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Ultra Performance Liquid Chromatographic Technique for the Estimation of Brivaracetam and it's Stress Degradation Studies

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ABSTRACT:

Purpose: Sophisticated analytical chromatographic methods are important, convenient and relevant for the rapid and accurate determination of drugs and their related compounds in pharmaceutical dosage forms. Ultra performance liquid chromatography one of the fast and accurate liquid chromatographic method adopted in most of the advanced laboratories. The proposed work aims to develop a simple, rapid, sensitive, precise, accurate, economical and validated reverse phase ultra-performance liquid chromatographic (UPLC) method for the estimation of Brivaracetam in pure form and pharmaceutical dosage form.

Materials and Methods: The chromatographic separation was carried out on an Endoversil (50 x 2.1mm, 1.7µm) UPLC Column, a mixture of 0.1% OPA Buffer and Acetonitrile in the ratio of 30:70% v/v was used as a mobile phase. Flow rate of 0.25ml/min, 5µl injection volume, PDA detector with detection wavelength 265 nm was used for the assay. The retention time (RT) of Brivaracetam was found to be 0.523 ± 0.01 min.

Results and Discussion: Brivaracetam was linear with a correlation coefficient value 0.9999 in the concentration range of 6-14%. Specificity, accuracy (% mean recovery, 100.195%), precision, detection limits; robustness (% RSD<2) and system suitability were found to be within limits. Degradation studies were performed under different stressed conditions, and the results of degradation studies reveal that the developed method was stable.

Conclusion: The developed method was simple, reliable, economical and stable and it can be applied for the routine quality control analysis of Brivaracetam in pure form and pharmaceutical dosage form.

INTRODUCTION

The principles of method development of drug substances and formulations which can be applied to new and revised analytical procedures are extensively described in ICH Q14 guidelines. The minimum attributes to be encouraged are selection of appropriate technology and instruments, and defining suitable analytical procedures[1]. The developed analytical method needs to be validated for the standard parameters including accuracy, precission,specificity, detection limit,

quantitation limit, linearity and range[2]. ICH Q1A, Q1B Q2B exemplify the forced degradation studies under stress conditions like light, oxidation, dry heat, acidic and basic hydrolysis etc.[3]. Brivaracetam is an anticonvulsant used for the treatment of partial-onset seizures that functions by binding to synaptic vesicle glycoprotein 2A (SV2A) in the brain. Brivaracetam is an orally bioavailable Levetiracetam derivative, with anticonvulsant activity. Although the exact mechanism through which Brivaracetam exerts its effects is not fully known, this agent targets and binds to synaptic vesicle protein 2A (SV2A) in the brain. This prevents synaptic vesicle exocytosis and the synaptic release of certain, as of yet not fully known, excitatory neurotransmitters. This may inhibit impulse conduction across synapses, decrease neuronal (hyper-) excitability, and may modulate epileptogenesis. SV2A, a membrane glycoprotein present in neuronal synaptic vesicles, plays a key role in action potential-induced neurotransmitter release in the brain. [4] Brivaracetam is a relatively unique anticonvulsant that is typically used in combination with other antiepileptic medications for partial onset seizures. Brivaracetam has been linked to rare instances of serum aminotransferase and alkaline phosphatase elevations during treatment and is suspected of causing rare cases of clinically apparent drug induced liver disease. The IUPAC Name of Brivaracetam is (2S)-2-[(4R)-2-oxo-4-propyl pyrrolidin-1-yl] butanamide. [5] The Chemical Structure of Brivaracetam is following

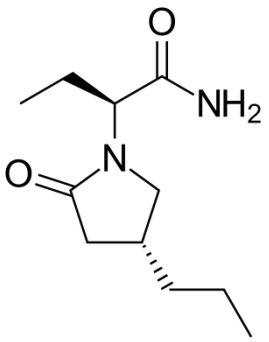

Fig-1: Chemical Structure of Brivaracetam

A survey of literature for the determination of Brivaracetam in pure and formulations revealed that various methods such as UV spectrophotometric, RP-HPLC methods and LC/MS/MS method for determining in rat plasma were available[6-16]. However, some of these methods have certain drawbacks like longer run time, complexity in the composition of the mobile phase, a higher amount of buffer that can affect column performance and elution technique. It affects sensitivity, precision, and accuracy of the method. So, an attempt was made to develop simple, fast and validated UPLC method for the estimation of Brivaracetam in pure and marketed pharmaceutical dosage forms.

MATERIALS AND METHOD

Materials: In the present investigation, UPLC-grade water, UPLC-grade methanol, Ortho phosphoric acid for the study were procured from Merck (India), UPLC grade acetonitrile, from Molychem and Sodium hydroxide and Potassium dihydrogen Phosphate from FINER Chemical Ltd.

Instrumentation: The analysis was performed using UPLC(ACQUITY separation module) equipped with Auto Sampler and PDA with Endoversil (50 x 2.1mm, 1.7µm) UPLC column, data handling system Empower software, UV-Visible double beam Spectrophotometer (LABINDIA UV 3000+), analytical balance(Afcoset ER-200A), Ph METER(Adwa-AD1020).

Preparation of the Brivaracetam Standard & Sample Solution for Analysis:

Standard Solution Preparation: 10 mg of Brivaracetam was accurately weighed and transferred into a 10ml clean dry volumetric flask, diluent was added and sonicate to dissolve it completely and volume was made up to the mark with the diluent. (Stock solution) Further 0.1ml of the above stock solution was pipetted into a 10ml volumetric flask and diluted upto the mark with diluent.

Sample Solution Preparation: Accurately weighed and transferred powder equivalent to 10 mg of Brivaracetam sample was taken into a 10ml clean dry volumetric flask, diluents was added to it and sonicated to dissolve it completely then the volume was made upto the mark with the diluent. 0.1ml of the above solution was pipetted into a 10ml volumetric flask and diluted upto the mark with diluent.

Wave length Selection: UV spectrum of 10µg/ml Brivaracetam in diluents (mobile phase composition) was recorded by scanning in the range of 200nm to 400nm. From the UV spectrum wavelength for maximum absorbance was selected as 265 nm. At this wavelength the drug shows good absorbance.

UV Spectrum:

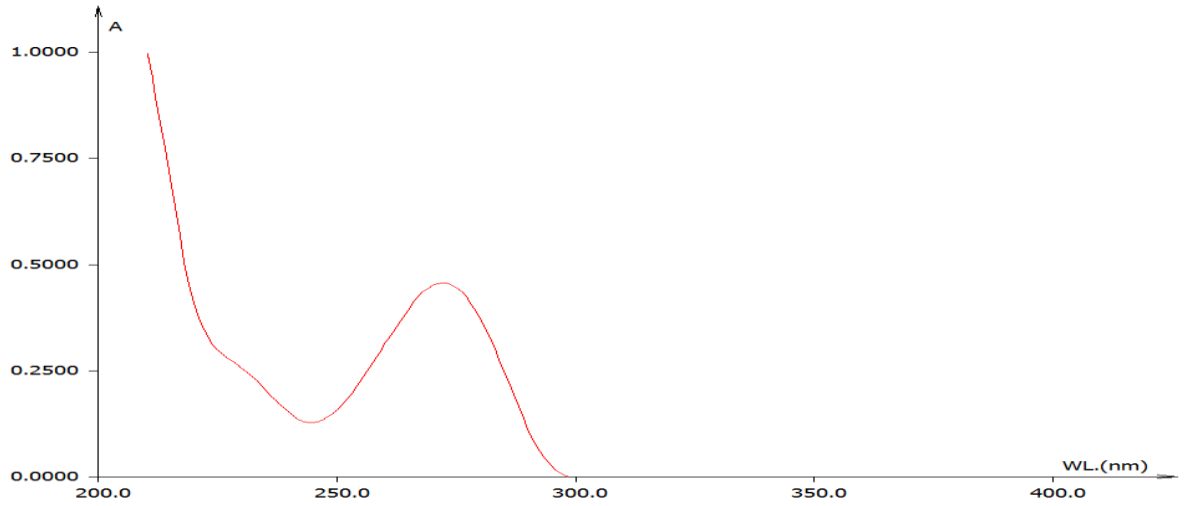

Fig-2: UV Spectrum of Brivaracetam (265nm)

RESULTS AND DISCUSSION

Method Development

Preparation of 0.1% OPA Buffer pH-3: 0.1% OPA buffer solution was prepared by adding 1ml of Ortho phosphoric acid in 1000ml water. The pH of this solution was adjusted to 3 by using Sodium Hydroxide solution.

Preparation of Mobile Phase: A mixture of 0.1% OPA buffer 300 ml (30%) and 700 ml Acetonitrile UPLC (70%) were degased in ultrasonic water bath for 5 minutes and filter through 4.5 µ filter under vacuum filtration.

Diluents Preparation: 0.1% OPA buffer: Acetonitrile (30:70) ratio.

Procedure: 5 µL of the standard, sample were injected into the chromatographic system and the corresponding areas for the Brivaracetam peaks were measured and retention time recorded.

Summary of Optimized Chromatographic Conditions:

Equipment	: Ultra performance liquid chromatography equipped with Auto Sampler and PDA detector
Column	: Endoversil (50 x 2.1mm, 1.7µm) UPLC COLUMN
Mobile phase ratio	: 0.1% OPA Buffer: Acetonitrile (30:70% v/v)
Detection wavelength	: 265 nm
Flow rate	: 0.25ml/min
Injection volume	: 5µl
Run time	: 3min

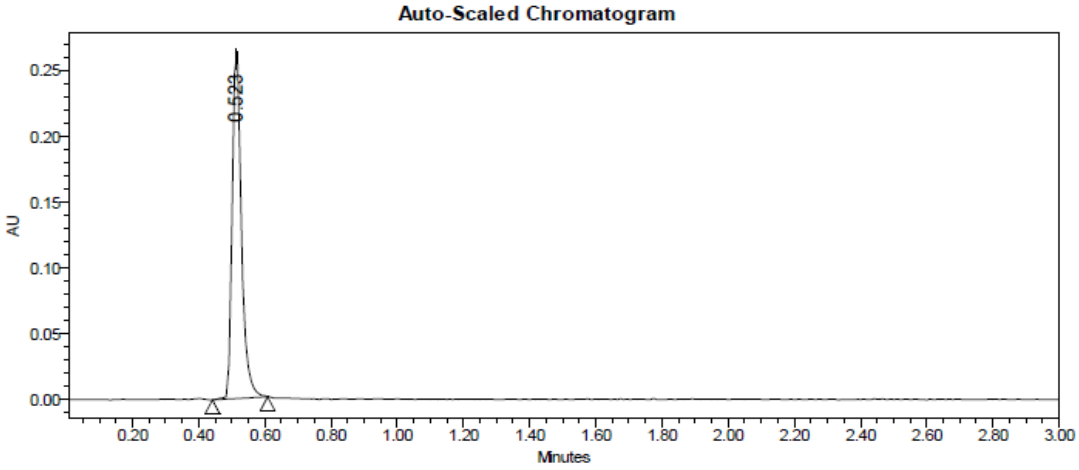

Fig-3: Optimized Chromatogram of Brivaracetam

Method Validation

The proposed methods were validated in accordance to ICH Q2(R1) guideline for precision, accuracy, linearity, robustness, limit of detection and limit of quantification.

System Suitability:

System suitability is generally performed to check whether the developed method suits the intended purpose or not. It can be demonstrated by injecting six replicates of standard stock solutions into UPLC system.

- ✓ Tailing factor for the peaks due to Brivaracetam in Standard solution should not be more than 2.0.
- ✓ Theoretical plates for the Brivaracetam peaks in Standard solution should not be less than 2000.

Table-1: Results of System Suitability for Brivaracetam

Sl. No.	Peak Name	RT (min)	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Brivaracetam	0.519	515867	275841	3652.48	1.36
2	Brivaracetam	0.521	516854	275486	3568.75	1.38
3	Brivaracetam	0.517	515752	275864	3695.49	1.37
4	Brivaracetam	0.521	514986	275684	3745.28	1.39
5	Brivaracetam	0.520	515874	275468	3865.42	1.34
6	Brivaracetam	0.518	516423	275649	3598.47	1.36
Mean			515959.3			
Std. Dev.			635.8596			
% RSD			0.123238			

Precision:

Preparation of stock solution:

10 mg of Brivaracetam was accurately weighed and transferred into a 10ml clean dry volumetric flask, diluents was added to this and sonicated to dissolve it completely. The volume was made upto the mark with the diluent. (Stock solution) 0.1ml of the above solution was pipetted into a 10ml volumetric flask and diluted upto the mark with diluent.

Procedure:

The standard solution was injected for six times and measured the area for all six injections in UPLC. The %RSD for the area of Six replicate injections was found to be within the specified limits. The results are summarized below for Brivaracetam.

Table-2: Results of Repeatability for Brivaracetam

Sl. No.	Peak name	Retention time	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Brivaracetam	0.520	516854	273564	3568.69	1.39
2	Brivaracetam	0.525	514857	274865	3685.47	1.35
3	Brivaracetam	0.521	515863	274981	3598.78	1.37
4	Brivaracetam	0.519	516985	278685	3659.84	1.34
5	Brivaracetam	0.522	514256	279863	3785.24	3.36
6	Brivaracetam	0.520	517854	275258	3692.41	3.38
Mean			516111.5			
Std. Dev			1373.246			
%RSD			0.27			

Intermediate Precision/Ruggedness:

Preparation of stock solution

10 mg of Brivaracetam was accurately weighed and transferred into a 10ml clean dry volumetric flask, diluents was added to this and sonicated to dissolve it completely. The volume was made upto the mark with the diluent. (Stock solution) 0.1ml of the above solution was pipetted into a 10ml volumetric flask and diluted upto the mark with diluent.

To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on three consecutive days by using different make column of same dimensions.

Procedure: The standard solution was injected for six times and measured the area for all six injections in UPLC. The % RSD for the area of six replicate injections was found to be within the specified limits.

Table-3: Results of Intermediate precision for Brivaracetam

Sl.No.	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Brivaracetam	0.523	518659	278543	3658.75	1.39
2	Brivaracetam	0.521	518696	275465	3768.45	1.38

3	Brivaracetam	0.524	519632	278564	3898.38	1.34
4	Brivaracetam	0.519	518748	274584	3785.96	1.38
5	Brivaracetam	0.522	519865	274869	3648.74	1.37
6	Brivaracetam	0.523	518523	273542	3895.24	1.36
Mean			519020.5			
Std. Dev.			573.5604			
% RSD			0.11			

Acceptance Criteria: The % RSD for the area of six standard injections results should not be more than 2%.

Accuracy:

The accuracy of the method was determined by calculating the recoveries of Brivaracetam using spike method. Known quantities of sample solutions corresponding to 80%, 100% and 120% of the lable claim were added to pre quantified standard solution and the amount of Brivaracetam was estimated by calculating the amount found and amount added for Brivaracetam from peak areas and regression equation of the calibration curve.

Table-4: The accuracy results for Brivaracetam

Sample ID	**Concentration (mg/ml)**			**% Recovery of**	**Statistical Analysis**
	Amount Added	**Amount Found**	**Peak Area**	**Pure drug**	
S1 : 80%	8	7.943	421867	99.292	Mean = 99.18
S2 : 80%	8	7.94	421685	99.248	S.D. = 0.15
S3 : 80%	8	7.921	420689	99.008	% R.S.D. = 0.15
S4 : 100%	10	9.987	527868	99.866	Mean = 99.93
S5 : 100%	10	10.002	528679	100.022	S.D. = 0.084
S6 : 100%	10	9.989	527989	99.889	% R.S.D.= 0.084
S7 : 120%	12	12.024	633574	100.201	Mean = 99.96
S8 : 120%	12	12.005	632589	100.043	S.D. = 0.31
S9 : 120%	12	11.953	629898	99.611	% R.S.D. = 0.31

Acceptance Criteria: The % Recovery for each level should be between 98.0 to 102.0%.

Linearity:

10 mg of Brivaracetam was accurately weighed and taken into a 10ml clean dry volumetric flask diluent was added and sonicate to dissolve it completely and the volume was made upto the mark with the diluent. (Stock solution)

Further pipette 0.1ml of Brivaracetam of the above stock solution into a 10ml volumetric flask and dilute upto the mark with

diluent.

Preparation of stock solution:

Accurately weighed and transferred 10 mg of Brivaracetam is taken into a 10ml clean dry volumetric flask, diluent was added and sonicate to dissolve it completely and volume was made upto the mark with the diluent. (Stock solution)

Preparation of Level – I (6ppm of Brivaracetam):

0.06 ml of stock solution was taken in 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of Level – II (8ppm of Brivaracetam):

0.08 ml of stock solution was taken in 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of Level – III (10ppm of Brivaracetam):

0.1 ml of stock solution was taken in 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of Level – IV (12ppm of Brivaracetam):

0.12 ml of stock solution was taken in 10ml of volumetric flask diluted up to the mark with diluent.

Preparation of Level – V (14ppm of Brivaracetam):

0.14 ml of stock solution was taken in 10ml of volumetric flask diluted up to the mark with diluent.

Procedure: Injected each level into the chromatographic system and measured the peak area. Plotted a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculated the correlation coefficient.

Table-5: Linearity Results: (for Brivaracetam)

S. No.	Linearity Level	Concentration	Area
1	I	6	323566
2	II	8	421274
3	III	10	528589
4	IV	12	632787
5	V	14	736598
Correlation Coefficient			0.9998

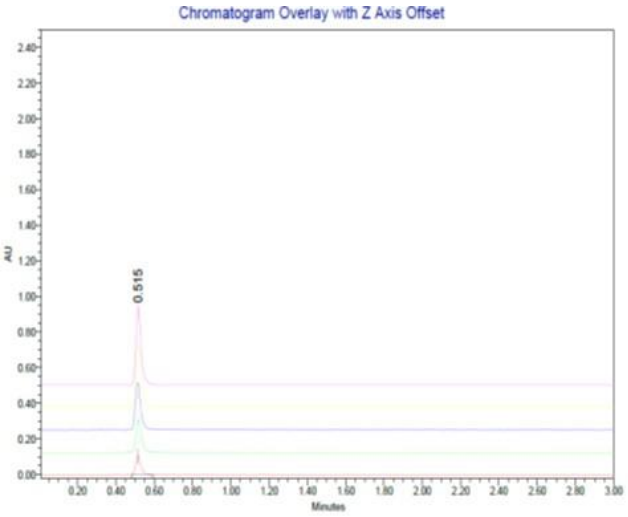

Figure-4: Linearity overlay Report

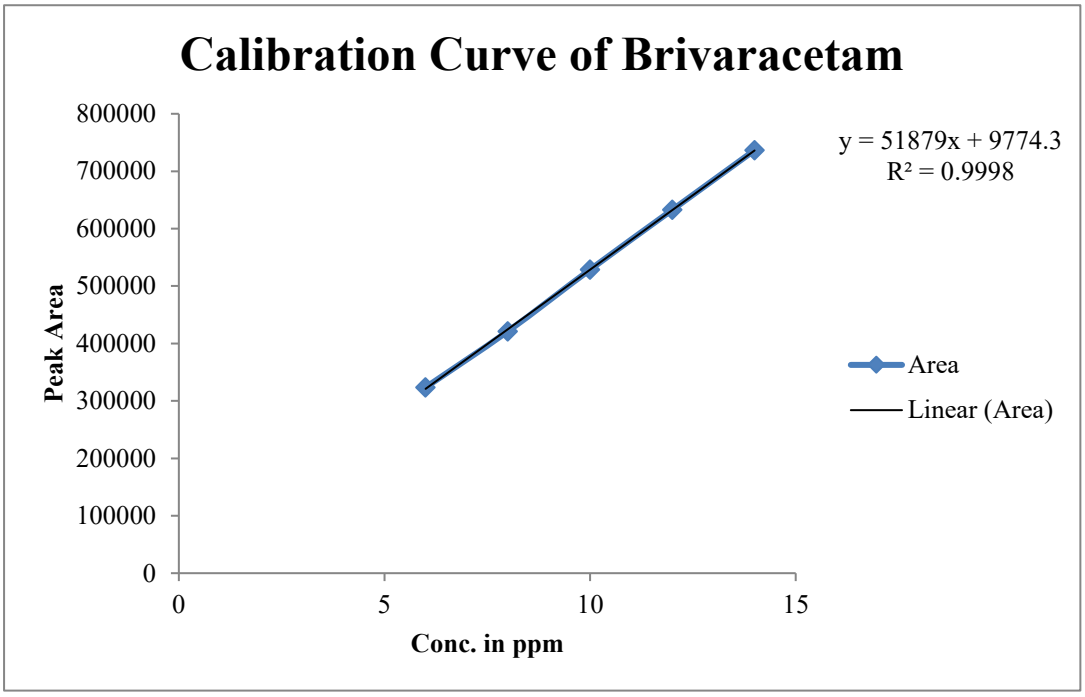

Fig 5: Calibration Curve of Brivaracetam

Acceptance Criteria: Correlation coefficient should be not less than 0.9998

Robustness:

As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition Temperature Variation was made to evaluate the impact on the method.

a). The flow rate was varied at 0.225 ml/min to 0.275 ml/min.

Standard solution 10 ppm of Brivaracetam prepared and analysed using the varied flow rates along with method flow rate.

On evaluation of the above results, it can be concluded that the variation in flow rate affected the method significantly. Hence it indicates that the method is robust even by change in the flow rate ±10%.

The method is robust only in less flow condition.

Table-6: System suitability results for Brivaracetam

S. No.	Flow Rate (ml/min)	System Suitability Results	
		USP Plate Count	USP Tailing
1	0.225	3862.95	1.48
2	0.25	3352.58	1.23
3	0.275	3373.58	1.11

b). The Organic composition in the Mobile phase was varied from 60% to 80%

Standard solution 10µg/ml of Brivaracetam was prepared and analysed using the varied Mobile phase composition along with the actual mobile phase composition in the method.

The results are summarized

On evaluation of the above results, it can be concluded that the variation in 10% Organic composition in the mobile phase

affected the method significantly. Hence it indicates that the method is robust even by change in the Mobile phase ± 10.

Table-7: System suitability results for Brivaracetam

S.No.	Change in Organic Composition in the Mobile Phase	System Suitability Results	
		USP Plate Count	USP Tailing
1	10% less	4284.43	1.53
2	*Actual	3352.58	1.23
3	10% more	3174.59	1.04

LOD and LOQ:

LOD: The detection limit[24] 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.

$$\mathbf{LOD = 3.3 \times \sigma / s}$$

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Observation: On the evaluation of above results the LOD and LOQ for the Brivaracetam was found to be 0.5853 µg/ml and 1.7738µg/ml respectively.

Assay of Marketed Formulation:

Twenty Tablets were taken and the I.P. method was followed to determine the average weight. Above weighed tablets were finally powdered and triturated well. A quantity of powder equivalent to 25 mg of drugs were transferred to 25 ml volumetric flask, make and solution was sonicated for 15 minutes, there after volume was made up to 25 ml with same solvent. Then 10 ml of the above solution was diluted to 100 ml with mobile phase. The solution was filtered through a membrane filter (0.45 µm) and sonicated to degas. The solution prepared was injected in five replicates into the HPLC system and the observations were recorded.

Assay % =

$$\frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{100} \times \text{Avg. Wt} = \text{mg}$$

Where:

AT = Peak Area of drug obtained with test preparation

AS = Peak Area of drug obtained with standard preparation

WS = Weight of working standard taken in mg

WT = Weight of sample taken in mg

DS = Dilution of Standard solution

DT = Dilution of sample solution

P = Percentage purity of working standard

Brand Name of Tablet	Labelled Amount of Drug (mg)	Mean Amount (mg) (± SD) found by the Proposed Method (n=6)	Mean %Assay (± SD) (n = 6)
Brevipil 25 Tablet	25	24.698 (± 0.574)	99.97 (± 0.825)

RESULT & DISCUSSION:

The %Purity of Marketed Formulation of Brivaracetam was found to be 99.97%.

FORCED DEGRADATION STUDIES:

The International Conference on Harmonization (ICH) guideline entitled stability testing of new drug substances and products requires that stress testing to be carried out to elucidate the inherent stability characteristics of the active substance. The aim of this work was to perform the stress degradation studies on the Brivaracetam using the proposed method.

Preparation of Stock Solution: Accurately weighed 10 Tablets crushed in mortor and pestle and transfered equivalent to 10 mg of Brivaracetam in sample into a 10mL clean dry volumetric flask add about 7 mL of Diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution).

1.Hydrolytic Degradation under Acidic Condition:

Pipetted 0.1ml of above solution into a 10ml volumetric flask and 1ml of 0.1N HCl was added. Then, the volumetric flask was kept for 24 hours and then neutralized with 0.1 N NaOH and made up to 10ml with diluent. Filter the solution with 0.45 microns syringe filters and placed in vials.

2. Hydrolytic Degradation under Alkaline Condition:

Pipetted 0.1ml of above solution into a 10ml volumetric and 1ml of 0.1N NaOH was added in 10ml of volumetric flask. Then, the volumetric flask was kept for 24 hours and then neutralized with 0.1N HCl and made up to 10ml with diluent. Filtered the solution with 0.45 microns syringe filters and placed in vials.

3. Oxidative Degradation

Pipetted 0.1ml above stock solution into a 10ml volumetric flask and 1ml of 30% w/v of hydrogen peroxide was added in 10 ml of volumetric flask and the volume was made up to the mark with diluent. The volumetric flask was then kept at room temperature for 24 hours. Filtered the solution with 0.45 microns syringe filters and placed in vials.

4. Thermal induced Degradation

Brivaracetam sample was kept in Hot air oven at 110^0 C for 24 hours. Then the sample was taken and diluted with diluents upto 10ppm and injected into UPLC and analyzed.

5. Photolytic Degradation:

Brivaracetam sample was exposed to sunlight for 24hrs. Then the sample was taken and diluted to 10ppm with diluent, filtered the solution with 0.45 micron syringe, injected into UPLC and analysed.

Table-8: Results of Degradation Studies

Sample Name	Brivaracetam	
	Area	**% Degraded**
Standard	511519	0.000
Acid	496859	2.866

Base	495047	3.221
Peroxide	499327	2.384
Thermal	490258	4.157
Photo	509289	0.436

CONCLUSION

This developed Ultra Performance Liquid Chromatographic method was validated according to ICH guidelines in terms of linearity, precision, accuracy, and repeatability and stress stability studies. All validation parameters were found to be within the acceptable limit according to ICH guidelines. The developed method with a retention time of 0.523±0.01 min was successfully applied for the estimation of Brivaracetam in pure form and selected commercial formulation. Here we conclude that the developed UPLC method is precise, accurate, sensitive, and reproducible for the quantitative estimation of Brivaracetam bulk and its marketed formulations. The developed method can be used by the pharmaceutical industries for the routine analysis of Brivaracetam. Further the same method can be extended for analysis of drug and their metabolites in the biological fluids. In future if degradation products are isolated and their structure illucidated by advance techniques it could provide the insight of route of metabolism and degradation pathways.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

The proposed research investigation was carried out under the supervision of U S Mishra, he also conceived and designed the research work. B Behera conducted the experiments. S K Sahoo contributed to the analytical tools and data analysis of the experimental work. B Behera and S K Sahoo skillfully drafted the manuscript. All authors reviewed the final manuscript and provided necessary corrections.

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DECLARATION

The manuscript is not under consideration for publication in any journal. On behalf of all co-authors, I shall bear full responsibility of the manuscript.

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