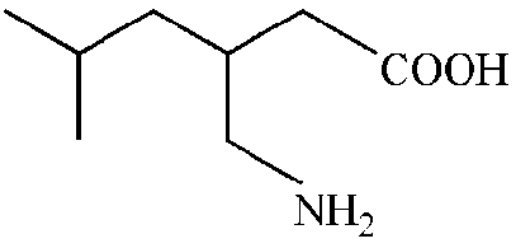

Figure 1: Structure of Pregabalin

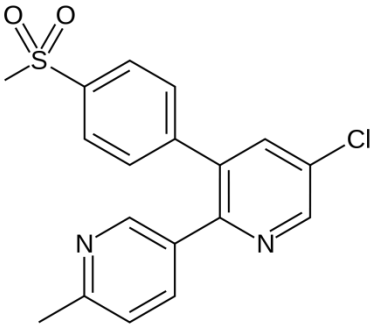

Figure 2: Structure of Etoricoxib

Extensive literature research has unearthed a multitude of recorded analytical procedures, including the discovery of more economically efficient ways. Nevertheless, there is currently few approach for calculating

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stability studies. Hence, a reliable and cost-effective approach is suggested for assessing the stability of Pregabalin, Etoricoxib, and their medicinal dose form using RP-HPLC[5- 9] must be validated and developed as per ICH guidelines

Materials and Methods: Spectrum pharma Research Solution with Pregabalin and Etoricoxib pure drugs (API) gift samples and Combination Pregabalin and Etoricoxib tablets (Toricox Plus). The chemicals and buffers utilized in this estimation were obtained from Rankem, an Indian supplier.

Instrumentation: The development and method validation were conducted using a WATERS HPLC, specifically the model 2695 SYSTEM, equipped with a Photo diode array detector. The system also included an automated sample injector and the Empower 2 software.

Objective: In order to fulfill ICH standards, we need to design and test an HPLC technique that can detect Etoricoxib and Pregabalin in pharmaceutical formulations at the same time.

Table 1: Chromatographic Conditions

Mobile phase	Acetonitrile and 0.01N Ammonium acetate (30:70 v/v)
Flow rate	1 ml/min
Column	Agilent C18 (4.6 x 150mm, 5µm)
Detector wave length	234 nm
Column temperature	30°C
Injection volume	10mL
Run time	5.0 min
Buffer	Ammonium acetate

API Preparation:

Preparation of Standard stock solutions: Accurately Weighed and transferred 7.5 mg of Pregabalin and 6 mg of Etoricoxib working Standards into a 50 ml clean dry volumetric flask, add 3/4th volume of diluent, sonicated for 5 minutes and make up to the final volume with diluents. (150ppm of Pregabalin and 120 ppm of Etoricoxib)

Preparation of Standard working solutions (100% solution): 1ml from the above two stock solutions was taken into a 10ml volumetric flask and made up to 10ml. (15ppm of Pregabalin and 12 ppm of Etoricoxib)

Formulation Preparation:

Preparation of Sample stock solutions: 5 tablets were weighed and the average weight of each tablet was calculated, then the weight equivalent to 1 tablet was transferred into a 100ml volumetric flask, 5 ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters (750µg/ml of Pregabalin and 600 µg/ml of Etoricoxib)

Preparation of Sample working solutions (100% solution): 0.2ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (15ppm of Pregabalin and 12 ppm of Etoricoxib)

System suitability parameters: Pregabalin (15 ppm) and Etoricoxib (12 ppm) standard solutions were prepared, injected six times, and metrics such as peak tailing, resolution, and USP plate count were measured in order to evaluate the system suitability parameters. The region of six standard injection results should have an RSD of no more than 2%.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So, this method was said to be specific.

Table 2: System suitability results

S no	**Pregabalin**				**Etoricoxib**				
Inj	**RT**	**area**	**Plate Count**	**Tailing**	**RT**	**area**	**Plate Count**	**Tailing**	**RS**
1	2.25	508495	11261	1.3	2.812	461163	9954	1.38	5.9
2	2.251	509303	11531	1.32	2.813	461994	9963	1.4	5.9
3	2.252	509222	11625	1.3	2.814	461352	9986	1.41	9
4	2.264	509732	11342	1.31	2.815	460203	9912	1.4	6
5	2.265	510406	11256	1.31	2.815	461378	9975	1.39	6
6	2.266	508473	11653	1.31	2.816	463465	9998	1.4	6
Mean		**509272**				**461593**			
Std ev		**740.7**				**1085.0**			
RSD		**0.1**				**0.2**			

The % RSD for the peak areas of Pregabalin and Etoricoxib obtained from six replicate injections of standard solution was within the limit.

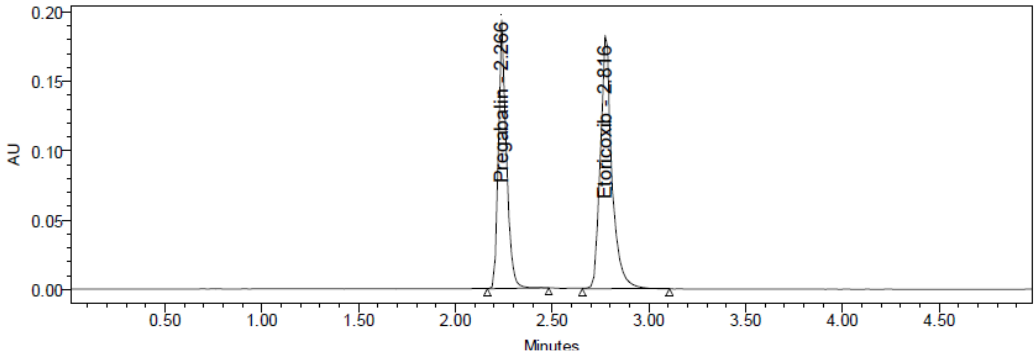

Figure 3: System suitability Chromatogram

Specificity: Checking of the interference in the optimized method. And no interference was observed so, it is specific.

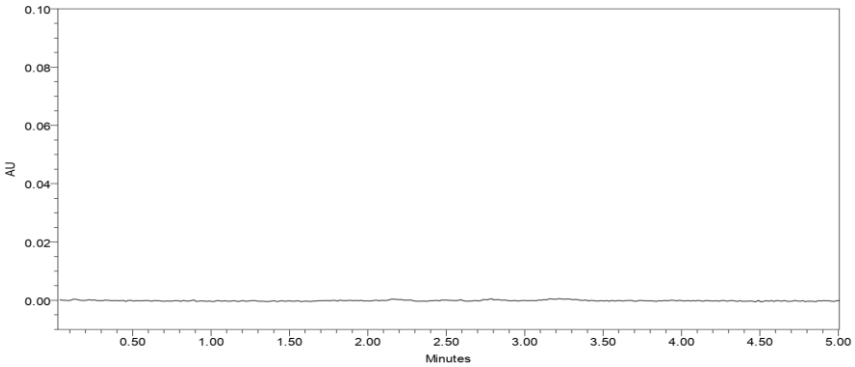

Figure.4 Specificity of Pregabalin and Etoricoxib

Linearity:

Calibration data is given in table and regression data in table and calibration curve in figure.

Table 3: Calibration data of Pregabalin and Etoricoxib

Pregabalin		**Etoricoxib**	
Conc (µg/mL)	**Peak area**	**Conc(µg/mL)**	**Peak area**
0	0	0	0
3.75	126183	3	113423
7.5	253354	6	233456
11.25	391431	9	348379
15	509441	12	463403
18.75	636478	15	560563
22.5	754909	18	678561

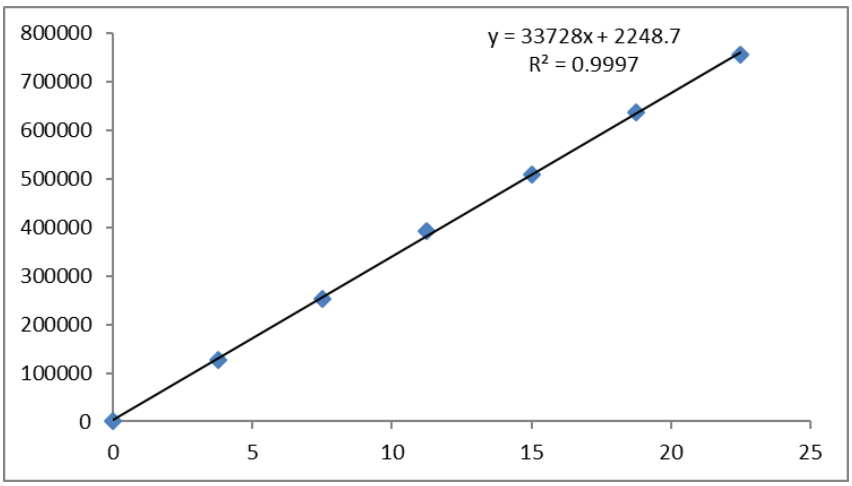

Figure 5 Calibration curve of Pregabalin

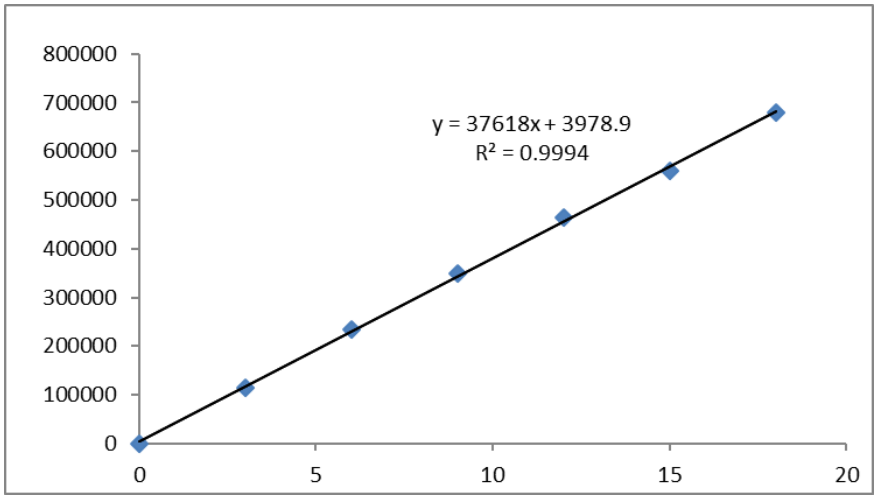

Figure 6 Calibration curve of Etoricoxib

Table 4: regression data

Parameter	Pregabalin	Etoricoxib
Conc range (µg/mL)	3.75 – 22.5	3-18
Regression Equation	y = 33728x + 2248.7	y = 37618x + 3978.9.
Co-relation	0.999	0.999

Accuracy:

Recovery data shown in table

Table 5: recovery data of Pregabalin and Etoricoxib

	Pregabalin			Etoricoxib		
% Level	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**
50%	7.5	7.59	101.24	6	5.97	99.57
		7.56	100.82		5.97	99.49
		7.54	100.57		6	99.96
100%	15	14.96	99.71	12	11.88	99.01
		14.95	99.69		11.89	99.06
		14.96	99.72		11.90	99.21
150%	22.5	22.48	99.90	18	17.97	99.81
		22.37	99.40		17.99	99.97
		22.39	99.50		17.97	99.81
% recovery	100.06			99.54		

Method Precision: The precision of the method was determined by analyzing a sample of Pregabalin and Etoricoxib and shown in table.

Table 6: Method Precision

S. No	Area of Pregabalin	Area of Etoricoxib
1.	508666	460107
2.	509617	460690
3.	505928	464540
4.	506965	466896
5.	509699	462091
6.	503841	462180
Mean	**507453**	**462751**
S.D	**2315.6**	**2544.9**
%RSD	**0.5**	**0.5**

From the above results, the % RSD of method precision study was within the limit for Pregabalin and Etoricoxib.

Robustness: Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.0ml/min), mobile phase minus (40B:60A), mobile phase plus (50B:50A), temperature minus (27°C) and temperature plus(33°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

Table 7: Robustness data for Pregabalin and Etoricoxib.

Parameter	Optimized condition	Used condition	Pregabalin	Etoricoxib
			Obtained %RSD	
Flow rate (±0.1ml/min)	1ml/min	0.9ml/min	0.2	0.4
		1.1 ml/min	0.5	0.2
MP (5%v/v)	60:40	65:35	0.3	0.5
		75:25	0.2	0.8
Column temp. (±3^{0}c)	30^{0}c	27 ^{0}C	0.2	0.6
		33 ^{0}C	0.1	0.3

Sensitivity:

Table 8: Sensitivity of Pregabalin and Etoricoxib

Molecule	LOD	LOQ
Pregabalin	0.03 µg/ml	0.09 µg/ml
Etoricoxib	0.02 µg/ml	0.04 µg/ml

Force Degradation Studies: table shows degradation conditions and table 10 shows the obtained degraded data and chromatogram in figure.

Table 9: degradation conditions

Stress condition	Solvent	Temp(^{0}C)	Exposed time
Acid	2N HCL	60^{0}c	60 mins
Base	2N NAOH	60^{0}c	60 mins
Oxdation	20% H_2O_2	60^{0}c	60 mins
Thermal	Diluent	105^{0}c	6 hours
Photolytic	Diluent	-	-
Hydrolytic	Water	60^{0}c	60 mins

Table 10: Degradation data

Conc of degradation study	Pregabalin		Etoricoxib	
	% drug Undegraded	% drug degraded	% drug Undegraded	% drug degraded
2N HCl, 60 min	93.75	6.25	94.83	5.17
2N NaOH, 60min	96.36	3.64	95.40	4.60
Oxidative, 60 min	94.23	5.77	94.92	5.08
Thermal, 1 hr	99.35	0.65	95.70	4.30
Photo, 6 hr	99.46	0.54	97.26	2.74
Neutral, 1 hr	99.46	0.54	99.72	0.28

Acid degradation chromatogram

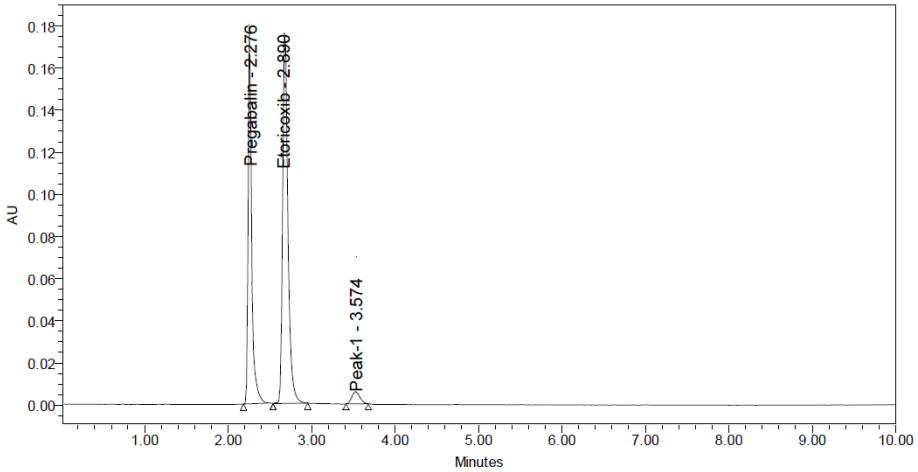

Figure.7 Acid

Base degradation chromatogram

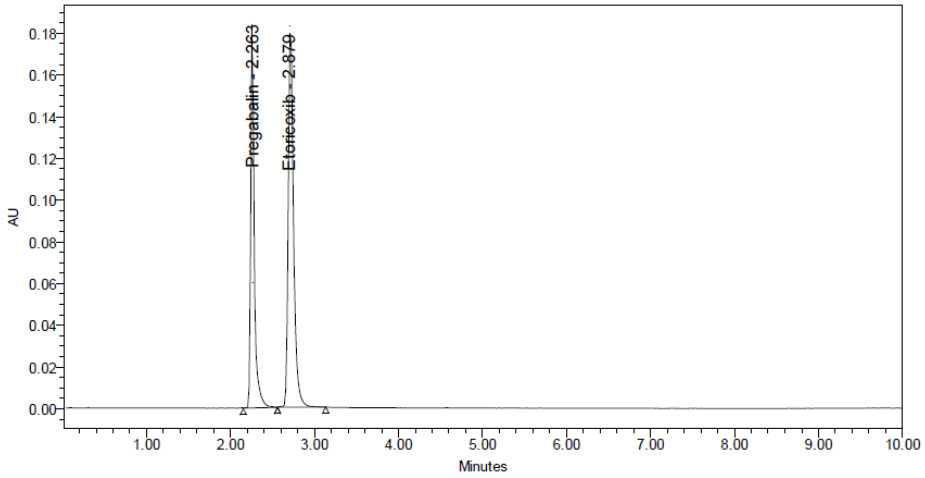

Figure.8 Base

Peroxide degradation chromatogram

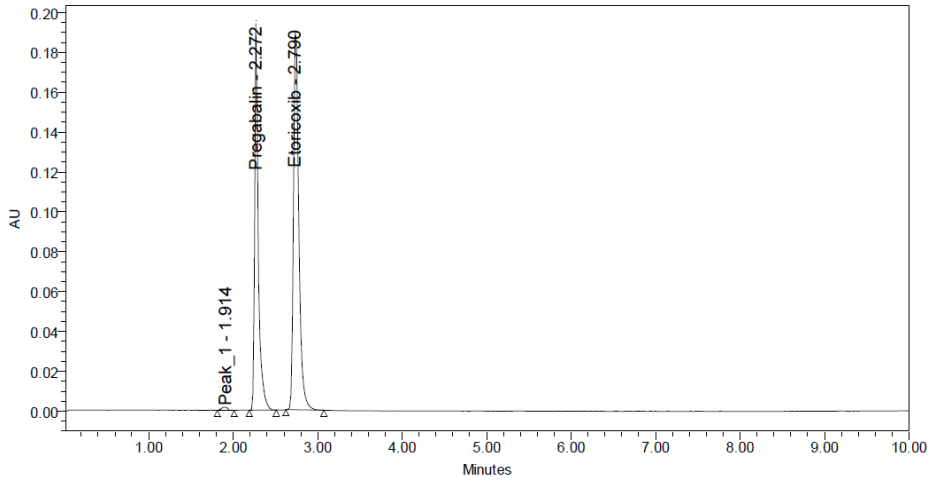

Figure.9 Peroxide

Thermal degradation chromatogram

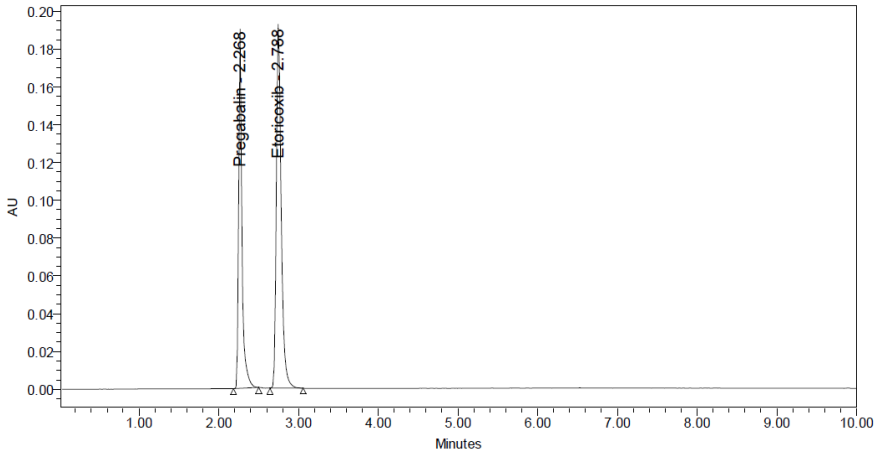

Figure.10 Thermal

UV degradation chromatogram

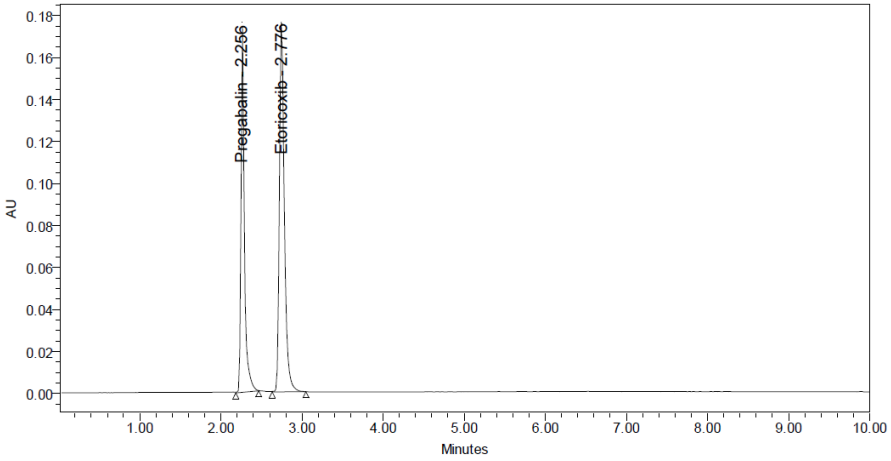

Figure.11 UV

Water degradation chromatogram

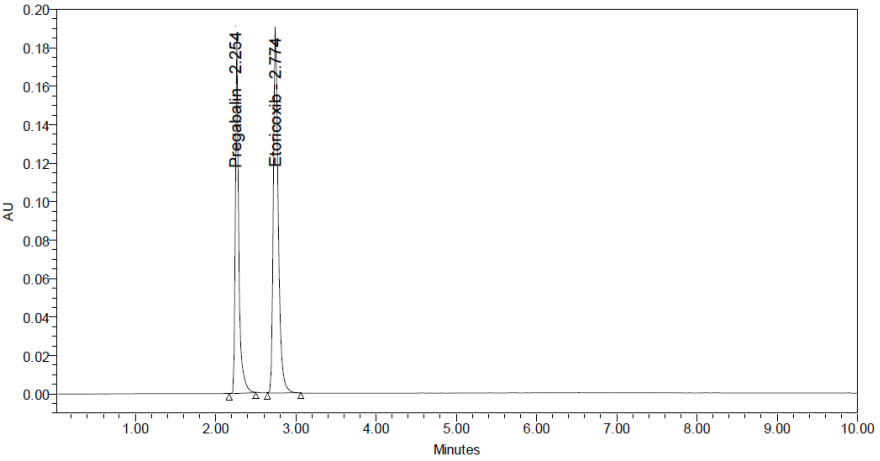

Figure.12 water

Assay: Average % Assay for Pregabalin and Etoricoxib obtained was 99.58% and 99.65% respectively.

Table 11: Assay data

	Pregabalin			**Etoricoxib**		
S.no	**Std Area**	**Sample area**	**% Assay**	**Std Area**	**Sample area**	**% Assay**
1	508495	508666	99.68	461163	460107	99.48
2	509303	509617	99.87	461994	460690	99.60
3	509222	505928	99.14	461352	464540	100.44
4	509732	506965	99.35	460203	466896	100.95
5	510406	509699	99.88	461378	462091	99.91
6	508473	503841	98.74	463465	462180	99.93
Avg	**509272**	**507453**	**99.44**	**461593**	**462751**	**100.05**
Stdev	**740.7**	**2315.6**	**0.45**	**1085.0**	**2544.9**	**0.6**
%RSD	**0.1**	**0.5**	**0.5**	**0.2**	**0.5**	**0.5**

CONCLUSION:

The results of the study will be very useful in assessing the quality of affordable medications that contain pregabalin and etoricoxib. This might be the consequence of the study's simple sample preparation procedure, which called for a short analysis time and minimal mobile phase. The evaluation of two drugs together in a single dosage showed that the newly developed analysis method was nearly full success.

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