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Review Article

An overview on various analytical methods for estimation of safinamide from its bulk and pharmaceutical dosage form

Pranali C. Baviskar[1] and R.S. Bachhav[2]

[1]Research Scholar and [2]Associate Professor, Dept. of Pharmacology, R.G. Sapkal College of Pharmacy, Nashik, India

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ABSTRACT

Safinamide mesylate (SAF)(S1), also known as (S)-2-(4-((3-Fluorobenzyl) oxy) benzyl) amino) propanamide methane sulfonate, is a medication that was recently created to treat Parkinson's disease (PD). Safinamide is an MAO-B inhibitor that is used to supplement levodopa/carbidopa in the treatment of Parkinson's disease during "off" episodes. According to the literature, High Performance Thin Layer Chromatography (HPTLC), Bioanalytical Method Development of Safinamide by UPLC-MS/MS, and RP-HPLC Stability Indicating Assay Method Development and Validation were used to monitor safinamide. Selectivity, precision, linearity, and accuracy were all used to validate the authors' proposed technique. All the validation parameters were within acceptable limits. There have been numerous ways for determining safinamide.

Keywords: Safinamide, Parkinson's disease, RP-HPLC, HPTLC

INTRODUCTION

After Alzheimer's disease, Parkinson's disease (PD) is the second most common chronic progressive neurological condition among the elderly. [1] Dopamine insufficiency results from the progressive death of nigrostriatal dopaminergic cells, and the condition is diagnosed mostly through observational criteria such as muscle rigidity, resting tremor, or postural instability in association with bradykinesia. [2] Although levodopa (L-dopa) is the most effective treatment for PD's motor symptoms, long-term use is linked to motor fluctuations, or periods of normal functioning (ON-time, i.e., good motor system control) that alternate with periods of diminished performance (OFF-time, i.e., periods of poor mobility, slowness, and stiffness). Furthermore, when the severity of the condition worsens, many patients develop involuntary movements known as L-dopa-induced dyskinesia because of high dosages of L-dopa. Non-dopaminergic pathways (e.g. glutamate) get implicated as the condition advances, and patients require add-on medication to ameliorate motor fluctuations without increasing dyskinesia. [3,4]

Chemistry: Newron developed Safinamide (Xadago) mesylate (SAF), an orally accessible derivative from the chemical class of amino amides with several modes of action, including inhibition of MAO-B and Dopamine reuptake, for the

Address for Correspondence: Pranali C. Baviskar, Research Scholar Dept. of Pharmacology, R.G. Sapkal College of Pharmacy, Nashik India; E-mail: pranalibaviskar1918@gmail.com

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treatment of epilepsy and Parkinson's disease. [5,6,7] In Europe, it was approved in February 2015, and in the United States, it was approved on March 21, 2017.

Safinamide mesylate (SAF)(S1), also known as (S)-2-(4-((3-Fluorobenzyl) oxy) benzyl) amino) propanamide methane sulfonate, is a medication that was recently created to treat Parkinson's disease (PD). [8]

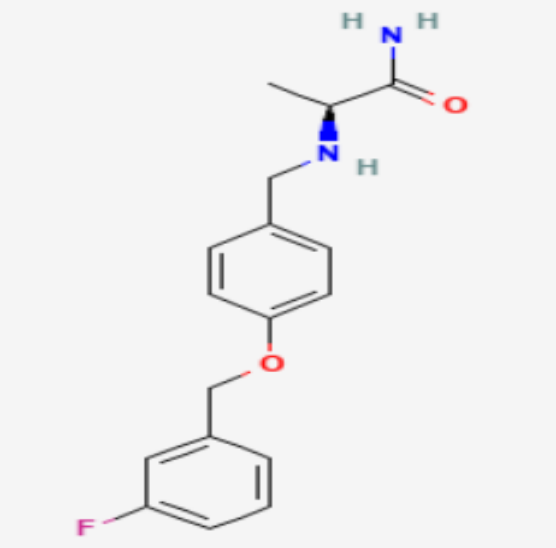

Fig. 01. Molecular formula of Safinamide

Pharmacology:

Mechanism of Action: Safinamide is a one-of-a-kind chemical with several action mechanisms and a high therapeutic index. It combines MAO-B inhibition that is effective, selective, and reversible with voltage-dependent Na^+ and $Ca2^+$ channel blockage and glutamate release inhibition. In MPTP-treated mice, rat kainic acid, and gerbil ischemia models, safinamide possesses neuroprotective and neurorescuing actions.

Absorption: Total bioavailability is 95%, with peak plasma concentrations ranging from 2 to 4 hours. Food increased the rate of absorption but had no effect on the amount of safinamide absorbed.

Distribution: 1.8 litres/kg, Protein binding: 88–90%

Metabolism: The main phase, which creates safinamide acid, is mediated by amidases that have yet to be found. It can also be converted to O-debenzylated safinamide and N-dealkylated amine by metabolism. After that, the N-dealkylated amine is oxidised to a carboxylic acid before being glucuronidated. Cytochrome P450s (CYPs), particularly CYP3A4, are involved in dealkylation processes. Although safinamide acid binds to the organic anion transporter 3 (OAT3), no clinical significance has been discovered. Safinamide binds to ABCG2 in a transitory manner. In preliminary research, no further transporter affinities have been discovered.

Elimination: 76% renal, 1.5% faeces, Half-life- 72 hrs [2,4,6,9-11]

Nausea, vomiting, headache, abdominal pain, pyrexia, cough, hypertension, impaired vision, and tremor are the most commonly reported side effects of SAF. [9]

VALIDATION OF RP-HPLC METHOD

Parameters for Method Validation

The following are the parameters for method validation as established by the ICH (International Conference on Harmonization) guidelines:

Accuracy: The closeness of agreement between the values, which is acknowledged either as a conventional true value or an approved reference value found, is expressed by the accuracy of an analytical technique. The accuracy studies' results are provided as a percentage recovery (the results must be followed within a range of 98–102%).

Precision: The degree of dispersion (closeness of agreement) between a set of measurements acquired from multiple sampling of the same homogeneous sample under the stipulated conditions is expressed by the precision of an analytical method. It's usually represented as a percentage of the standard deviation.

Precision may be considered at three levels:

a) **Repeatability:** Expresses precision under the same operating conditions for a short period of time. It's also known as intra-assay precision (Relative Standard). The variance in repeatability studies must be less than 2%.

b) **Intermediate Precision:** Expresses the precision within laboratory variability, such as various days, different analysts, different equipment, reagents, and so on. (Intermediate precision studies must have a relative standard deviation of less than 2%).

c) **Reproducibility:** Describes the degree of precision between laboratories (collaborative studies, usually applied for standardisation of methodology).

Specificity: Specificity refers to the ability to assess the analyte unequivocally in the presence of components that might be present. Impurities, degradants, matrix, and other substances are examples of these.

Limit of Detection*:* The lowest amount of analyte in a sample that can be detected but not necessarily quantified as an exact number is the detection limit

of an individual analytical method. The Limit of Detection (LOD) is a concentration at a given signal-to-noise ratio. The injected amount in chromatography that results in a peak with a height at least twice or three times that of the baseline noise level is known as the detection limit.

S/N=2/1 or 3/1

Where, S= Signal, and N= Noise.

It may be calculated based on standard deviation (SD) of the response and slope of the curve(S):

LOD= 3.3(SD)/S Where,

SD= Standard deviation, and S= Slope.

Limit of Quantitation*:* The lowest amount of analyte in a sample that can be quantitatively measured with sufficient precision and accuracy is the quantitation limit of a particular analytical process. The Limit of Quantitation (LOQ) is a concentration at a given signal-to-noise ratio. The quantitation limit in chromatography is the injected amount that produces a peak with a height ten times that of the baseline noise level.

S/N=10/1

Where, S= Signal, and N=Noise.

It may be calculated based on Standard Deviation (SD) of the response and slope of the curve(S). LOQ=10 (SD)/S

Where, SD= Standard deviation, and S= Slope.

Linearity*:* The capacity of an analytical process to produce test results that are directly proportional to the concentration of analyte in the sample (within a certain range) is known as linearity (the correlation coefficient for linearity studies must be r>0.999).

Range*:* The difference between the sample's upper and lower analyte concentrations for which the analytical technique has been proved to have a reasonable degree of precision, accuracy, and linearity is the range of an analytical procedure.

Robustness: The robustness of an analytical technique is a measure of its capacity to remain unaffected by small but deliberate changes in system characteristics, and it demonstrates its dependability when used frequently.

Ruggedness*:* An analytical technique's robustness/ruggedness is a measure of its capacity to remain unaffected by tiny but deliberate changes in process parameters, and it reflects its reliability throughout routine use [12-17].

Only a few methods for determining SAF have been documented. They included the RP-HPLC technique for determining SAF in bulk and tablet dosage form, the HPLTC method for estimating SAF in bulk and tablet dosage form, and the identification, characterization, and quantification of SAF process-related impurities and degradation products. The enantiomeric separation of SAF was also reported using a validated chiral liquid chromatography method. For SAF estimate, a validated UPLC-MS-MS method was also established.

Redasani V. K. et.al. developed a method for the measurement of Safinamide Mesylate in bulk and tablet dosage form, a simple, specific, and precise high-performance thin-layer chromatographic technique has been devised and validated. Using a mobile phase of Toluene: Methanol: Triethylamine (4: 1: 0.5 v/v), chromatographic development was carried out on aluminium plates precoated with silica gel 60 F254. The detection was done using a densitometric method at 226 nm. The drug's RF value was found to be 0.54 0.02. The method's linearity, accuracy, precision, and robustness were all tested. Over a range of 400–2400 ng L1, the calibration curve was determined to be linear. The percent assay was found to be 100.27 (Mean S.D.). Percentage recovery was used to determine the method's accuracy, which was found to be 99.770.71 percent. As a result, the proposed HPTLC approach was discovered to provide quick and cost-effective quantitative control for regular analysis of Safinamide mesylate in bulk and tablet dosage form. [18]

Adhao, V. S et.al. developed a new, simple, specific, accurate, and exact RP-HPLC method was devised for determination of Safinamide Mesylate. Stress testing of Safinamide Mesylate was carried out in this study according to ICH recommendations Q1A. (R2). Hydrolysis, oxidation, photolysis, and neutral decomposition stress conditions were applied to Safinamide Mesylate. On a Hypersil BDS C18 column (250 mm 4.6 mm, 5.0 particle size), successful separation of medication from degradation products generated under stress conditions was obtained using Methanol: Phosphate Buffer pH 6.8 (80:20 percent v/v) at a flow rate of 1.0 mL/min and a column temperature of 40°C. In acidic, alkaline, oxidative, and photolytic conditions, higher deterioration was seen. Thermal circumstances resulted in less deterioration. Safinamide Mesylate was quantified and linearized at 226 nm at a concentration range of 40 to 180 g/mL. Specificity, linearity, accuracy, precision, LOD, LOQ, and resilience were all tested. The described method can be used for both regular analysis and stability assessments. [19]

Redasani, VK. et.al. Worked on the detection of Safinamide mesylate in bulk and tablets, a quick, extremely sensitive high performance liquid chromatographic technique has been devised. Safinamide mesylate was eluted from a NEOSPHER RP C18 reversed phase column at a flow rate of 1 mL/min using a mobile phase of methanol and water (80:20, v/v) with UV detection at 226 nm. Safinamide mesylate had a retention time of 5.2 minutes. In the range of 5 - 30 g/mL, the linear response (r 2 = 0.9998) was observed, with limits of detection (LOD) and quantitation

(LOQ) of 0.27 and 0.83 g, respectively. The approach yielded good results, with intra- and inter-day relative standard deviations of less than 1%. Specificity, accuracy, ruggedness, and robustness were all determined as validation metrics. For routine analysis of Safinamide mesylate in bulk and tablet dosage form, the suggested approach provides an accurate and precise quality control tool. [20]

Zhang, K. et.al. developed a method on the enantiomeric resolution of safinamide mesylate, 2(S)-[4-(3-fluorobenzyloxy) benzyl amino] propionamide methane sulfonate, a neuroprotectant with antiparkinsonian and anticonvulsant activity for the treatment of Parkinson disease, an enantioselective reversed-phase high performance liquid chromatographic method was developed. On a Chiralcel OD-RH (150 mm 4.6 mm, 5 m) column, the enantiomers of safinamide mesylate were baseline resolved using a mobile phase system containing 300 mM sodium di-hydrogen phosphate buffer (pH 3.0):methanol: acetonitrile (65:25:10, v/v/v). There was a resolution of at least 3.0 between the enantiomers. The pH of the buffer solution in the mobile phase has been shown to have a significant impact on chromatographic efficiency and resolution between the enantiomers. The proposed method was tested and found to be reliable. For a 20 L injection volume, the limit of detection and limit of quantification of the (R)-enantiomer were found to be 15 and 50 ng/mL, respectively. In bulk medication samples of safinamide mesylate, the % recovery of the (R)-enantiomer ranged from 94.2 to 103.7. For at least 48 hours, the sample solution and mobile phase were confirmed to be stable. The final optimised approach was successfully used to isolate (R)-enantiomer from safinamide mesylate and was found to be reproducible and accurate for quantifying (R)-enantiomer in bulk pharmaceuticals. [21]

El-Kosasy A.M. et.al. detected safinamide mesylate (SAF) in the presence of its basic degradation and co-administered medications levodopa and ondansetron, a simple, precise, quick, and accurate reversed-phase high-performance liquid chromatography (RP-HPLC) approach was designed and validated. Acetonitrile and a 20 mM potassium dihydrogen orthophosphate buffer with a pH of 5 (40:60 v/v) made up the mobile phase. Quantification was accomplished using a 226 nm UV detector. With a mean recovery SD of 99.72 1.59, the linear range was 0.5–10 g/mL. The symmetry factor (999.8) of SAF in pharmaceutical product spiked with its degradation and co-administered medicines was found to be within the calculated criterion (>998.1). The proposed method was validated in accordance with ICH criteria and statistically compared to the manufacturer's HPLC method, with no significant differences in terms of accuracy and precision. With good percentage recoveries, the assay method was successfully employed to determine SAF in tablets. The new HPLC method's excellent sensitivity (lower than the drug's Cmax of 0.65 g/mL) allowed for the accurate detection of SAF in human plasma in the presence of its basic degradation and co-administered medication, ondansetron. The proposed HPLC approach could be employed in a Quality Control (QC) lab for drug analysis in pharmaceutical production. [22]

Tammisetty, M. R., et.al. developed a UPLC-MS/MS to estimate Safinamide in aqueous solution and human plasma using a validated analytical method with Safinamide-D4 as an internal reference. The chromatographic separation was obtained using CORTECS C18 with 100 x 4.6, 2.7 and 0.1 percent formic acid solution: Methanol, 30:70 percent v/v. The flow rate was set at 0.8 mL/min and the entire analytical time was 4 minutes. Safinamide and Safinamide-D4 have mass transitions of 303.3 and 215.2 and 307.3 and 215.2, respectively. Using the linear regression model, the standard curve has a correlation coefficient (r2) greater than 0.998 and a range of 113.0-338.0 pg/mL. For both analytes, the method demonstrated good repeatability, with intra- and interday precisions of less than 10% and accuracies of less than 8% of nominal values. The method has been used to study forced degradation under various stress situations with great effectiveness. [23]

CONCLUSIONS

In persons with Parkinson's disease, safinamide is combined with a combination of levodopa and carbidopa (Duopa, Rytary, Sinemet, and others) to treat "off" episodes (times of difficulty moving, walking, and speaking that can occur when medicine wears off or at random) (PD; a disorder of the nervous system that causes difficulties with movement, muscle control, and balance). The authors of this paper attempt to assemble a number of analytical methods for estimating safinamide from pharmaceutical dosage forms, including HPTLC, UV, and RP-HPLC Methods, bioanalytical, and UPLC-MS-MS. To monitor safinamide, certain RP-HPLC test techniques were applied. Bioanalytical methods have also been published for the identification of active and inactive metabolites of safinamide in plasma. The devised approach was validated according to the ICH Q2(R1) requirements.

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