A Novel LC-MS Method Development And Validation For The Estimation of Tert-Butyl 4-((2-Aminopyridin-3-yl) (Nitroso) Amino) Piperidine-1-Carboxylate in Rimegepant

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Abstract

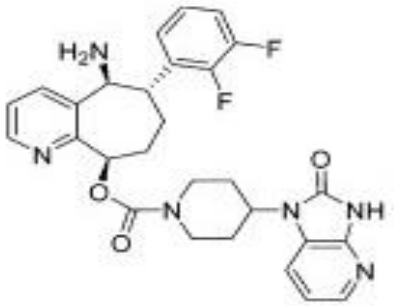
Using a method that combines liquid chromatography, a mass spectrometer, and a single mass analyzer, tert-butyl4-((2-aminopyridin-3-yl)(nitroso)amino)piperidine-1-carboxylate) has been found (LC-MS).For Rimegepant Impurityseparation and quantification attain by using Hypersil BDS (C18, 100 x 4.6 mm, 3 m) column at the threshold of toxicological concern levels, no acceptable approach has yet been developedIn this work, a sensitive and reliable liquid chromatography-mass spectrometry method for the quantitative detection of impurity in rimegepant was developed and validated in accordance with the criteria of the International Council for Harmonization (ICH).The correlation coefficient of fitting for impurity exceeded 0.998, and the calibration curves displayed satisfactory linearity within the examined range. The proposed method's sensitivity was between 0.6 and 10.0 mg/mL. This method can be used to identify the impurity in rimegepant drug substance during manufacturing.

Keywords: Anti-Migraine drug, Genotoxic impurity, Liquid chromatography, Rimegepant.

1. Introduction:

Rimegepant is a strong antimigraine medication that is marketed under the trade name Nurtec ODT and is used to prevent or treat migraines. Triptans and/or non-steroidal anti-inflammatory drugs are used to treat migraines (NSAIDS).There are also times when central analgesics may be used. Rimegepant is a small molecule that blocks the calcitonin gene-related peptide (CGRP) receptor. Vasodilators like CGRP have been linked to migraine headaches.

Rimegepant stops CGRP from causing the receptor to become active. The medicine has a half-life of 11 hours. After being taken by mouth, 77% of the drug's metabolite will have a therapeutic effect for about 30 minutes, and 20% of the drug will still be in the plasma after 3–4 hours. It was shown that only 3% of the protein in plasma. Chemical is the word used to describe rimegepant (5S,6S,9R) -5-Amino-6-(2,3-difluorophenyl) -6,7,8,9-tetrahydro-5H-cyclohepta[b] pyridin-9-yl4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b] pyridin-1-yl)piperidine-1-carboxylate.Its molecular weight is 534.6 g/mol and its empirical formula is C28H28F2N6O3. RGT nitrso impurity has the molecular formula C15H23N5O3 C16H28N2O4, and its molecular weight is 312.4 g/mol. . Fig.1 shows the structure of Rimegepant and the impurities that come from the way it is made. A review of the literature showed that stability indicating methods and rimegepant method development were carried out. Diverse related substances are observed via various synthetic routes, but never simultaneously via a particular synthetic route. DNA and RNA, the genetic material's building blocks, may be harmed by substances referred to as "genotoxic impurities". Because genotoxic contaminants are bad for people's health, pharmaceutical companies and regulatory agencies paid more attention to their presence in APIs and drug products [1].At parts per million levels, related compounds and contaminants are measured using the well-liked and flexible LC-MS method.



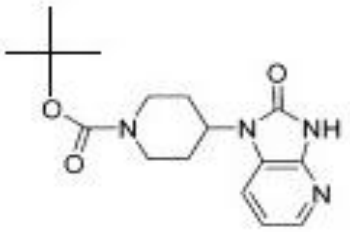


Figure.1. (a) Rimegepantstucture Figure.1. (b) Rimegepant Impurity

2. Materials and Methods:

2.1 Chemicals and reagents:

Tert-butyl4-((2-aminopyridin-3-yl)(nitroso)amino)piperidine-1-carboxylate) reference standard was given away as a sample by Fortune Pharma, Hyderabad (claim 99.32%). Methanol and acetonitrile of HPLC quality were bought from Merck in Mumbai, India. During the study, a

Millipore purification system was used to make HPLC-grade water. From SD Fine Chemicals in Mumbai, India, a grade AR of ammonium acetate was bought.

2.2 LC-MS/MS Instrumentation and optimization of chromatographic conditions:

An auto sampling Waters LC-MS was used to carry out the procedure. The phenyl vinyl sulfone was separated using a Hypersil BDS (C18, 100 x 4.6 mm, 3 m) column with a mobile phase of 5 mM ammonia acetate to methanol (5:95 v/v), a flow rate of 0.45 mL/min, an injection volume of 20 mL, and methanol as the diluent. The column was kept at room temperature, while the auto sampler was kept at 5 degrees Celsius. Table 1 incorporates all MS characteristics.

2.3Stock, standard and test solution preparation: 250 mg of Rimegepant-A Impurity standard material was carefully weighed and transferred to a 10 ml volumetric flask, and diluted with diluent. To reach a concentration of 1000 ppm, the aforementioned 0.4 ml solution was diluted to 10 mL.

2.4 Preparation of buffer solution and mobile phase:

Ammonium acetate, which was precisely weighed at 0.39 g, was diluted to a volume of 1000 mL with milli Q water, had its pH changed to 5.0 using formic acid, and was then passed through a 0.22 nylon membrane filter. In order to make the mobile phase, 5mM ammonium acetate was mixed with methanol (5:95 v/v) and filtered through a 0.45 membrane filter before being ultrasonically degassed.

2.5 Optimization of mass spectrometer:

Rimegepant-A was given as a 1 mg/mL solution using the direct infusion method. This method uses a syringe and a syringe pump to make a steady flow of liquid sample. When the mass parameters were changed in different ways with a flow rate of 10 L/min, the initial low sensitivity of ions was shown. Later, the flow rate was raised to 30 L/min so that ions could be as sensitive as possible. Table 1 shows the final mass parameters that were found to be best.

Table-1: Optimized Mass parameters data

Ionization mode	ESI
Acquisition mode	SIM

Mode of polarity	Positive
Ch1	321.4
Temperature of the light source	120^0C
Block heat	350^0C
Cone gas flow	50L/Hr
Desolvation gas flow	950 L/Hr
Capillary (KV)	3.50(KV)
Cone (V)	25.00V
Extractor (V)	3.0V

3. Results and discussion:

Following ICH guidelines, the method was checked to make sure it worked. In this study, the following validation parameters were set up: system suitability, specificity, stability of the solution, LOD and LOQ, accuracy, method precision, linearity, and intermediate precision.This was done so that the results of the technique could be reproduced. By injecting the six standard solutions, the system's suitability was tested, and the %RSD result was within acceptable limits. By testing for specificity, it was found that there is no peak interference during the time that rimegepant-A stays in the body. The blank, standard, and spiking solutions were used to do this. At 5°C, rimegepant-A standard solution was collected, and after 7 and 11 hours, its stability was checked. LOD and LOQ were found by taking into account the amount of RIMEGEPANT-A that would lead to signal-to-noise ratios of 3:1 and 10:1, respectively. Six LOQ standard solutions were used to measure precision so that the results could be used again and again. At the LOQ, 50%, 100%, and 150% intervals, accuracy was determined, and recovery was found to be within the specification limit. Adding RIMEGEPANT-A to the Rimegepant test sample helped figure out how accurate the method was, and the %RSD result was good. A linearity study was done for RIMEGEPANT-A that looked at the range from the LOQ level to 150% of the limit.

3.1 Method development:

system suitability, specificity, solution stability, LOD and LOQ, accuracy, method precision, linearity, and intermediate precision. To attain RIMEGEPANT-A sensitivity at the limit of detection, method development experiments were broadened to include liquid chromatography connected to a single mass spectrophotometer (LC/MS).Additionally, a number of additives have been tested, including acetonitrile, formic acid, methanol, and trifluoroacetic acid. After trying many different buffers, chemicals, and solvents like trifluoroacetic acid, formic acid, methanol, and acetonitrile, RIMEGEPANT-A and RIMEGEPANT were finally separated using a Hypersil BDS (C18, 100 x 4.6 mm, 3 m) column and a mobile phase of 95:5 v/v Methanol and buffer.1.5 mL/min was the flow rate. Analytical methods that aren't sensitive enough and limits on the amount of impurity samples make it hard to find rimegepant-A. So, it is very important to find a way to measure the amount of RIMEGEPANT-A in the rimegepant drug substance used to make rimegepant drug products without sacrificing how sensitive the test is.

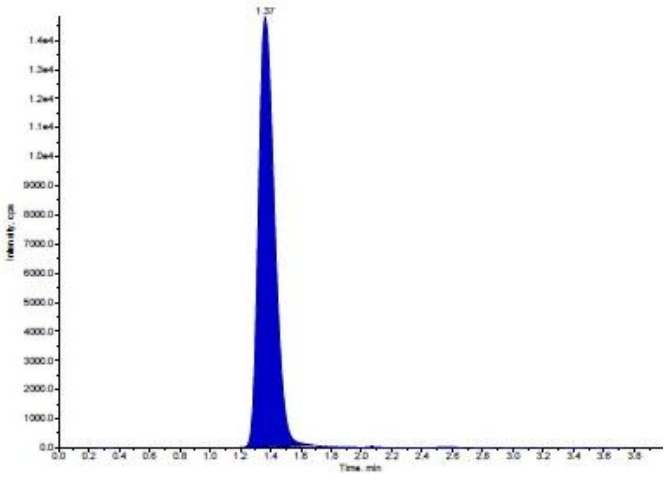


Fig-2 Optimized chromatogram of Rimegepant-A

3.2 Validation study: After trying many different buffers, chemicals, and solvents like trifluoroacetic acid, formic acid, methanol, and acetonitrile, RIMEGEPANT-A and RIMEGEPANT were finally separated by using a Hypersil BDS (C18, 100 x 4.6 mm, 3 m) column and a mobile phase of 95:5 v/v Methanol and buffer.The ICH guidelines were followed during the validation process. In order to validate the procedure, 0.01% solution of RIMEGEPANT-A was injected in relation to 5 mg/mL of Rimegepant, and their Signal/Noise ratios were calculated. Now, RIMEGEPANT-A concentration was gradually decreased to obtain S/N ratios of 3:1 and 10:1, respectively, in order to determine LOD and LOQ values.

RIMEGEPANT-linearity A's was set to be between LOQ and 150% (4.767–27.000 ppm) of the projected permissible level. Thus, RIMEGEPANT-A solutions at concentrations of 40%, 80%, 100%, 120%, and 150% were produced and administered one at a time. The calibration curve between RIMEGEPANT-A concentration and peak area was drawn. Repeatability was looked at by figuring out the %RSD of six measurements taken on the same day after injecting six new solutions with 0.01% RIMEGEPANT-A.To determine intermediate precision, the same experiment was conducted six times. By adding known amounts of RIMEGEPANT-A (LOQ to 100% level) to known amounts of material at given intervals, the accuracy of the procedure was evaluated.

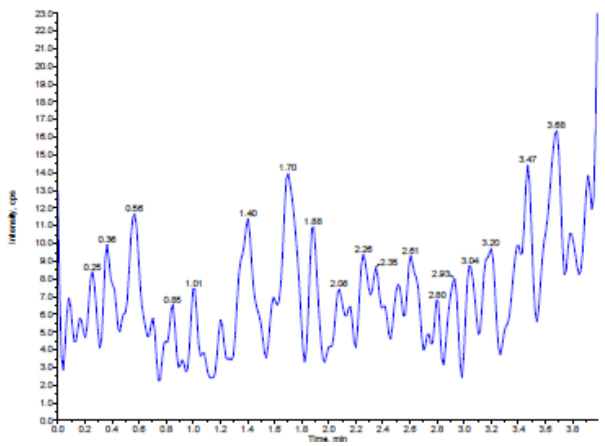
3.2.1. System suitability: One of the primary criteria to determine an instrument's precision is system suitability performance. So, the system's applicability was determined by injecting the standard solution six times, and then calculating the peak area's %RSD for rimegepant-related compound A. Table 2 contained the information. The cumulative%RSD from six standard injections with online standards and the%RSD of the RIMEGEPANT-A peak were both within the pre-defined specification limit, which said that the%RSD should not be more than 15.0%.

Table 2: System suitability parameters of RIMEGEPANT-A

Injection no.	Peak area
1	4665.99
2	4663.07
3	4560.94
4	4740.70
5	4584.62
6	4624.78
Average	4640.02
%RSD	1.39

3.2.2. Specificity: The specificity study for RIMEGEPANT-A was set up by injecting the blank solution, the standard solution, and the standard solution that had been tampered with. This was done to find out how any known or unknown impurities affected the retention time of

RIMEGEPANT-A. At the RIMEGEPANT-retention A time of 1.160 minutes in the blank, there was no interference.The RIMEGEPANT-A retention times in the standard and spiked standard solutions were comparable. Figures 2 and 3 display the chromatographic specifics.



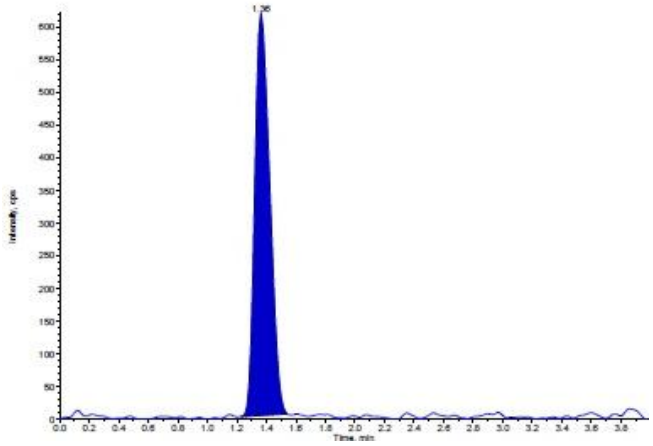


Figure-2 Blank chromatogram of Rimegepant- A Figure-3LOQ chromatogram of Rimegepant- A

3.2.3. Limit of Detection (LOD): With RIMEGEPANT-A, a test was done to find out what the method's lowest detection limit was. The 0.00015% test concentration was taken into account when making the LOD standard solution. This led to a signal-to-noise ratio of 3.71 and the values in table 3.

Table-3 LOD & LOQ data of Remigepant-A

parameter	Signal to noise ratio (S/N)	Concentration(ppm)
LOD	3.71	1.43
LOQ	14.19	4.77

3.2.4. Limit of Quantification (LOQ): Based on the concentration found in the LOD, three times the LOD concentration (0.0005%) was added to the LOQ standard solution, resulting in a S/N ratio of around 14.19 for RIMEGEPANT-A. The method's sensitivity is sufficient as evidenced by the low values of LOD and LOQ.

3.2.5. Method Precision: A six-time specification level rimegepant test sample spike with rimegepant-A was applied, and the sample was then analysed for the method precision study.

3.2.6. Intermediate precision: Precision studies were carried out using different columns and freshly made solutions on a different day, with a different analyst, to demonstrate the method's

reproducibility. Table 6 shows how the procedure precision is different from the intermediate precision. The procedure and results of intermediate precision are found to be within the limits that were set.RIMEGEPANT-content A's had a 4.26 percent RSD for technique precision (acceptance limits not more than 10.0). RIMEGEPANT-content A's RSD for intermediate precision is 4.00 percent. (Not more than 10.0 for acceptance limits). Table 4 gives a brief summary of what happened.

Table 4: Precision Results of Rimegepant-A

No. of preparations	**Peak area**	
	Method precision	**Intermediate precision**
1	4220.62	4210.62
2	4218.18	4218.18
3	4350.34	4340.34
4	4157.12	4137.12
5	4183.75	4283.75
6	4134.87	4134.87
Average	4210.81	4220.81
Standard deviation	76.15	80.93
% RSD	1.88	1.91

3.2.7. Accuracy: When different amounts of a sample with an unknown concentration are added to a sample whose concentration is known, this is called an accuracy study. So, the test sample was spiked three times with RIMEGEPANT-A at LOQ, 50%, 100%, and 150% levels from three different preparations, and the amount of RIMEGEPANT-A in Rimegepant was calculated. The percentage of RIMEGEPANT-recovery A ranged from 80 to 101 at LOQ, 50%, 100%, and 150%. Table 5 shows a summary of the results for accuracy. Within the given range, the method was found to be correct.

Table 5: Accuracy Results of Rimegepant-A

Accuracy levels	No. of preparations	Peak area	% Recovery

LOQ	1	1380.02	101.00
	2	1346.10	99.00
	3	1383.94	102.10
50%	1	2388.88	103.00
	2	2267.30	97.50
	3	2304.20	98.70
100%	1	4220.62	91.00
	2	4218.18	91.50
	3	4350.34	93.90
150%	1	6354.88	90.90
	2	6499.08	92.80
	3	6114.37	87.50

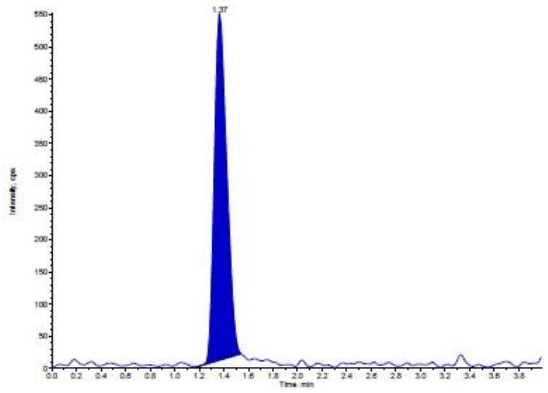


Figure-4 Chromatogram of LOQ

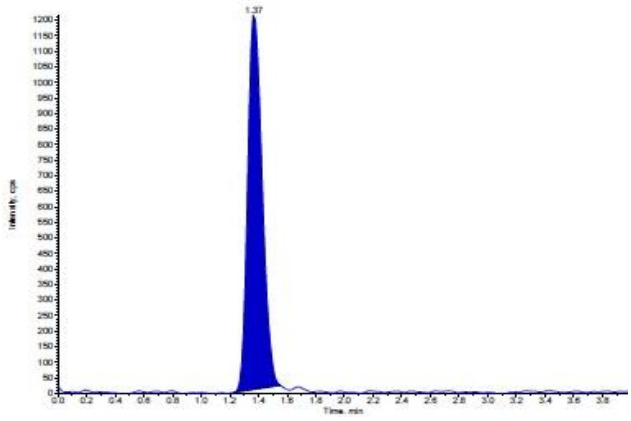
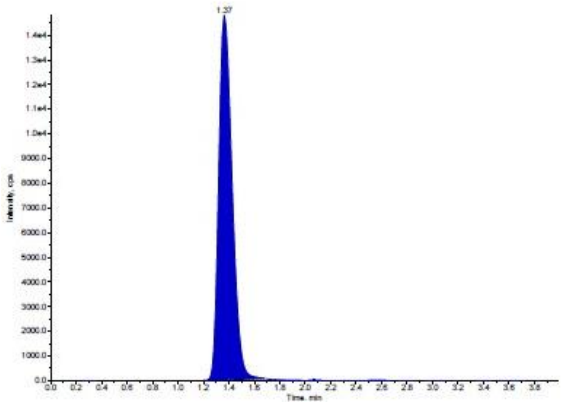


Figure-5 Chromatogram of 50%



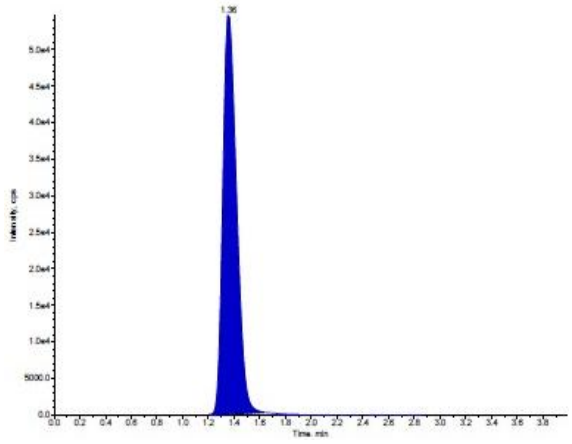


Figure-6 Rimegepant-A Chromatogram of 100%

Figure-7 Rimegepant-A Chromatogram of 150%

3.2.8. Linearity: A study was done on the linearity of the rimegepant-related compound A. The linearity ranged from the LOQ level to 150% of the limit. The linearity graph was used to figure out RIMEGEPANT-correlation A's coefficient, which was found to be 0.9990.Table 6 presents the results, and Figure 8 shows the graph.

Table 6: Linearity results of Rimegepant-A

level	**Concentration(ppm)**	**Peak Area**
LOQ	4.767	1380.85
50	9.00	23.58.16
75	13.50	3555.80
100	18.00	4747.76
125	22.50	5878.87
150	27.00	7121.44
Regression coefficient(r^2)		0.9990

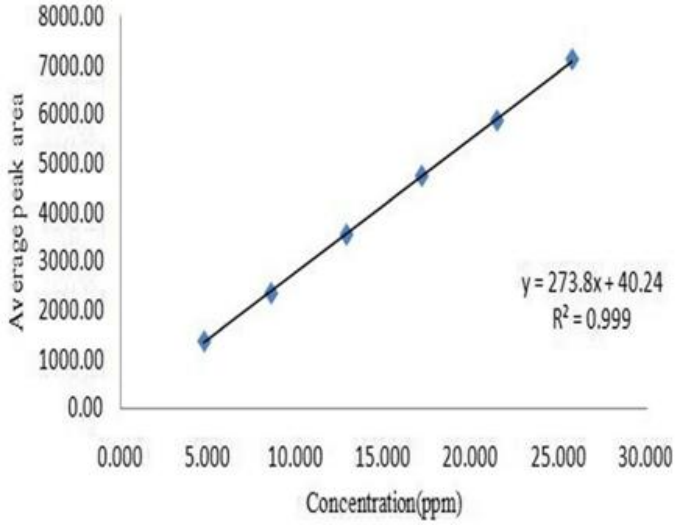


Figure 8: Linearity graph of Rimegepant-A

4. Conclusion:

For the quantification of genotoxic impurities at the trace level, a straightforward analytical approach was created and validated. Using liquid chromatography and a mass spectrometer, RIMEGEPANT-A in the drug compound rimegepant was identified. The method's complete validation established its specificity, linearity, accuracy, precision, and toughness. Even though only one mass analyzer and isocratic mode chromatography were used to design and test the method, it worked well in terms of sensitivity and specificity. It was also simple, right, and a good deal. Both the LOD and the LOQ were found to be 4.79 and 13.46 at low concentrations. The sample that was made with the analytical solution was still stable after 24 hours.So, this method can be used to find contaminants.When making rimegepant pharmacological compounds, rimegepant-A is used.

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7.Conflicts of Interest: There are no conflicts of interest, according to the authors, regarding the publishing of this paper.

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