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A Brief Review of Analytical Methods for the Estimation of Brivaracetam in Pharmaceutical Formulation and Biological Matrices

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Abstract

Partial-onset seizures are treated with Brivaracetam, which is a chemical butanamide derivative. Brivaracetam (BRV) in pharmaceutical and biological samples can be determined using various analytical techniques, including HPLC, UV-visible, and hybrid techniques including LC-MS, LC-MS/MS, UPLC-MS/MS, & other techniques, all of which are discussed in this review article. The review will analyze BRV determination using a variety of analytical approaches in comparison with each other. The findings of this review paper can be used as a starting point for future analysis of BRV.

Keywords: Brivaracetam, Butanamide, Biological Matrices, HPLC, Levetiracetam, Briviact

INTRODUCTION

A chronic, non-communicable neurological condition, epilepsy is marked by seizures, periods of odd behavior and sensations, and even loss of consciousness in some cases. Epilepsy can be divided into generalized and partial onset seizures (POS). Generalized seizures originate in both hemispheres of the brain, while POS occurs in one hemisphere (1,2). A medication called brivaracetam (BRV) is used to treat epilepsy. Levetiracetam's 4-n-propyl analog, BRV, is a new racetam derivative (3,4).

MATERIAL AND METHODS

Experimental:

Physiological Properties: Essentially, it is a two-selective-2-[(4R)-2-oxo-4-propylpyrrolidin-1yl] butanamide. In terms of its molecular weight and formula, it weighs 212.29 gmol/L and contains $C_{11}H_{20}N_2O_2$, respectively.(*Brivaracetam | C11H20N2O2 - PubChem*,). There is no restriction on the amount of solubility of this product in water, ethanol, methanol, glacial acetic acid, or dimethyl sulfoxide. UCB pharma sells it under the name briviact by UCB pharma, and it is made by that company [Fig. 1]. FDA approval for Briviact was granted in February 2016 (6,7).

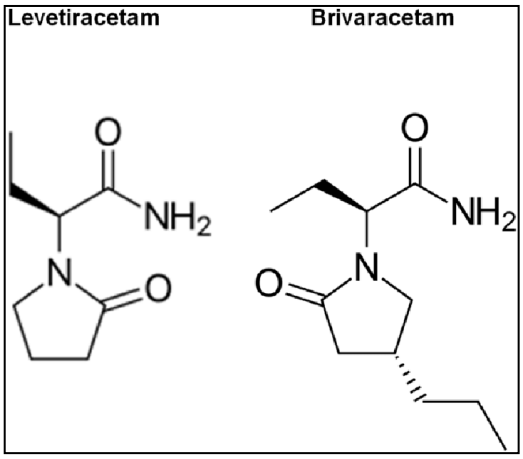

Fig. 1: Structure of Brivaracetam and levetiracetam, its racemate

Mechanism of Action:

To treat partial-onset epilepsy, this drug is employed. To put it another way, Brivaracetam has a 20 times greater affinity for SV2A (a modulator of synaptic vesicle glycoprotein two A/epoxide hydrolase inhibitor). Neuronal hyperexcitability is reduced by blocking impulse transmission across synapses, however, the mechanism behind this action is still unknown. It binds exclusively to synaptic vesicles protein in the brain. Na+ channels may play a role in brivaracetam's anti-epileptic properties (8). Patients under the age of 16 have not been studied for the product's efficacy or safety(9)(4). Brivaracetam is an analogue of levetiracetam, a derivative of racetam with anticonvulsant characteristics (3,10,11). Sleepiness, dizziness, nausea, and vomiting are the most common side effects, but there are also chances that changes in behavior and coordination issues will also occur (12).

Pharmacokinetics and Pharmacodynamics:

BRV forms carboxylic acid metabolite during hydrolysis of its acetamide moiety (9). It was quickly absorbed when administered orally, exhibiting half-lives of 7–8 hours and a t_{max} of 1 and 2 hours. The distribution volume was 0.5L/kg less than the total body water. In the first 72 hours after taking BRV, a minor percentage (5–8 percent) of the dose was eliminated unaltered via urine along with a significant amount of metabolites, which suggests primarily metabolic clearance. To treat partial-onset epilepsy, this drug is employed. To put it another way, Brivaracetam has a 20 times greater affinity for SV2A (a modulator of synaptic vesicle glycoprotein two A/epoxide hydrolase inhibitor). Neuronal hyperexcitability is reduced by blocking impulse transmission across synapses, however, the mechanism behind this action is still unknown. It binds exclusively to synaptic vesicles protein in the brain. Na+ channels may play a role in brivaracetam's anti-epileptic properties (8). When taken orally, BRV is fast and completely absorbed, reaches its half-life for elimination in 7-8 hours, and binds little more than 20% of plasma proteins (13). This is believed to be the result of BRV attaching to the ubiquitous glycoprotein in synaptic vesicles(14).

The primary focus of this work is on determining BRV in a variety of formulations and matrixes. An analysis of the BRV can be done with the data collected.

RESULT

Pharmaceutical Methods of BRV:

Analytical Methods:

Methods of UV-Visible Spectrophotometry (UV-Vis Methods):

BRV has only been determined using one UV-Visible spectrophotometric technique so far. This method was created by Imam Pasha and colleagues, and it relies on BRV's reaction with the Folin Ciocalteu Reagent (FCR) as it contains an amino functional group to measure BRV in bulk drugs and their formulations in a simple, precise, cost-effective, and time-saving manner (0.1 N NaOH). At 475 nm, the complex formed when the solutions were heated for 5 minutes at less than 60°C. The developed method's optimization was tested on a variety of variables, including the effect of reaction temperature, reagent quantity, concentration, and

sequence of addition. In their study, the authors found that colored species remained stable for more than 24 hours. Between 2 and 20 g/ml of the drug concentration, recovery was 98.10–99.60 percent; according to the results, 0.998 and 0.269% were the correlation coefficient (r) and the relative standard deviation (RSD), respectively (4). [Table-1]

Table 1: UV-Vis spectrophotometric methods for the determination of BRV

S. No.	Drug	Matrix	Wavelength	Linearity	% Assay	Reagent	Ref.
1	BRV	Tablet	475 nm	2-20 µg/ml	98.10-99.60%	F.C. reagent	(15)

High-Performance Liquid Chromatography Methods:

Analysis of BRV in combination with different drugs has been reported by several HPLC methods.

Brivaracetam, Piracetam, and Carbamazepine may all be detected simultaneously using a new HPLC approach established by Mansour et al., (16)for pharmaceutical dosage forms, laboratory mixes, and human plasma. A Promosil C18 column, acetonitrile: water in combination as solvent phase, with 0.6 mL/min flow rate was used in the separation. UV detection was possible at 215nm. Mean recovery rates ranged from 94.8 to 101.05 percent when using the developed approach, whereas LOD values ranged from 1.23, 0.77, and 0.61 g/mL for PIR, BRV, and CRZ, respectively, & LOQ values ranged from 3.74 to 2.33 g/mL.

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Brivaracetam's stability in HPLC investigations has been confirmed by Mali et al.,(17). A Hypersil Gold C18 column was used for separation, with a methanol, water, and acetonitrile stream flowing at 1.0 ml/min. Further detection of UV content was carried out using 242nm. The correlation coefficient (CC) (r2) of 0.999 & mean recovery rates between 98% and 101.66% were found when the newly devised approach was put to use. Acidic conditions weaken the drug to a greater extent, while alkaline conditions make it extremely unstable. For example, photochemical conditions indicate 22% degradation within 48 hours and 10% degradation with two products during hydrogen peroxide-induced degradation.

Brivaracetam isomers can be quantified using a chiral analytical approach described by Choppari et al. (18). The development of the method was performed in water, with acetonitrile and ammonium bicarbonate as the mobile phase, using several polysaccharide-based chiral stationary phases. Measurements were made at 212 nanometers (nm). All four isomers of BRV were shown to have a LOD/LOQ of 0.0066/0.02, 0.0035/0.0107, and 0.0036/0.0109 micrograms per milliliter, respectively.

For the measurement of BRV from tablets, Bhamare et al., (19) have established an in vitro dissolution research utilizing the HPLC technique. Water containing trifluoroacetic acid: acetonitrile served as mobile phase for a flow rate of 1.0ml/min on an Inertsil C18 column. At 210nm, further UV detection of the substance was carried out.

A UPLC method for determining BRV, its associated impurities, and degradation products has been published by Vishweshwar et al. (20). To separate the samples, a UPLC BEH SHIELD RP C18 column was used at 0.3ml/min with buffer: water: acetonitrile as the solvent phase. According to the r2 value of 0.993, the devised approach was found to be linear across 0.06-0.4 g/ml.

BRV in bulk and its dose forms may now be accurately measured via a simple reverse-phase liquid chromatographic method devised by Salomi et al.,(23). To separate the samples, a C18 column was used, with a flow rate of 1.2 ml/min of methanol: buffer as the mobile phase. The 290 nm wavelength was used to detect more UV light. Rt was found to be 2.35 minutes for BRV. As a result of the implementation of the

developed approach, the linear response ranged from 40 to 120 ug/ml, and the mean recovery was 100%. [Table-2]

BRV in bulk and pharmaceutical dosage forms can be accurately measured using a reverse-phase HPLC approach, as described by Spandana et al., (21). In this experiment, phosphate buffer: methanol was used as the mobile phase, and Agilent columns were used to separate the samples at a flow rate of 1.0 ml/min. PDA detectors were used for further detection using the 270 nm wavelength. BRV's Rt was determined to be 2.182 minutes. For this method's application, LOD and LOQ were determined at 3.67 and 8.87 g/mL, respectively, with a linear response between 20 and 100 ppm.

Table 2: A BRV determination method based on HPLC/UPLC

S. No.	Drug	Matrix	Column	Mobile phase	Linearity	Wave length	Ref.
1	PIR BRV CRZ	Plasma	Promosil C18 column (100 mm x 4.6 mm, 5µm)	ACN : H_2O containing 0.1% TEA with a ratio of 30: 70 v/v at pH 6.5 adjusted with OPA	2-100, 1-140 & 0.1-80 µg/mL for BRV, PIR, and CRZ, respectively	215 nm	(22)
2	BRV	Bulk	Hypersil Gold C18 column (250 mm x 4.6 mm, 5µm)	MeOH:H2O:ACN (30:10:60 v/v)	1-10 µg/mL	242 nm	(17)
3	BRV	Tablet	CHIRALPAK IG-U (100 × 3.0 mm; 1.6 µm)	ACN:10mM Amm.Bicarbonate (40:60 v/v)	---------	212 nm	(18)
4	BRV	Tablet	Inertsil ODS (150 × 4.6 mm; 5 µm)	ACN:0.1% v/v TFA in H20 (40:60%)	1.106-143.785 µg/mL	210 nm	(23)
5	BRV	Bulk	UPLC BEH SHIELD RP18 (100 mm x 2.1 mm, 1.7 µm)	H_2o:ACN & 0.1% v/v TFA in H20 gradient	0.0675-0.405 µg/mL	230 nm	(20)
6	BRV	Tablet	Waters C18 (250 × 4.6 mm; 5 µm)	0.02M phosphate buffer: MeOH (40:60, v/v)	25-100 µg/mL	290 nm	(23)
7	BRV	Tablet	Agilent C18 (150 × 4.6 mm; 5 µm)	Phosphate buffer: methanol (25:75% v/v),	20-100 µg/mL	270 nm	(21)

High-Performance Thin-Layer Chromatography-Densitometric Method:

Using HPTLC, Deepali et al. (1) quantified BRV in tablet and bulk medication dosage forms. The saturation duration was 20 minutes, and development was done in an ascending linear fashion on silica gel 60F254 plates (10 cm X 10 cm). The solvent system used was an ammonium acetate: methanol: n propanol mixture (8:1.6:1.6, v/v/v). Densitometry scanning at 242nm was used for further detection. The brivaracetam Rf value was found to be 0.40. For samples between 200-1200ng/mL, the devised approach demonstrated a linear response, with a recovery rate of 97.53 percent to 102.84 percent. A purity of 986.4% was discovered in terms of brivaracetam, which was determined to have LOD and LOQ values of 60 and 600 ng/spot, respectively.

Hyphenated Techniques:

LC-MS/MS

LC-MS/MS has been developed by D Atul Vasanth et al.,(24) for assessing the pharmacokinetics of BRV in healthy rabbits. In this study, the authors used the Chromolith C18column (100 x4.6 mm 5 µm) containing 0.1% formic acid, adjusted to pH 3.2 with a flow rate of 1.0 ml/min as an isocratic mobile phase. The developed method was linear from 0.16 to 8µg/ml. With the coefficient of correction (r2) = 0.998, the regression equation for the analysis was Y=0.0053x+0.0018. In terms of BRV, the % mean recovery ranged from 95.7% to 106.5%. For quality control standards, the mean intraday and inter-day precision ranged from 0.77 to 3.72%.

UPLC-MS/MS

A UHPLC-MS/MS method developed by Susan Mohamed et al.,(25) is being used to examine the plasma concentrations of BRV in patients with epilepsy. A simple precipitation step in acetonitrile was used in this study to prepare the sample (100 mL). As an internal standard, Brivaracetam-d7 was implemented. In equal time (at 1.01 minutes) BRV and the internal standard eluted. Plasma concentrations of brivaracetam were measured at a trough and one hour following the post-morning dose in 11 epilepsy patients. Validation was conducted over a concentration range of 0.10–10 mcg/mL. A mean recovery rate of 95% was achieved. For all quality control samples, the inaccuracy and imprecision of the assay were 15% for both intra- and inter-assay. In this experiment, the lower limits of quantitation and detection were 0.10 and 0.05 µg/mL, respectively. Neither interferences nor carry-overs were observed. It was found that the median (25%–75% quartiles) BRV plasma concentrations at a trough and 1-hour post dosing were 0.61 mcg/mL (0.47–0.83 µg/mL) and 1.55 µg/mL (1.24–2.12 µg/mL) respectively, at a median dose of eighty mg/d (fifty–one hundred fifty mg/d). A large, up to eight fold, intra-subject variation in BRV concentrations was noted between a trough and one hour after dosing.

Miscellaneous Methods:

Researchers led by Jugun Prakash Chinta et al., (26) used magnetic graphene oxide—cyclodextrin composite as sorbents to measure the antiepileptic drug concentration in human plasma. Antiepileptic medicines brivaracetam, eslicarbazepine acetate (ESL), and carbamazepine were studied utilizing a graphene oxide—cyclodextrin-based magnetic porous medium for solid-phase extraction (MGO-CD). FT-IR, SEM, XRD, and VSM were used to characterize the synthesized MGO morphology, CD's magnetic characteristics, and structure. The analytes were extracted from human plasma using SPE techniques. Extracting drug molecules from MGO-CD was done using a variety of solvents, including acetonitrile (ACN), methanol (MeOH), acetone, chloroform ($CHCl_3$), TBDE, and EtOAc, all of which had a different polarity. A binary pump HPLC system with a diode array detector (Shimadzu, Japan) was developed with LC-Solutions software. An ambient temperature column oven was used to maintain the temperature of the Luna RP C18 (4.6 150 mm, 5µ) column. Formic acid (0.1 percent) was used as a mobile phase along with acetonitrile in 35:65. According to the linearity study, the correlation coefficient (R2) for BVC, ESL, and CBZ was 0.9989, 0.9995, and 0.9982, respectively. As a result of this study, we have determined that the LOD and LOQ ranges lie between 6.14–28.32 ng/mL and 20–94.31 ng/mL, respectively.

It is relatively unknown what the alkaline hydrolytic degradation product of BRV consists of. Rupal Dubey et al. (27) published a research paper that identified this product, isolated it, characterized it structurally, and predicted its in-silico toxicology. An isocratic reverse-phase HPLC–UV technique was developed to determine BRV in the presence of impurities and degradation products. With an ODS 3V, 5 inertsil, and eluent monitored at 210nm in a flow rate of 1mL/min, efficient chromatographic separation was achieved. In the mobile phase, 0.1% wt acetonitrile was mixed with 0.1% trifluoroacetic acid solution at a ratio of 60:40 v/v. A linear calibration plot was obtained at concentrations between 141µg/mL to 262µg/mL, with a correlation coefficient (r2) of 0.99981. Between 0.0147 to 2.93 µg/mL/ml, both plots showed linear behavior, with a correlation coefficient (r2) of 0.99994. The new approach was used to study the degradation kinetics of Brivaracetam under various stress conditions. Basic degradation tests showed that the medication was less stable than expected. There are consistent recovery rates for BRV using this approach (100.22% at a 70%

level; 100.02% at 100%; 99.14% at a 130 percent level, i.e., 200 µg/mL of BRV). With the proposed method, they identified, isolated, and characterized the commercially available formulation (brand name: Briviact). LC-PDA, Preparative HPLC, LC/HESI/LTQ, FTIR, and 1H NMR were all used to estimate the alkaline hydrolytic breakdown product of BRV's toxicity in-silico.

CONCLUSION

In this review, a summary of numerous analytical methods is presented that have been used to determine BRV in bulk and drug dosage forms, as well as in biological matrices like blood plasma. Separation chromatography, spectroscopy, and hyphenated techniques comprised the methods. In this review, we sum up the most recent and significant data concerning BRV and characteristic assessment methods. Several methods are in circulation regarding HPLC and UV-visible spectrophotometry, but there are hardly any articles with information about hyphenated methods. According to the extracted data, HPLC with UV detection is a frequent technique. In biological matrices, especially blood plasma, HPLC with UV detection is an appropriate strategy for analyzing BRV that yields precise outcomes. Similarly, LC using MS techniques offered unique selectivity and sensitivity for the analysis of BRV and its metabolites analysis. There are also reports of hyphenated techniques, like LC-MS, LC-MS/MS, and UPLC-MS/MS being used to quantify BRV in plasma and other biofluids.

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