RESEARCH PAPER

A STABILITY-INDICATING ULTRA-PERFORMANCE LIQUID CHROMATOGRAPHY–MASS SPECTROMETRY METHOD FOR BRIVARACETAM: DEVELOPMENT, VALIDATION, AND FORCED DEGRADATION STUDY

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ABSTRACT
Brivaracetam is a third-generation antiepileptic drug used for the treatment of partial-onset seizures. Reliable analytical methods are essential to ensure the quality, safety, and efficacy of pharmaceutical formulations.
This study describes the development and validation of a rapid, sensitive, and stability-indicating UPLC-MS method for the quantitative estimation of brivaracetam in pharmaceutical dosage forms. Chromatographic separation was achieved on a Waters Acquity H-Class Plus UPLC system using an Acquity UPLC C18 column (2.1 × 100 mm, 1.7 µm) with a gradient mobile phase of 0.1% formic acid and acetonitrile at a flow rate of 0.3 mL/min.
Brivaracetam produced a sharp, symmetrical peak with a retention time of 4.72 min. The method was validated according to ICH Q2 (R1) guidelines for system suitability, specificity, linearity, accuracy, precision, robustness, LOD, and LOQ. Excellent linearity was obtained over the concentration range of 250–450 µg/mL ($R^2 = 0.9991$), with a mean recovery of 100.55%. The LOD and LOQ were 0.13 µg/mL and 0.40 µg/mL, respectively.
Forced degradation studies under acidic, alkaline, oxidative, and thermal stress conditions confirmed the stability-indicating capability of the method. The validated UPLC-MS method is suitable for routine quality control and stability analysis of brivaracetam in pharmaceutical dosage forms.

KEYWORDS: Brivaracetam,Ultra-Performance Liquid Chromatography–Mass Spectrometry, Method Development, Method validation, Forced degradation
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INTRODUCTION

EPILEPSY is a chronic neurological disorder affecting approximately 70 million people globally, with an annual incidence of 80 per 100,000 and a prevalence of 5–10 per 1,000 individuals.[1]It is characterized by sudden abnormal electrical activity in the brain, leading to seizures, convulsions, or loss of consciousness.[2]

Inside the intensive care unit (ICU), acute seizures appear as a common event. These acute seizures happen because the person had a main cause for entry into the hospital or because a severe metabolic disorder created a neurologic complication. Medical professionals claim that acute seizures appear when the body is in a critical illness state. Identification of acute seizures must happen quickly. Since these events cause harm, acute seizures are managed immediately with a fast-acting antiepileptic drug (AED). Potential negative results are reduced by the use of this medicine. Ischemic and excitotoxic neuronal cell loss is prevented through fast treatment, which is necessary since brain damage begins within minutes while the seizure activity is continuing.[3]

Brain excitability mechanisms are modified by current antiepileptic drugs (AEDs) through the obstruction of sodium channels including phenytoin, carbamazepine, and lamotrigine, or by increasing GABA transmission through barbiturates and benzodiazepines. Despite the availability of several antiepileptic drugs, approximately one-third of patients continue to experience uncontrolled seizures.Because current antiepileptic drugs (AEDs) do not help everyone, the existence of a strong requirement for fresh therapeutic choices is observed by medical professionals.[4]

Recognition has been granted to Brivaracetam (BRV; Briviact) as a fresh antiepileptic drug (AED) for the supplementary management of focal (partial-onset) seizures in mature individuals. Experts claim that Brivaracetam (BRV; Briviact) possesses a high level of fat-dissolving ability which allows for fast movement into the brain

tissue. Connection with the target molecule, SV2A, is achieved by Brivaracetam (BRV; Briviact) within a very short duration of minutes after the medicine is provided to the person.[5]The chemical structure of brivaracetam is shown in Figure 1.

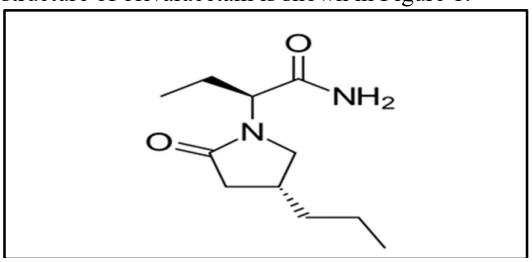

Figure 1: Chemical structure of Brivaracetam (BRV)[6]

Drug Profile of Brivaracetam[7-12]

Attributes	Description
Name	Brivaracetam
Category	Antiepileptic drug (AED) / Anticonvulsant
Molecular Formula	C11H20N2O2
Molecular Weight	212.29 g/mol
IUPAC and Chemical Name	(2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl] butanamide
Melting Point	72 to 77 °C (162 to 171 °F)
Solubility	Freely soluble in water, Soluble in methanol and ethanol, freely soluble in acetonitrile and acetone, Soluble in buffer solutions of pH 1.2, 4.5, and 7.4
Route of Administration	Oral, intravenous
Storage	Store at controlled room temperature (20–25°C)

Table 1: Drug Profile of Brivaracetam Drug

The drug profile of brivaracetam is presented in Table 1.Liquid Chromatography–Mass Spectrometry (LC–MS) is a powerful hyphenated technique that couples' liquid chromatography for the separation of complex mixtures with mass spectrometry for the accurate identification of components, enabling comprehensive and reliable analysis.[13]

Ultra Performance Liquid Chromatography (UPLC) is an advanced version of High-Performance Liquid Chromatography (HPLC) providing higher resolution, faster analysis and increased sensitivity. According to the Van Deemter principle, the use of columns with very small particle size (<2.5 µm) enhances the separation efficiency. Also, smaller particles result in faster analysis times and less solvent consumption. Therefore, the performance of UPLC is much better than conventional HPLC.[14-15]

Sr. No.	Title	Column/stationary phase	Mobile phase	Flow rate	Detection	Linear range
1	A validated lc-ms/ms method for pharmacokinetic study of brivaracetam in healthy rabbits	Chromolith c18 (100 x 4.6 mm, 5 µm	0.1% formic acid (ph 3.2) isocratic	1.0 ml/min	Mrm (esi negative) : m/z 213.0/168.0	0.16-8 µg/ml[16]
2	LC–ESI-MS Characterization of Degradents of Brivaracetam; Development and Validation of a Stability-Indicating RP-	Hi-Q silic-18 (250 x 4.6 mm, 5 µm)	Isocratic (not detailed)	1 ml/min	LC-ESI-MS	Stability-indicating[5]

	HPLC Method					
3	Development of bioanalytical method and validation for quantification of brivaracetam in human plasma by rp-hplc : research article	C18 (details in pdf)	Methanol: 0.1% formic acid (80:20)	0.8 ml/min	Esi-ms/ms positive	5-500 ng/ml[17]
4	Development and validation of an uhplc-ms/ms assay for therapeutic monitoring of brivaracetam plasma concentrations in patients with epilepsy	Synergi fusion (details not specified)	0.1% formic acid in water/acetonitrile gradient	0.3 ml/min	Ms/ms (esi)	0.10-10 µg/ml (lloq 0.10 µg/ml)[18]

Table 2: Comparative review of previously reported analytical methods for the estimation of brivaracetam.

Previously reported analytical methods for the estimation of brivaracetam are summarized in Table 2.Several analytical methods have been reported for the determination of brivaracetam, but there is a need of a rapid, sensitive and stability indicating method suitable for routine quality control analysis of pharmaceutical formulations. UPLC-MSis providing better sensitivity, selectivity and shorter analysis time which is an important tool for pharmaceutical analysis. Hence, the current work was carried out to develop and validate a simple, accurate, precise and robust UPLC-MSmethod for the quantitative estimation of brivaracetam in pharmaceutical dosage forms as per the ICH guidelines. Forced degradation studies were performed to assess the stability indicating property of the developed method.

MATERIALS AND METHODS

Chemicals & Reagent: Brivaracetam (API & tablets), Formic acid LC-MS grade, Acetonitrile LC-MS grade , Water-Mili Q, Ammonium acetate LC-MS grade, Methanol LC-MS grade,

Instrumentation: Ultra-performance liquid chromatograph (Waters Acquity H-Class Plus UPLC) equipped with an autosampler and controlled by MassLynx software was used for the analysis. Chromatographic separation was carried out using an Acquity UPLC C18 column (2.1 mm × 100 mm, 1.7 µm).The optimized chromatographic conditions used for the developed method are presented in Table 3.

Chromatographic conditions:

Sr No	SPECIFICATIONS	Description
	Equipment	Waters Acquity H Class Plus UPLC
	Software	MassLynx
	Column	Acquity UPLC CHS C18 1.7µm
	Dimensions	1.7 µm (2.1× 100 mm)
	Mobile phase	Line A: 0.1% FA(Formic Acid) Line B: 100% ACN(Acetonitrile)
	Stationary Phase	C18 Column
	Elution method	Gradient
	Injection Volume	10 µL
	Flow rate	0.3 ml/min
	Retention Time	4.72 min

	Autosampler Temperature	5°C
	Column Temperature	30°C
	Run Time	10 Minutes
	Detection Wavelength	Diode array (190 nm to 800nm)
	Diluent	ACN:H20 & 0.1% FA

Table 3: Chromatographic conditionsdata

Time	Flow	%A: 0.1%FA	%B:100%ACN
1.0	0.300	90.0	10.0
2.0	0.300	90.0	10.0
3.0	0.300	85.0	15.0
4.0	0.300	30.0	70.0
5.0	0.300	10.0	90.0
6.0	0.300	10.0	90.0
7.0	0.300	90.0	10.0

Table 4: Gradient elution program for the developed UPLC-MS method Preparation of Solution

The gradient elution program used for chromatographic separation is presented in Table 4.

Preparation of Diluent

The diluent was prepared by mixing 0.1% Formic acid buffer with Acetonitrile & Water (ACN:H2O) in equal proportion (50:50, v/v). The mixture was prepared freshly and used for the preparation of standard and sample solutions.

Preparation of Standard Stock Solution

A standard stock solution of **Brivaracetam**(1000 ppm or 1000µg/ml) was prepared by accurately weighing 100 mg of brivaracetam API and transferring it into a 100 mL volumetric flask. After complete dissolution, the solution was diluted with the prepared diluent and mixed properly (sonicated) to obtain a homogeneous solution.

Working Standard Solutions

From the 1000 µg/mL stock solution, 1 mL was pipetted into a 10 mL volumetric flask and diluted up to the mark with the diluent to obtain a **100 µg/mL working solution**. Further dilutions were prepared from this working solution using the same diluent to achieve the required concentrations of brivaracetam for validation and analysis. All solutions were mixed thoroughly before use.

Preparation of Tablet Powder Solution

The weighed tablets of brivaracetam were ground to a powder in a mortar and pestle to obtain a homogenous mixture. A quantity of tablet powder equivalent to 100 mg of brivaracetam was accurately weighed and transferred into 100 mL volumetric flask followed by addition of diluent. The solution was sonicated for 10-15 min for complete extraction of the drug from the tablet powder. The prepared solution was filtered through 0.45 µm membrane filter and diluted with diluents before use.

Solubility Determination:

The solubility of Brivaracetam was determined in different solvents. The solubility profile of brivaracetam in the evaluated solvents is presented in Table 5.

Sr. No.	Solvent	Procedure
1.	Water	Excess drug added to 10 mL water; stirred for 24 h at 25 ± 2°C; filtered through 0.22 µm membrane
2.	100% Methanol	Excess drug added to 10 mL methanol; stirred for 24 h at 25 ± 2°C; filtered through 0.22 µm membrane
3.	100% Acetonitrile	Excess drug added to 10 mL acetonitrile; stirred for 24 h at 25 ± 2°C; filtered through 0.22 µm membrane
4.	Acetonitrile: Formic acid	Excess drug added to 10 mL buffer; stirred for 24 h at 25 ± 2°C; filtered through 0.22 µm membrane
5.	Methanol: Formic acid	Excess drug added to 10 mL buffer; stirred for 24 h at 25 ± 2°C; filtered through 0.22 µm membrane
6.	Acetonitrile: Ammonium acid	Excess drug added to 10 mL buffer; stirred for 24 h at 25 ± 2°C; filtered through 0.22 µm membrane

Table 5: Solubility profile of Brivaracetam in different solvents evaluated during preformulation studies.

Method Validation:

Validation of the method is carried out as per ICH guidelines for the following parameters such as system Suitability, linearity, specificity, precision, accuracy, limit of detection, limit of quantification and robustness.

RESULTS AND DISCUSSION

Pre-formulation studies were carried out to evaluate the suitability of the drug for analysis. The drug was found to be **soluble in organic solvents such as formic acid, acetonitrile, and methanol**,which were selected for further studies. The solubility behaviour aided in the selection of appropriate diluent and mobile phase for chromatographic analysis.

Method Development

The chromatographic conditions were optimized to achieve a sharp, symmetrical and well-resolved peak for brivaracetam in short analysis time. During the method development, various

parameters like mobile phase composition, column type, flow rate and detection settings were assessed. The final optimized conditions gave satisfactory peak shape, good reproducibility and acceptable retention time of 4.72 min.The standard chromatogram of brivaracetam showing a retention time of 4.72 min is presented in Figure 2.

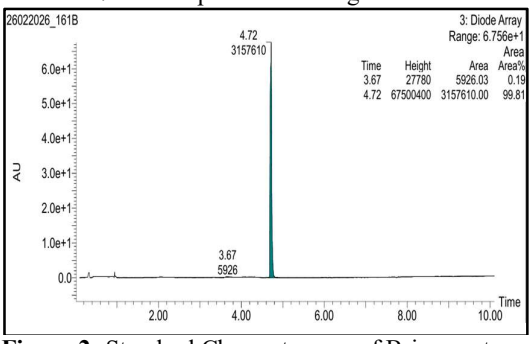

Figure 2: Standard Chromatogram of Brivaracetam Chromatogram of BRV showing a retention time of 4.72 min (X-axis: time; Y-axis: response) is depicted in figure 2.

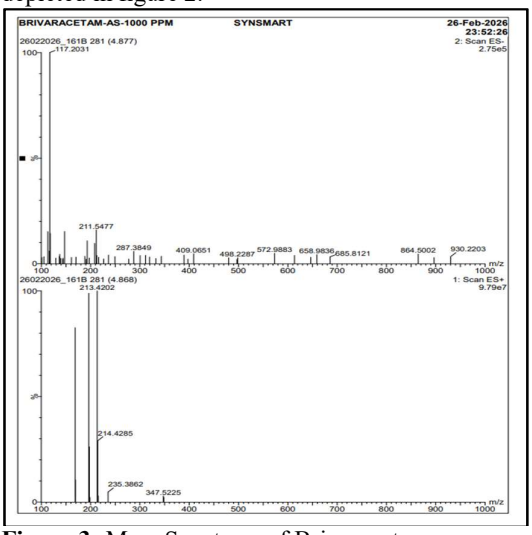

Figure 3: Mass Spectrum of Brivaracetam

LC–MS spectrum of BRV showing ionization in both positive electrospray (+ES) and negative electrospray (–ES) modes, with the corresponding molecular ion mass displayed in figure 3.

Analytical Method Validation:

1. System suitability

System suitability was evaluated by injecting five replicate injections of brivaracetam standard solution (400 µg/mL) under the optimized chromatographic conditions. The results of the system suitability study are presented in Table 6.

Parameter	Result	Acceptance Criteria
Mean Peak Area	1889069.23	--
Standard Deviation	168.20	--
%RSD of Peak Area	0.009%	NMT 2.0%
Theoretical Plates (N)	21579.25	N > 2000
Retention Time (min)	4.72	Consistent retention time

Table 6: Demonstrates theresults of System Suitability

2. Linearity

The method showed good linearity over the concentration range of 250–450 µg/mL. The calibration curve exhibited a correlation coefficient of 0.9991, which indicates a strong linear relationship between concentration and response. This confirms that the method is suitable for quantitative analysis of brivaracetam within the selected range.

Concentration (µg/mL)	Area
250	1269470.25
300	1469013.63
350	1666777.00
400	1889291.25
450	2113004.75

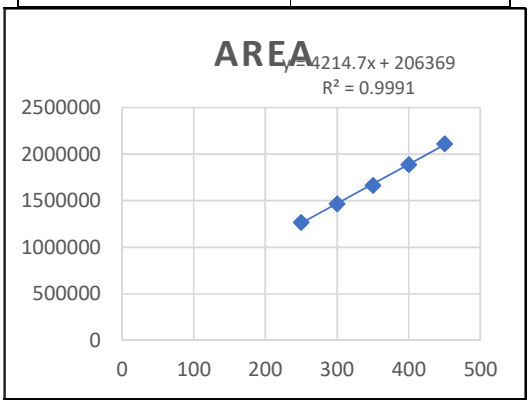

Figure 4: Calibration curve of Brivaracetam showing linearity over the concentration range of 250–450 µg/mL (R^2 = 0.9991).

Acceptance criteria: Correlation coefficient,R≥0.999.

3. Accuracy (Recovery Studies)

Accuracy of the method was evaluated by the standard addition method using the calibration curve equation. The results demonstrated good agreement between the measured and expected values, confirming the accuracy of the developed analytical method. The results of the accuracy experiments are shown in Table 7.

Amount Taken	Amount Added	Total Amount	Peak Area	%Recovery	Mean Rec

(µg/mL)	d(µg/mL)	nc. in (µg/mL)	found	a		overy
300	50	350	354.86	1702012.5	101.38	101.10
300	50	350	353.07	1694491.63	100.87	
300	50	350	353.70	1697111.63	101.05	
300	100	400	399.25	1889101	99.81	100.91
300	100	400	399.62	1890654.25	99.90	
300	100	400	412.15	1943492.63	103.03	
300	150	450	447.00	2090379.5	99.33	99.63
300	150	450	449.06	2099062.5	99.79	
300	150	450	449.05	2099002.25	99.79	
					Mean	**100.55**
					SD	**1.165**
					%RSD	**1.16%**

Table 7: Demonstrates the results of accuracy experiments

Mean recovery was found to be **100.55%** which is inside the acceptance criteria

Acceptance criteria: The mean recovery should be: 98–102%

4. Range

The optimized concentration range of **250-450µg/ml** was selected based on method development studies, where brivaracetam exhibited a linear, precise, and reproducible response, indicating the suitability of this range for quantitative analysis and validation.

5. Precision

Precision studies showed excellent repeatability and intermediate precision, with %RSD values of **0.009% and 0.0063%** for intra-day and inter-day analyses, respectively. The results of intraday precision (repeatability) and Interday are presented in Table 8 and 9 respectively.

Repeatability (Intraday Precision)

Sr No.	Retention time	Concentration µg/ml	Peak area	Peak height
1	4.72	400	1888814.38	49139056
2	4.72	400	1888986.50	49139672
3	4.72	400	1889138.50	49141140
4	4.72	400	1889221.13	49141060
5	4.72	400	1889185.63	49141692
Mean			**1889069.228**	
Standard Deviation			**168.2**	
%RSD			**0.009%**	

Table 8: Shows results of Intraday precision

Interday

Sr No.	Retention time	Concentration µg/ml	Peak area	Peak height
1	4.72	400	1889405.13	49141740
2	4.72	400	1889173.13	49140764
3	4.72	400	1889236.75	49140753
Mean			**1889271.67**	
Standard Deviation			**119.90**	
%RSD			**0.0063%**	

Table 9: Shows results of Interday precision

The %RSD values for repeatability and intra-day precision were within the acceptable limits as per ICH guidelines (≤ 2%), demonstrating good precision of the developed analytical method.

Acceptance criteria: %RSD ≤ 2% (repeatability/intra-day); %RSD ≤ 2–3% (intermediate precision/inter-day).

6. Limit of Detection (LOD) and Limit of Quantification (LOQ)

LOD and LOQ were calculated using the standard deviation of replicate peak areas at 400 ppm and the slope of the calibration curve (y = 4214.7x + 206369). LOD and LOQ were found to be approximately **0.13µg/ml** and **0.40µg/ml**, respectively. These are indicative values.

7. Specificity

The specificity of the developed method was evaluated using blank and standard solutions. No interfering peaks were observed at the retention time of brivaracetam (4.72 min). Hence, the method was found to be specific for the quantitative determination of brivaracetam.The chromatogram of the blank preparation is shown in Figure 5.

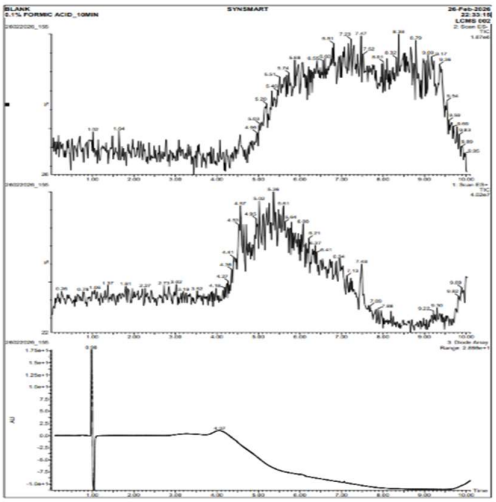

Figure 5: Chromatogram showing blank preparation

Acceptance Criteria: No interference should be observed at the retention time of the analyte.

8. Robustness

The robustness of the method was evaluated by making small deliberate changes in flow rate and column temperature. No significant changes were observed in peak area, retention time, or overall chromatographic performance. This indicates that the method is robust and reliable under slightly varied analytical conditions. The results for robustness of the method are tabulated below in table 10.

Sr No.	Parameter	Variation	Result	%RSD
1.	**Flow rate**	0.27 mL/min	3158421	0.72
		0.30 mL/min	3160572	0.65
		0.33 mL/min	3159785	0.69
2.	**Column Temperature**	28°C	3161025	0.74
		30°C	3160572	0.65
		32°C	3159950	0.71

Table 10: Demonstrates result of robustness studies

Acceptance criteria: %RSD of peak area or retention time ≤ 2%; no significant change in resolution or recovery.

9. Assay

The assay of BRV in the formulation was performed in triplicate. The percentage of BRV recovered ranged from **100.09–100.12%**, with a mean of **100.11 ± 0.02%** (mean ± SD). The results are within the acceptable pharmacopeial limits, indicating that the method is accurate and precise.The representative chromatogram of brivaracetam obtained from the marketed formulation is shown in Figure 6.

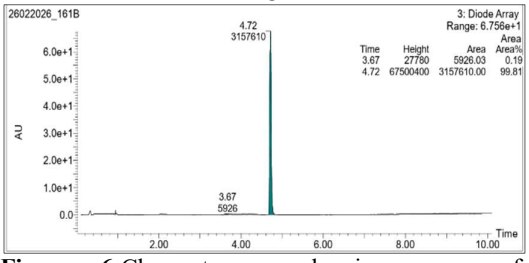

Figure 6: Chromatogram showing assay of Brivaracetam marketed formulation.

10. Forced Degradation Studies

Forced degradation studies were conducted under acidic, basic, oxidative, and thermal stress conditions to evaluate the stability of the drug and the specificity of the developed method. The method successfully distinguished brivaracetam from degradation products, confirming its stability-indicating capability.Representative chromatograms obtained after acidic, basic, oxidative, and thermal stress conditions are shown in Figures 7–10, respectively.

Stress Condition	Degradation Condition	Peak Area of Degraded Sample	Time	% Degradation	Observation
Acidic Hydrolysis	0.1 N HCl	2711263.50	6h	14.14	Moderate degradation observed
Basic Hydrolysis	2 N NaOH	2335830.75	6h	26.03	Significant degradation

					observed
Oxidative Degradation	20% H2O2	2333099.00	24 h	26.11	Oxidative degradation observed
Thermal Degradation	60 °C	3225 5.28	24 h	89.79 %	Extensive degradation observed

Table 11: Shows Forced degradationstudies data

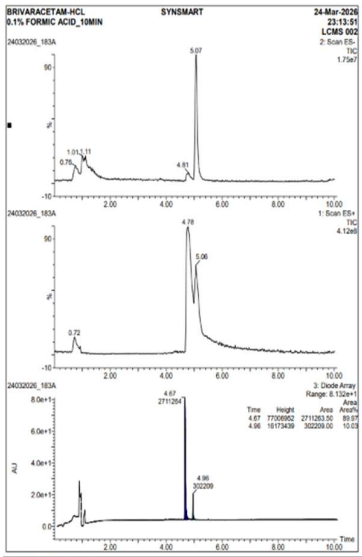

Fig 7:

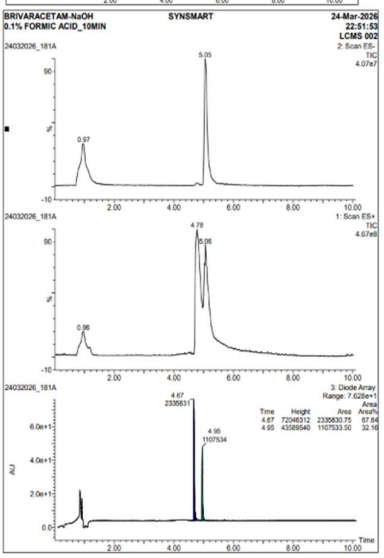

Fig 8:

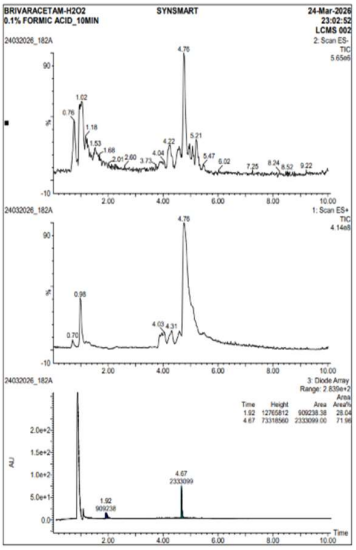

Fig 9:

Figure 7:Representative chromatogram of Brivaracetam after acid degradation under 0.1 N HCl stress conditions.

Figure 8:Representative chromatogram of Brivaracetam after base degradation under 2 N NaOH stress conditions.

Figure 9:Representative chromatogram of Brivaracetam after oxidative degradation under 20% H_2O_2 stress conditions.

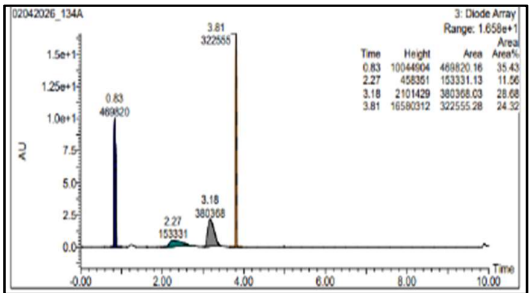

Figure 10: Representative chromatogram of Brivaracetam after Thermal Degradation under 60 °C temperature stress condition.

CONCLUSION

A rapid, accurate and stability-indicating UPLC-MS method was developed and validated successfully for quantitative estimation of brivaracetam in pharmaceutical dosage forms. The method was in accordance with ICH Q2(R1) guidelines and exhibited excellent linearity, accuracy, precision, specificity and robustness . The stability-indicating capability was shown by the successful separation of brivaracetam from its degradation products in forced degradation studies. Thus, the developed method is appropriate for routine quality control and stability studies of brivaracetam formulations.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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