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MINI REVIEW

Brexpiprazole: Characteristics, Biological Activities, Synthesis And Methods For Determination In Different Matrices

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Abstract: Background: Brexpiprazole (BRZ) is a "third generation" antipsychotic D_2 (dopaminergic) and $5HT_{1A}$ (serotonin) partial agonist, approved in July 2015 by the US Food and Drug Administration for the treatment of major depression (MDD) other than schizophrenia in adults. Antipsychotics are known to produce extrapyramidal effects as side effects. The recent development in this segment is the development of piperazine based antipsychotic BRZ, which is more specific towards indented indications and fewer side effects. **Objective:** The presented review is written to critically review the different analytical methods available in the literature. **Method:** Eight spectrophotometry, nineteen chromatography, and two other methods were found in the literature search. A brief discussion on pharmacokinetics and mechanism of action is also included. **Conclusion:** The presented review can be used for the development of more robust and suitable analytical methods for the determination of drugs in different matrices. Brief conversation with respect to the approach towards the advancement of green analytical methods is likewise one of the points of this review.

Keywords: Brexpiprazole, analytical method, green analytical method, stability indicating method, spectrophotometry, chromatography

1. INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent, persistent, disabling, and multidimensional mental disorder. [1] Major Depressive Disorder (MDD) is a prevalent, persistent, disabling, and multidimensional mental disorder. It is assessed that up to half of the 800,000 suicides each year overall happen within a depressive episodes and patients with MDD are very nearly 20 times more likely to die by suicide than the normal population.[2]

MDD is perhaps the most well-known type of psychopathology, one that will influence around one of every six men and one out of four ladies during their lives. It is by and large the following most pervasive issue, with lifetime commonness in the 4–10% range and year predominance in the 3–6% range.[3]

Schizophrenia occurs initially during young adulthood and adolescence is known as progressive disease with poor prognosis. This follows a constant course as it shows exceptionally factor mental symptoms variations and recurs repeatedly.[4] Schizophrenia is a handicapping gathering of brain disorders described by side effects like delusions, hallucinations, disarranged correspondence, lack of common sense, diminished inspiration, and blunted effect.[5] Schizophrenia is a chronic and severe brain disease, of which the existence time predominance is assessed around 4/1,000 all throughout the planet.[6]

Individuals with schizophrenia are 2-3 times more likely to die than a normal people. This is frequently because of problems like infections, cardiovascular illness, and metabolic sickness.[7] Pharmacological therapy alternatives for schizophrenia incorporate the utilization of first and second-generation antipsychotics (FGAs and SGAs), dopamine receptor antagonist (D_2) with added antagonism of serotonin 5-HT_{2A} (SGAs).[8]

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Brexpiprazole (BRZ) (CAS 913611-97-9) (**Figure 1**) is 7-(4-(4-(1-benzothiophen-4-yl)piperazin-1-yl)butoxy)quinolin-2(1H)-one, molecular formula is $C_{25}H_{27}N_3O_2S$, and molecular weight is 433.57. BRZ is an atypical antipsychotic used in the treatment of schizophrenia and MDD.[9] Non-hygroscopic**,** white to off-white crystal or crystalline powder, melting point 183°C (decomposition). It is almost insoluble in water, and at pH 2, the solubility is 0.56 mg/mL.[10]

BRZ (RexultiVR) is SGA approved in 2015 in United States for the treatment of schizophrenia and as an adjunctive option for MDD.[11] The drug also got approval from the authorities of Australia, European, Asian countries like Japan for the treatment of schizophrenia.[12]

BPZ is BCS class II drug with lower solubility and high permeability. The solubility reported was 0.0714 mg/ml in pH 4.3 acetate buffer.[13] BPZ has shown less intrinsic agonistic movement at dopamine receptors than aripiprazole, in light of *in vitro* information in human cells and *in vivo* information in rodents. A few specialists suggest that this might prompt fewer side effects like nausea, vomiting, insomnia, and akathisia, which are believed to be dopamine interceded.[8]

The contraindication reported were hypersensitivity to the drug or any component. The reactions reported are facial swelling, anaphylaxis, rashes, and urticaria.[14] BRZ is well tolerated and adverse events are insignificant statistically and available in 0.25, 0.5, 1-4 mg tablets, once daily without regard to food.[15] The suggested dosage is 0.5 to 1 mg OD, increasing weekly to 2 mg depends on tolerability of patient and response.[16]

2. MECHANISM OF ACTION AND PHARMACOKINETICS

The BRZ is a partial agonist of D_2 and 5-HT_{1A} receptors and a potent antagonist of 5-HT_{2A} receptors, through which it may mediate its action, however, the actual mechanism of action is still unknown.[17] BRZ lacks significant 5-HT_{2C} antagonism, may be reason of less chances of induced weight gain, and metabolic syndrome as other atypical antipsychotics, including olanzapine and quetiapine are having.[18] The mechanism of action including affinity for various receptors and pharmacokinetics are shown in **Figure 2 and 3** respectively.

3. SYNTHESIS

BRZ was developed in collaboration with H. Lundbeck A/S (Valby, Denmark), by Otsuka Pharmaceutical Co Ltd. (Tokyo, Japan).[19] BRZ was endorsed by FDA in 2015 for the treatment of MDD, showing differing levels of nonresponse to the sole antidepressant drugs.[20] The synthesis reaction for BRZ[21] started with 7-Hydroxy-1*H*-quinolin-2-one and details are shown under Figure 4.

4. ANALYTICAL METHODS

Analytical chemistry assumes a colossal part in our society, such as in process control in industry, drug manufacturing, medical diagnostics, environmental monitoring, forensic surveys, and food production.[22] The main objective of an analytical method is to get consistent, realistic, and correct information.[23] The different analytical methods reported till date for BRZ are presented under Figure 5. The UV, NMR, MS and IR spectrums are shown under Figures 6,7,8 and 9 respectively.

4.1. Spectrophotometry

The significance of UV-vis spectroscopy for analysis has acquired wide acceptance for over twenty years.[24] Spectroscopy is a "branch of science (analytical chemistry) which deals with the study of the interaction of electromagnetic radiation with matter".[25] Another significant gathering of strategies which track down a significant spot in pharmacopeia are spectrophotometric techniques dependent on natural UV absorption and chemical reactions. The main advantages are less labour cost and time consumption in analysis.[26] This strategy is based on estimating the transmission of light through a known sample, in which light absorption esteemed at explicit wavelengths are used to quantify the analyte concentration.[27] The summary of spectrophotometry methods of BRZ is given under Table 1.

4.2 Chromatography

Analytical scientists working in numerous areas have since quite a while ago communicated the requirement for progressively quick chromatographic separation. The pharmaceutical industry, for instance, has a developing interest for high-throughput strategies to speed up the discovery and development of new chemical entities.[31] Pharmaceutical and drug development research are perhaps the biggest areas which vigorously depend on liquid chromatographic analysis.[32]

4.3 Electroanalytical

BRZ was additionally determined in tablets and pure by utilizing two distinctive anodic stripping methods; differential pulse (AS-DP) and square wave (AS-SWV) at a modified carbon paste electrode with gold nanoparticles. The LOD and LOQ for the AS-DP was 3.99×10^{-7} and 3.32×10^{-8} moles/L and for AS-SWV are 1.20×10^{-6} and 1.06×10^{-7} moles/L respectively.[51] In voltammetric studies using cyclic voltammetry (CV), anodic stripping differential pulse (AS-DP) and anodic stripping square wave (AS-SWV) voltammetry using functionalized carbon paste electrode (FCPEs). For AS-DP and AS-SWV, the minimum detection limit were 1.74×10^{-7} and 1.32×10^{-8} mol L^{-1} respectively and successfully applied in tablets and pure.[52]

5. REVIEW OF ANALYTICAL METHODS

The problem with UV Spectrophotometry is the superimposition of rotational and vibrational transitions, due to which the actual structural elucidation is difficult by spectrum analysis. Every molecule is having a wavelength of maximum absorption when exposed under light. Thus, the technique is not routinely used for identification, but widely accepted for estimating solute concentration in solution.[53] While searching for UV spectrophotometry method, eight different methods[28-30] are found in the public domain. This is known fact that the interferences in determination of the compound of interest can be minimized by using

derivative spectrophotometry.[54] Out of eight methods, two are based on derivative spectrophotometry[29], and not proved to be any advantageous in terms of sensitivity, analysis or data related to other validation parameters.

The HPLC-UV analysis of BRZ with fluoxetine is the first paper published related to chromatographic analysis using a C18 column for routine quality control.[35] another published research of chromatographic separation is HPLC-UV determination of drug substances with a linear range of 0.05 to 0.15 mg/ml.[34] The LC-QTOF method for identification of *N*-dealkylation metabolite (OPC-3952) of BRZ in human urine is also available in the literature. As stated earlier, DM-3411 is the major metabolite in serum, while the carboxylic acid metabolite, OPC-3952, was observed to be the most plentiful metabolite in urine. Metabolite DM-3411 outcomes from oxidation of the sulfur molecule in the terminal ring design to a sulfoxide which is not active. The BRZ splits into metabolites (OPC-3952) through CYP3A4 mediated *N*-dealkylation.[35]

Another HPLC-UV method for analysis of related substances in BRZ using gradient elution.[36] Determination of BRZ in the presence of degradation products by oxidation is also available. In this method, HPTLC was also used for separation and the oxidative stress degradation product was identified using IR and MS spectra. The degradation product is formed due to the oxidation of olefinic bond and secondary amine of BRZ. The olefinic bond was first converted to epoxide and finally to a vicinal bonds. Secondary amine converted to hydroxyl amine and then converted to nitroso group.[37]

The first UPLC–MS-MS determination of BRZ in human plasma was developed by Zou *et al.[38],* The method was utilized for pharmacokinetic studies of the drug in beagle dogs after a single-dose oral administration of a 4 mg tablet.

The forced degradation studies of BRZ were performed by Bhatt *et al.*[39]. The amino group of BRZ is vulnerable to oxidize to get *N*-oxide impurity. The researchers found that the drug is stable in all stress conditions except oxidative degradation conditions. The *N*-oxide BRZ generated was separated and identified. The method aimed for quantification of BRZ in bulk and tablets developed by Thakkar *et al.* [28] including forced degradation studies. The researchers found the drug to be susceptible under acid and alkali hydrolysis, chemical oxidation, photo degradation, and dry heat. However, the research not further explains the chemical structure of degradants.

The LC-MS method was used to determine the unknown impurities in the synthetic route of BRZ. This is the only method that separates the process-related impurities.[40] The LC-MS/MS method was developed and validated in the published study for establishing pharmacokinetics and safety in Japanese schizophrenia patients. This is the first paper used in clinical studies. Limited details about the method were described and was aimed for the determination of DM-3411 and BRZ in human plasma.[41] The LC-MS method[42] was described with the aim to perform forced degradation stability studies. The drug was reported to be stable under acidic and alkaline conditions but degradation was observed under oxidative conditions. The researchers reported the formation of two metabolites under oxidative stressed conditions.

The HPLC method for determination of BRZ and related substances was performed using PDA detector.[43] forced degradation study was also performed in this study and the results were the same as shown by Bhatt *et al.*[39], degradation performed only under oxidative stress condition. Another stability indicating HPLC method[44] has shown slight decomposition on exposure of BRZ drug solution when subjected to acidic, alkaline, and thermal stress conditions but observed 8.64% degradation by peroxide treatment.

The only stability indicating HPTLC method for determination in bulk and tablets was developed and validated by Thakkar *et al.* [45] using *n*-butanol as the mobile phase. The densitometric analysis was carried out in absorbance mode at 215 nm. The study found the drug to be susceptible to various stress conditions.

Another stability indicating RP-HPLC method in the presence of its degradation products was published by Pulusu *et al*.[46] and overall concedes the results of previous published research i.e. the BRZ molecule is more sensitive to peroxide degradation. The UPLC-MS/MS method for determination in rat plasma using protein precipitation method and was applied to the pharmacokinetic study after orally given drug.[47]

ICH Q8 (R2) guideline does not directly discuss quality-based design in analytical development, however, the concepts can apply. One of such recent methods is Quality-by-design-based UPLC method [48] for the separation of analytes from five impurities. The method was applied for *in vitro* dissolution of drugs.

Another utilization of quality by design concept was implemented in separation using an HPLC method with a UV detector for routine quality control/analysis of bulk and tablets.[49] The HPLC-UV (325 nm) analysis for *in vitro* and *in vivo* metabolism is one of the recent papers. The radiolabeled BRZ was orally administered to male rats and cynomolgus monkeys. After treatment of plasma and brain homogenates, the supernatant fractions were analysed to search for unchanged BRZ and its metabolites in the plasma and brain. The radioanalyses of *in vitro* and *in vivo* samples was performed by using a flow scintillator analyser. Later on, plasma determination of the drug and its metabolite DM-3411 was performed by LC-ESI-MS/MS.[50]

One of the factors seriously affecting safety and efficacy in the case of pharmaceutical molecules is chemical stability. The way to generate degradants in a shorter time span (mostly in weeks) is conducting forced degradation study.[55] Any combination of HPLC with MS, Diode Array Detection (DAD), NMR or GC-MS can provide information related to the structure of unknown analytes.[56] This approach was used by some researchers for identification of degradants (also refer Table 3). While going through the forced degradation studies available, this is clear

that BRZ is susceptible to oxidative degradation. The metabolite identified is given under Figure 10.

Implementing green analytical methodologies has been one of the fundamental goals of the analytical scientist's community for the last twenty years.[57] The objective of green analytical chemistry is to utilize logical methods that create less dangerous waste and that are more secure to utilize and more generous to the climate.[58] This is already explained that BRZ is poorly soluble in aqueous media and it is clear that in all available analytical methods, various solvents (especially methanol), were used in different compositions. The stability indicating methods reported clearly mentioned degradation of the drug by oxidation using various concentrations of hydrogen peroxide. With proper optimization of reaction conditions, this approach can be used for the development of a green analytical method for BRZ in the future.

CONCLUSION

Major depressive disorder (MDD) is generally associated with neurocognitive dysfunction and because of causing disability, one of the reasons for large economic and social burden on the world. The piperazine ring structural-based antidepressants are considered more suitable because of its better tolerability, efficacy, and safety profile. Schizophrenia has been regarded as a progressive disease. BRZ is one of the additions in this segment. Analytical methods are an important part of drug development. In this review, the mechanism of action and pharmacokinetics of the drug was discussed briefly (also refer Figures 2 and 3). The analytical profile of BRZ is briefly shown in different spectrums. The summary of different spectrophotometry and chromatography methods is discussed under Tables 1 and 2, respectively. The stability indicating methods were summarized under Table 3. The accelerated stability indicating method according to the long and short-term storage conditions specified in ICH guidelines is not found in the available literature. The solubility of BRZ is more in solvents and the development of suitable green analytical methods is another field of research.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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