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STABILITY INDICATING RP HPLC METHOD DEVELOPMENT AND VALIDATION OF TEPOTINIB IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A new simple, selective, rapid, precise reversed phase high performance liquid chromatography method has been developed and validated for the estimation of Tepotinib in bulk and its pharmaceutical dosage form. The separation was made using Symmetry ODS C18 (4.6×150mm, 5µm) column. Mobile phase used contained Methanol: Phosphate Buffer pH-4.2 adjusted with orthophosphoric acid solution in the ratio of 35:65% v/v in isocratic mode at wavelength of 236nm. The mobile-phase flow rate and the sample volume injected were 1 ml/min and 10 µl, respectively. Retention time of Tepotinib was found to be 2.8 ±0.2mins. A good linear relationship Tepotinib r^2=0.999) was observed over a concentration range of 20 to 100µg/ml of Tepotinib. The limit of detection (LOD) and limit of quantification (LOQ) for Tepotinib was found to be 2.6 µg/ml and 6.35µg/ml. % recovery was observed in the range of 98-102%. Relative standard deviation for the precision study was found <2%. The developed method is simple, precise, specific, accurate and rapid, making it suitable for estimation of Tepotinib in bulk and marketed pharmaceutical dosage form dosage form. It was concluded that in the present developed RP- HPLC method is simple, rapid, and accurate, hence can be used for routine quality control analysis in pharmaceutical industry. During force degradation, drug product was exposed to hydrolysis (acid and base hydrolysis), H_2O_2, thermal degradation and photo degradation. The % degradation was found to be 10 to 20% for both Tepotinib in the given condition. The method specifically estimates both the drugs in presence of all the degradants generated during forced degradation study. The developed methods were simple, specific and economic, which can be used for simultaneous estimation of Tepotinib in tablet dosage form.

KEYWORDS: Tepotinib, Methanol, H_2O_2, Thermal degradation, Photo degradation, RP-HPLC, Validation, Precision, ICH Guidelines.

INTRODUCTION

High-performance liquid chromatography (HPLC), formerly referred to as high-pressure liquid chromatography, is a technique in analytical chemistry used to separate, identify, and quantify each component in a mixture. It relies on pumps to pass a pressurized liquid solvent containing the sample mixture through a column filled with a solid adsorbent material. Each component in the sample interacts slightly differently with the adsorbent material, causing different flow rates for the different components and leading to the separation of the components as they flow out of the column.[1-8] In the 1960s, the column chromatography LC with its low-pressure suitable glass columns was further developed into the HPLC with its high-pressure adapted metal columns. HPLC is thus basically a highly improved form of column liquid chromatography. Instead of a solvent being allowed to drip through a column under gravity, it is forced through under high pressures of up to 400 atmospheres.[8-19]

DRUG PROFILE[20-21]

STRUCTURE

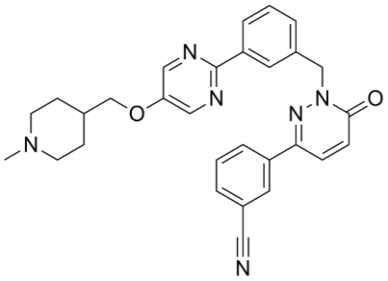

Figure 1: Structure of Tepotinib.

Table 1: Drug Profile of Tepotinib.

Drug	Tepotinib
Synonym	Tepotinib
Drug category	Antineoplastic Agents, Antineoplastic and Immunomodulating Agents.
IUPAC Name	3-{1-[(3-{5-[(1-methylpiperidin-4-yl) methoxy] pyrimidin2-yl} phenyl) methyl]-6-oxo-1, 6-dihydropyridazin3-yl} benzonitrile
Molecular Formula	$C_{29}H_{28}N_6O_2$
Molecular Weight	492.583 g/mol
Half-life	32 hours
Excretion	85% of the given dose is excreted in the feces with the remainder excreted in the urine.

As per our literature review, we found out that there are various methods which are being used for study on Tepotinib also there are two HPLC methods available. In our work/study we also carried out the stability study for Tepotinib under various stress conditions. Also, our method is economical and precise as compared to other available methods.[22-40]

METHOD DEVELOPMENT

Preparation of standard solution

Accurately weigh and transfer 10 mg of Tepotinib 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 0.6ml of the above Tepotinib stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

VALIDATION

PREPARATION OF BUFFER AND MOBILE PHASE

Preparation of Potassium dihydrogen Phosphate (KH_2PO_4) buffer (pH-4.2)

Dissolve 6.8043 of potassium dihydrogen phosphate in 1000 ml HPLC water and adjust the pH 4.2 with diluted orthophosphoric acid. Filter and sonicate the solution by vacuum filtration and ultra sonication.

Preparation of mobile phase

Accurately measured 350 ml (35%) of Methanol, 650 ml of Phosphate buffer (65%) were mixed and degassed in digital ultra Sonicator for 15 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation

The Mobile phase was used as the diluent.

VALIDATION PARAMETERS

SYSTEM SUITABILITY

Accurately weigh and transfer 10 mg of Tepotinib 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 0.6ml of the above Tepotinib stock solution into a 10ml volumetric flask and dilute up to the mark with diluent.

Procedure

The standard solution 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 STUDY OF DRUG

Preparation of Standard Solution

Accurately weigh and transfer 10 mg of Tepotinib 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 0.6ml of the above Tepotinib stock solutions into a 10ml volumetric flask and dilute up to the mark with diluents.

Preparation of Sample Solution

Take average weight of the powder and weight 10 mg equivalent weight ofTepotinib 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 0.6ml of Tepotinib 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 by using formula:

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

PREPARATION OF DRUGSOLUTIONS FOR LINEARITY

Accurately weigh and transfer 10 mg of Tepotinib 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)

Procedure

Inject each level into the chromatographic system 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

Preparation of Tepotinib Product Solution for Precision

Accurately weigh and transfer 10 mg of Tepotinib 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 0.6ml of the above Tepotinib 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. 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

Analyst 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.

Analyst 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.

Accuracy

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 Tepotiniband calculate the individual recovery and mean recovery values.

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 Tepotinib 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 0.6ml of the above Tepotinib stock solution into a 10ml volumetric flask and dilute up to the mark with diluents.

Stability studies

Forced degradation studies

The stability of the developed method was established by performing forced degradation studies of the drug in the presence of acid, alkali, H_2O_2, temperature, light.

Acid degradation

Degradation under acidic condition was evaluated by treating 1 ml of standard stock solution of Tepotinibwith 1 ml of 2N HCl and refluxed for 30 min at 60 ± 2 °C. The resulting solution was diluted to 10 ml with the diluent.

Alkali degradation

Under alkaline conditions, degradation was studied by refluxing 1 ml of standard stock solution of Tepotinibwith 1 ml of 2N NaOH for 30 min at 60 ± 2 °C. The stressed solution was made up to 10 ml with the diluent.

Oxidative degradation

About 1 ml of standard stock solution of Tepotinibwas subjected to oxidative degradation by refluxing with 20% *v*/*v* H_2O_2 in a 10-ml volumetric flask for 30 min at 60 ± 2 °C and made up with the diluent.

Thermal degradation

Thermal stability of the drugs was evaluated by placing the standard stock solution in the oven at 105 ± 2 °C for 6 h. About 1 ml of the stressed solution was diluted to 10 ml with the diluent.

Photolytic degradation

Photolytic degradation was studied by exposing the standard solution of Tepotinib to sun light for 7 days. The resulting stressed solution was diluted to 10 ml with the diluent.

About 10 µl of each of the solutions exposed to different stress conditions were injected separately into the column, and the chromatograms were recorded to evaluate the stability of the drugs.

RESULTS AND DISCUSSION

System suitability

Table 2: Results of System Suitability for Tepotinib.

S.No.	Peak Name	RT	Area
1	Tepotinib	2.824	1825658
2	Tepotinib	2.825	1836587
3	Tepotinib	2.827	1825654
4	Tepotinib	2.822	1835642
5	Tepotinib	2.830	1825787
Mean			1829866
Std.Dev.			5714.466
%RSD			0.312289

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 to measure accurately quantitate Tepotinib in drug product.

LINEARITY

Table 3: Linearity of Tepotinib.

Concentration µg/ml	Average Peak Area
20	668748
40	1278875
60	1886598
80	2458644
100	3028547

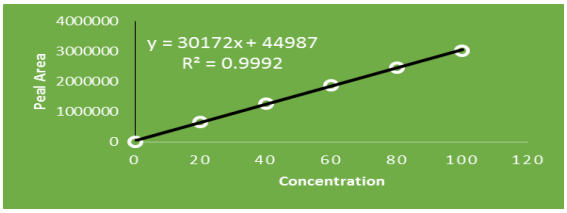

Figure 2: Calibration Curve of Tepotinib.

Precision

The precision 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.

Table 4: Precision Values of Tepotinib.

S. No	Peak Name	RT	Area
1	Tepotinib	2.823	1836524
2	Tepotinib	2.827	1836875
3	Tepotinib	2.828	1836958
4	Tepotinib	2.828	1836597
5	Tepotinib	2.825	1845689
6	Tepotinib	2.822	1845784
Mean	1839738		
Std.Dev.	4649.502		
%RSD	0.252726		

Intermediate Precision

Table 5: Results of Intermediate Precision for Tepotinib.

S. No	Peak Name	Retention Time	Area
1	Tepotinib	2.824	1825658
2	Tepotinib	2.827	1836587
3	Tepotinib	2.833	1825654
4	Tepotinib	2.833	1835642
5	Tepotinib	2.836	1825787
6	Tepotinib	2.833	1825564
Mean	1829149		
St. Deviation	5404.448		
% RSD	0.295462		

ACCURACY

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

Table 6: The accuracy results for Tepotinib.

% Concentration (At specification Level)	Area	Amount Added (ppm)	Amount Found (ppm)	% Recovery	Mean Recovery
50%	952225.3	30	30.068	100.226%	100.27%
100%	1863056	60	60.256	100.426%	
150%	2764762	90	90.142	100.157%	

LIMIT OF DETECTION FOR TEPOTINIB

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.

LOD= 3.3 × σ / s

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Result: = 2.6µg/ml

QUANTITATION LIMIT OF TEPOTINIB

The quantitationlimit of an individual analytical procedure is the lowest amount ofanalyte in a sample which can be quantitatively determined.

LOQ=10×σ/S

Were

σ = Standard deviation of the response

S = Slope of the calibration curve

Result: = 6.35µg/ml

Robustness

The robustness was performed for the flow rate variations from 0.8ml/min to 1.0ml/min and mobile phase ratio variation from more organic phase to less organic phase ratio for Tepotinib. The method is robust only in less flow condition and the method is robust even by change in the Mobile phase ±5%. The standard and samples of Tepotinib 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 7: Results for Robustness.

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 1.0mL/min	1825462	2.826	5365	1.6
Less Flow rate of 0.8mL/min	1818987	3.13	5126.3	1.7
More Flow rate of 1.0mL/min	1812658	2.589	5168.4	1.6
More Organic phase	1815897	2.514	5268.9	1.6
Less Organic phase	1805896	3.344	5264.4	1.7

STABILITY

From the forced degradation conditions, it was observed that degradation of Tepotinib. As per ICH guidelines, the limit of acceptable forced degradation is less than 20%. In the proposed method, the degradation of Tepotinib was less than 20%, which represents the stability-indicating method.

Table 8: Summary of forced degradation studies of Tepotinib.

Stress Condition	% of Degradation
Acid	Nil
Base/Alkaline	1.31
Oxidative	Nil
Photolytic	0. 575
Thermal	0.256

SUMMARY

The analytical method was developed by studying different parameters. First of all, maximum absorbance was found to be at 236nm 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 ODS C18 (4.6×150mm, 5µm) because it was giving good peak. 35 º C temperatures was found to be suitable for the nature of drug solution. The flow rate was fixed at 1.0ml/min because of good peak area and satisfactory retention time. Mobile phase is Methanol: Phosphate Buffer pH-4.2 (35:65% v/v) was fixed due to good symmetrical peak. So, this mobile phase was used for the proposed study.

Methanol was selected because of maximum extraction sonication time was fixed to be 15min 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 2.826 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 were found to be accurate and well within range. The analytical method was found linearity over the range of 20-60ppm of the Tepotinib target concentration. The analytical passed both robustness and ruggedness tests. On both cases, relative standard deviation was well satisfactory.

CONCLUSION

In the present investigation, a simple, sensitive, precise and accurate RP-HPLC method was developed for the quantitative estimation of Tepotinib in bulk drug and pharmaceutical dosage forms. This method was simple, since diluted samples are directly used without any preliminary chemical derivatization or purification steps. Tepotinib was slightly soluble in methanol, DMSO, water. Methanol: Phosphate Buffer pH-4.2 (35:65% v/v) was chosen as the mobile phase. The solvent system used in this method was economical. The %RSD values were within 2 and the method was found to be precise. The results expressed in Tables for RP-HPLC method was

promising. The RP-HPLC method is more sensitive, accurate and precise compared to the Spectrophotometric methods. This method can be used for the routine determination of Tepotinib in bulk drug and in pharmaceutical dosage forms. The results indicated the suitability of the method to study stability of Tepotinib under various forced degradation conditions acid, base, dry heat, oxidation and photolytic degradation. It can be concluded that the method separates the drugs from their degradation products; it may be employed for analysis of stability for their tablet dosage form. However, characterization of degradation products was not carried out.

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