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Stability indicating RP-HPLC analytical method development and validation for the estimation of safinamide in bulk and marketed pharmaceutical dosage form

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Abstract
A rapid and precise reverse phase high performance liquid chromatographic method has been developed for the validated of Safinamide, in its pure form as well as in tablet dosage form. Chromatography was carried out on a Symmetry C_{18} (4.6 x 150mm, 5µm) column using a mixture of Methanol and water (45:55% v/v) as the mobile phase at a flow rate of 0.8ml/min, the detection was carried out at 260nm. The retention time of the Safinamide was 2.379 ±0.02min respectively. The method produce linear responses in the concentration range of 24-120mg/ml of Safinamide. The method precision for the determination of assay was below 2.0%RSD. The method is useful in the quality control of bulk and pharmaceutical formulations. The method was validated for accuracy, precision, linearity, robustness, ruggedness and LOD & LOQ of standard solution. The developed RP-HPLC method was found to be accurate, precise, linear, and robust and was successful applied to a pharmaceutical tablet formulation for qualitative estimation of Safinamide in Bulk form and Marketed Pharmaceutical Dosage forms.

Keywords: Safinamide, RP-HPLC, Method Development, Validation, Accuracy

Introduction

Safinamide is an inhibitor of monoamine oxidase used as adjunctive therapy in combination with levodopa and carbidopa in the management of Parkinson's disease. Safinamide has been associated with a low rate of serum enzyme elevations during treatment, but has not been linked to instances of clinically apparent acute liver injury1.The pharmacological profile of Safinamide includes reversible monoamine oxidase B inhibition, blockage of voltage-dependent Na+ channels, modulation of Ca2+ channels, and inhibition of glutamate release. Safinamide is administered once daily at oral doses of 50-100 mg; it is well-tolerated and safe2.Safinamide is a unique molecule with multiple mechanisms of action and a very high therapeutic index. It combines potent, selective, and reversible inhibition of MAO-B with blockade of voltage-dependent Na+ and Ca2+ channels and inhibition of glutamate release. Safinamide has neuroprotective and neurorescuing effects in MPTP-treated mice, in the rat kainic acid, and in the gerbil ischemia model2.Safinamide is used with another medication (levodopa/carbidopa) to treat symptoms of Parkinson's disease. It can help improve symptoms such as shakiness, stiffness, and difficulty moving3. It can also help reduce the amount of "off" time (periods of slow movement or stiffness). The IUPAC name of Safinamide is ((2S)-2-[[4-[(3-fluorophenyl)methoxy]phenyl]methylamino]propanamide. The Chemical Structure of Safinamide is shown in fig-1.

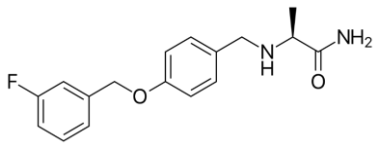

Fig 1: Chemical Structure of Safinamide

Experimental

Table 1: Instruments used

S. No.	Instruments and Glasswares	Model
1	HPLC	WATERS Alliance 2695 separation module, Software: Empower 2, PDA 996 Detector.
2	pH meter	LabIndia
3	Weighing machine	Sartorius
4	Volumetric flasks	Borosil
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil
7	Digital ultra sonicator	Labman

Table 2: Chemicals Used

S.No.	Chemical	Brand names
1	Safinamide (Pure)	Torrent Pharmaceuticals Ltd.
2	Water and Methanol for HPLC	LICHROSOLV (MERCK)
3	Acetonitrile for HPLC	Merck

HPLC Method Development

Preparation of Standard Solution

Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7ml of Methanol and sonicate to dissolve and removal of air completely and make volume up to the mark with the same Methanol.

Further pipette 0.72ml of the above Safinamide stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

Procedure

Inject the samples by changing the chromatographic conditions and record the chromatograms, note the conditions of proper peak elution for performing validation parameters as per ICH guidelines [13, 14].

Mobile Phase Optimization

Initially the mobile phase tried was methanol: Water and Acetonitrile: Water with varying proportions. Finally, the mobile phase was optimized to Methanol and Water in proportion 45:55 v/v respectively.

Optimization of Column

The method was performed with various C18columns like ODS column, Xterra, and X Bridge C18 column[4]. Symmetry C18 (4.6 x 150mm, 5µm) was found to be ideal as it gave good peak shape and resolution at 1ml/min flow.

Preparation of Mobile Phase

Accurately measured 450 ml (45%) of HPLC Methanol and 550 ml of HPLC Water (55%) were mixed and degassed in a digital ultrasonicator for 10 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation:

The Mobile phase was used as the diluent.

Method Validation Parameters

System Suitability

Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.72ml of the above Safinamide stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

Procedure:

The standard solution[5]was injected for five times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits.

Specificity

Preparation of Standard Solution

Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.72ml of the above Safinamide stock solutions into a 10ml volumetric flask and dilute up to the mark with diluents.

Preparation of Sample Solution

Take average weight of the Tablet and crush in a mortar by using pestle and weight 10 mg equivalent weight of Safinamide sample into a 10mL clean dry volumetric flask and add about 7mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent.

Further pipette 0.72ml of Safinamide above stock solution into a 10ml volumetric flask and dilute up to the mark with diluent.

Procedure

Inject the three replicate injections of standard and sample solutions and calculate the assay[6-8]by using formula:

%ASSAY =

$$\frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{\text{Label claim}} \times \frac{\text{Weight of tablet}}{100} \times 100$$

Linearity

Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Preparation of Level – I (24ppm of Safinamide)

Pipette out 0.24ml of stock solution in to a 10ml volumetric

flask and make up the volume up to mark by using diluent.

Preparation of Level – II (48ppm of Safinamide)
Pipette out 0.48ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Preparation of Level – III (72ppm of Safinamide)
Pipette out 0.72ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Preparation of Level – IV (96ppm of Safinamide)
Pipette out 0.96ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Preparation of Level – V (120ppm of Safinamide)
Pipette out 1.2ml of stock solution in to a 10ml volumetric flask and make up the volume up to mark by using diluent.

Procedure
Inject each level into the chromatographic system[9] and measure the peak area.
Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

Precision
Repeatability
Preparation of Safinamide Product Solution for Precision:
Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 0.72 ml of the above Safinamide stock solutions into a 10ml volumetric flask and dilute up to the mark with diluents.
The standard solution was injected for five times and measured the area for all five injections in HPLC[10]. The %RSD for the area of five replicate injections was found to be within the specified limits.

Intermediate Precision
To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different days by maintaining same conditions.

Procedure
Day 1: The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.
Day 2: The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits[11].

Accuracy
For preparation of 50% Standard stock solution:
Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 0.36ml of the above Safinamide stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

For preparation of 100% Standard stock solution
Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 0.72ml of the above Safinamide stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

For preparation of 150% Standard stock solution
Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 1.08ml of the above Safinamide stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

Procedure
Inject the Three replicate injections of individual concentrations (50%, 100%, 150%) were made under the optimized conditions. Recorded the chromatograms and measured the peak responses. Calculate the Amount found and Amount added for Safinamide and calculate the individual recovery and mean recovery values [12].

Robustness
The analysis was performed in different conditions to find the variability of test results. The following conditions are checked for variation of results.

For preparation of Standard solution
Accurately weigh and transfer 10 mg of Safinamide working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 0.72ml of the above Safinamide stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

Effect of Variation of flow conditions
The sample was analyzed at 0.7 ml/min and 0.9 ml/min instead of 0.8ml/min, remaining conditions are same. 10µl of the above sample was injected and chromatograms were recorded

Effect of Variation of mobile phase organic composition
The sample was analyzed by variation of mobile phase i.e. Methanol: Water was taken in the ratio and 40:60, 50:50 instead of 45:55, remaining conditions are same.10µl of the above sample was injected and chromatograms were recorded.

Results and Discussion

Analytical Method Development

Optimized Chromatographic Conditions:

Mobile phase ratio : Methanol: water (45:55 v/v)
Column : Symmetry C18 (4.6×150mm) 5µ
Column temperature : 40ºC
Wavelength : 260nm
Flow rate : 0.8ml/min
Injection volume : 10µl
Run time : 6minutes

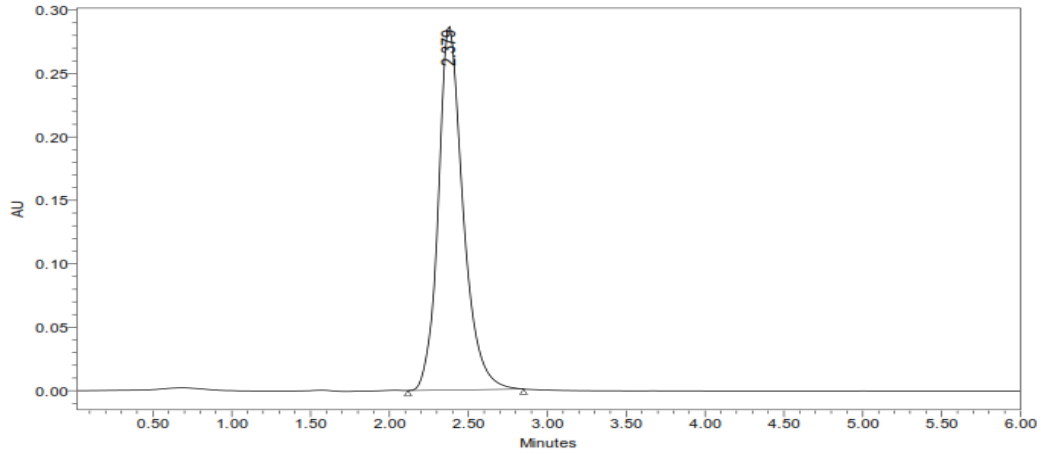

Fig 2: Optimized Chromatogram

The main objective of the chromatographic method [15] was to develop a precise, specific RP-HPLC method for the estimation of Safinamide. In order to develop a suitable isocratic RP-HPLC method, different buffer pH, organic solvent concentration and column chemistry were applied to achieve the isocratic elution of Safinamide. The mobile phase Methanol: Water (45:55% v/v) with the flow rate of 1.0 mL/min and detector wavelength at 260 nm was found to be satisfactory. The retention time of Safinamide was 2.379 min. Our proposed method has good symmetrical peak shape, theoretical plates and tailing factor as compared to reported studies. The mobile phase used in the present method has less organic phase as compared to other studies[25-28]. This may decrease cost of analysis, which may be economical to quality control labs. The typical chromatogram of the standard solution is shown in fig. 2.

Method Validation

All the method validation parameters such as accuracy, linearity, precision, detection limit, quantification limit and robustness were validated as per the International Conference on Harmonization (ICH) guidelines [13-14].

System Suitability

Table 3: Results of System Suitability for Safinamide

S.No.	Peak Name	RT	Area (µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Safinamide	2.317	2274631	239458	5728	1.2
2	Safinamide	2.302	2284721	239582	5093	1.2
3	Safinamide	2.323	2238127	236493	5391	1.2
4	Safinamide	2.343	2259349	249482	6139	1.2
5	Safinamide	2.321	2204850	239452	5281	1.2
Mean			2252336			
Std.Dev.			31827.08			
%RSD			1.41307			

Specificity

The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components.
Analytical method was tested for specificity [16] to measure accurately quantitate Safinamide in drug product.

$$\%ASSAY = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

The % purity of Safinamide in pharmaceutical dosage form was found to be 99.7%.

Linearity

The linearity[17] of the method was determined at seven concentration levels ranging from 24.0µg/ml to 120.0µg/ml for Safinamide.

Table 4: Linearity Data of Safinamide

Concentration Level (%)	Concentration µg/ml	Average Peak Area
33	24	791554
66	48	1647073
100	72	2283804
133	96	3058339
166	120	3839630

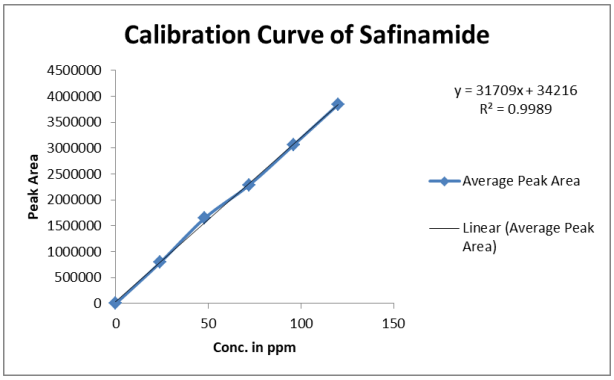

Fig 3: Calibration Curve of Safinamide

Linearity plot

The plot of Concentration (x) versus the Average Peak Area (y) data of Safinamide is a straight line.

Y = mx + c

Slope (m) = 31709

Intercept (c) = 34216

Correlation Coefficient (r) = 0.998

Validation Criteria: The response linearity is verified if the Correlation Coefficient [18] is 0.99 or greater.

Conclusion: Correlation Coefficient (r) is 0.99, and the intercept is 34216. These values meet the validation criteria.

Precision

The precision [19] of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Repeatability

Obtained Five (5) replicates of 100% accuracy solution as per experimental conditions. Recorded the peak areas and calculated % RSD.

Table 5: Results of Repeatability for Safinamide:

S. No.	Peak Name	Retention time	Area(µV*sec)	Height (µV)	USP Plate Count	USP Tailing
1	Safinamide	2.356	2259464	245362	5938	1.2
2	Safinamide	2.356	2275915	248293	5827	1.2
3	Safinamide	2.357	2282117	240795	5032	1.2
4	Safinamide	2.358	2278675	230139	5978	1.2
5	Safinamide	2.359	2282448	249605	6183	1.2
Mean			2275724			
Std. Dev			9476.485			
%RSD			0.416416			

Intermediate Precision

Analyst 1

Table 6: Results of Intermediate Precision for Safinamide

S. No.	PeakName	RT	Area (µV*sec)	Height (µV)	USPPlate count	USPTailing
1	Safinamide	2.380	2236184	202188	5472	1.2
2	Safinamide	2.383	2238020	201837	6193	1.2
3	Safinamide	2.385	2239352	201273	5980	1.2
4	Safinamide	2.385	2242466	203923	7163	1.2
5	Safinamide	2.389	2244692	202938	6182	1.2
6	Safinamide	2.389	2247654	201982	7684	1.2
Mean			2241395			
Std.Dev.			4333.851			
%RSD			0.193355			

Analyst 2:

Table 7: Results of Intermediate Precision Analyst 2 for Safinamide

S. No.	PeakName	RT	Area (µV*sec)	Height (µV)	USPPlate count	USPTailing
1	Safinamide	2.380	2236184	217363	5928	1.2
2	Safinamide	2.383	2238020	218467	6183	1.2
3	Safinamide	2.385	2239352	218346	5927	1.2
4	Safinamide	2.385	2242466	221736	5163	1.2
5	Safinamide	2.389	2244692	228361	4827	1.2
6	Safinamide	2.346	2263431	217553	5019	1.2
Mean			2244024			
Std.Dev.			9988.458			
%RSD			0.445114			

Accuracy

Accuracy [20] at different concentrations (50%, 100%, and 150%) was prepared and the % recovery was calculated.

Table 8: The Accuracy Results for Safinamide

%Concentration (at specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery	Mean Recovery
50%	1172485	36	35.8	99.4	99.5%
100%	2314753	72	71.6	99.4	
150%	3480210	108	107.9	99.9	

Limit of Detection for Safinamide

The detection limit 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[21].

LOD= 3.3 × σ / s

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Result

=5.5µg/ml

Quantitation Limit

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined [22].

LOQ=10×σ/S

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Result

=16.7µg/ml

Robustness

The robustness was performed for the flow rate variations from 0.7 ml/min to 0.9ml/min and mobile phase ratio variation from more organic phase to less organic phase ratio for Safinamide. The method is robust [23] only in less flow condition and the method is robust even by change in the Mobile phase ±5%. The standard and samples of Safinamide were injected by changing the conditions of chromatography. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

Table 9: Results for Robustness of Safinamide

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 0.8mL/min	3119086	2.379	5837	1.2
Less Flow rate of 0.7mL/min	2640811	2.763	5361	1.2
More Flow rate of 0.9mL/min	2640354	2.234	5231	1.2
Less organic phase	2640758	2.765	4503	1.5
More organic phase	2640125	2.236	4491	1.5

Stability Studies

Following protocol was strictly adhered to for forced degradation of Safinamide Active Pharmaceutical Ingredient (API).The API (Safinamide) was subjected to worry conditions in numerous ways that to look at the speed and extent of degradation that's seemingly to occur within the course of storage and/or when administration to body. This is often one style of accelerated stability studies that helps United States deciding the fate of the drug that's seemingly to happen when on time storage, at intervals an awfully short time as compare to the important time or future stability testing.The various degradation pathways [24] studied are acid chemical reaction, basic chemical reaction, thermal degradation, and photolytic degradation and Oxidation degradation.

Table 10: Results of Forced Degradation Studies of Safinamide API

Stress Condition	Time in hrs	Assay of active substance	Assay of degraded products	Mass Balance (%)
Acid Hydrolysis (0.1 M HCl)	24Hrs.	92.985	7.015	100.0
Basic Hydrolysis (0.1 M NaOH)	24Hrs.	91.062	8.938	100.0
Wet heat	24Hrs.	89.749	10.251	100.0
UV (254nm)	24Hrs.	95.625	4.375	100.0
3 % Hydrogen peroxide	24Hrs.	96.548	3.452	100.0

Summary and Conclusion

The analytical method was developed by studying different parameters. First of all, maximum absorbance was found to be at 260nm and the peak purity was excellent. Injection volume was selected to be 10µl which gave a good peak area. The column used for study was Symmetry C_{18} because it was giving good peak.40 ° C temperatures was found to be suitable for the nature of drug solution. The flow rate was fixed at 0.8ml/min because of good peak area and satisfactory retention time. Mobile phase is Methanol: water was fixed due to good symmetrical peak. So this mobile phase was used for the proposed study. Methanol: water was selected because of maximum extraction sonication time was fixed to be 10min at which all the drug particles were completely soluble and showed good recovery. Run time was selected to be 6min because analyze gave peak around 2.3 and also to reduce the

total run time. The percent recovery was found to be 98.0-102 was linear and precise over the same range. Both system and method precision was found to be accurate and well within range. The analytical method was found linearity over the range of 24-120ppm of the Safinamide target concentration. The analytical passed both robustness and ruggedness tests. On both cases, relative standard deviation was well satisfactory.

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