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GC-MS/MS: A TARGETED QUANTIFICATION OF POTENTIAL NITROSAMINE IMPURITIES IN APIXABAN

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Keywords:

Gas Chromatography-Mass Spectrometry (GC-MS), N-nitrosoethylisopropylamine (NEIPA), N-ethyl-N-nitrosoethanamine (NDEA), N-methyl-N-nitrosomethanamine (NDMA), Limit of Detection (LOD), Limit of Quantification (LOQ), etc

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ABSTRACT: The detection and quantification of nitrosamine impurities in pharmaceutical products are critical due to their potential carcinogenicity. This study presents the development of a sensitive Gas Chromatography-Mass Spectrometry (GC-MS) method for the analysis of nitrosamine impurities in Apixaban drug substance. The method demonstrates high specificity, sensitivity, and compliance with regulatory guidelines, ensuring the safety and quality of Apixaban for therapeutic use. The method, designed to detect harmful contaminants in apixaban, performs effectively and meets all essential standards. The Mass spectrometry technique accurately confirmed the presence of NDMA, NDEA, and NEIPA at specified retention times. In accordance with established guidelines, the method underwent multiple parameters during development & validation ensuring its accuracy, sensitivity, and reliability, confirming the ability to detect these pollutants even at trace levels. The system operates continuously without interference from other pharmaceuticals, making it particularly suited for targeting these specific impurities. The method demonstrates the ability to detect minute quantities of nitroso-contaminants, utilizing well-established limits of detection and quantification. Recovery rates ranged from 96% to 103%, indicating high accuracy, precision, and minimal variability in results. Overall, this method is sensitive, precise, and consistent, thereby ensuring the safety and quality of apixaban in pharmaceutical products.

INTRODUCTION: Apixaban selectively inhibits Factor Xa, an essential component in the coagulation cascade responsible for the conversion of prothrombin to thrombin. By blocking this step, apixaban reduces thrombin generation and the formation of blood clots, without directly affecting platelet aggregation.

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Apixaban (1 - (4 - methoxyphenyl) -7– oxo - 6 - [4-(2-oxopiperidin-1-yl) phenyl]-4, 5, 6,7-tetrahydro-1H-pyrazolo [3,4-c] pyridine-3-carboxamide) is a direct oral anticoagulant (DOAC) widely used to treat and prevent venous thromboembolic diseases, including atrial fibrillation and venous thromboembolism. As with any pharmaceutical treatment, ensuring the safety and quality of apixaban is paramount to minimize patient risks and maximize therapeutic effectiveness [1-5].

Apixaban: A critical aspect of apixaban's safety profile involves the detection and evaluation of contaminants, particularly those that may be genotoxic or carcinogenic. Genotoxic impurities

(GTIs) are chemical entities capable of causing genetic alterations or chromosomal damage, while carcinogens (CIs) have the potential to induce cancer. Even trace amounts of these substances can pose significant health risks over time. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH) have established guidelines to regulate the permissible levels of such toxins in pharmaceutical products, thereby safeguarding patient health [6, 7, 8].

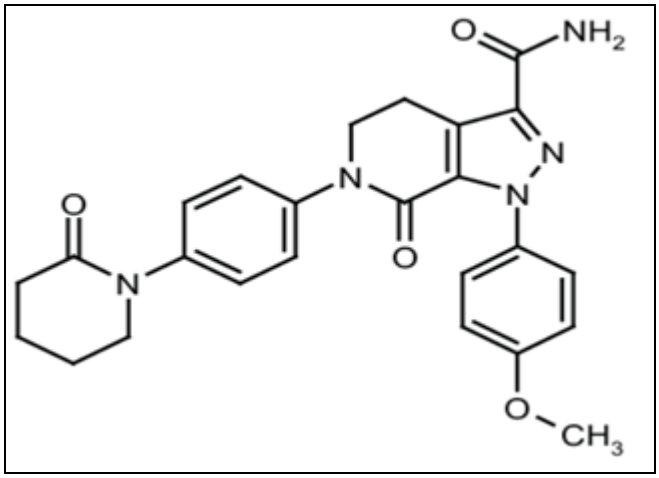

FIG. 1: 1 - (4 - METHOXYPHENYL) – 7 – OXO – 6 -[4-(2-OXOPIPERIDIN-1-YL) PHENYL]-4, 5, 6, 7-TETRAHYDRO- 1*H*-PYRAZOLO [3, 4-C] PYRIDINE-3-CARBOXAMIDE

Due to the widespread and increasing use of apixaban, there is a need for reliable, sensitive, and validated analytical methods (e.g., HPLC, LC-MS/MS, GC-MS) to monitor its levels in drug substance, pharmaceutical formulations and biological matrices for pharmacokinetic studies, and forensic applications. Given the complexity of pharmaceutical manufacturing and stringent control standards, reliable analytical techniques are essential for identifying and quantifying potential genotoxic and carcinogenic contaminants in apixaban. These methods must be sensitive, accurate, and capable of detecting minute levels of impurities, even in the presence of the active pharmaceutical ingredient and excipients. Furthermore, they should be suitable for both official documentation and ongoing quality control processes, ensuring consistency and repeatability [9-12]. This study aims to develop and evaluate an analytical approach for assessing the most likely genotoxic and carcinogenic compounds in apixaban [13, 14]. The Gas Chromatography-Mass Spectrometry (GC-MS) method will be employed to identify and quantify these contaminants, providing a robust tool for ensuring the safety and quality of apixaban formulations [15, 16].

MATERIALS AND METHOD:

Materials:

Chemicals: Merck Life Science sources all of the compounds utilized in this analysis NEIPA, NDEA, NDMA, methanol. The active pharmaceutical component under research, Apixaban, depends on these compounds to identify and quantify any genotoxic and carcinogenic contaminants. Apixaban was obtained as a gift sample from Anhui biochem (China).

Instruments:

- Gas Chromatograph equipped with programmable temperature, flow controller and MS detector (Shimadzu GC-2010 with MS detector)
- Liquid Auto sampler (Shimadzu AOC-20i Auto sampler)
- Data handling system (GCMS Solution version 2.61)
- Fused silica capillary column Rxi-1ms; 60 m long; 0.25mm internal diameter, coated with 100% Di methyl polysiloxane stationary phase of 0.25 µm film thickness.

Method:

Method Development: Several challenges were encountered during the development of the GC-MS method for apixaban quantification. These included low extraction efficiency, matrix interference, and poor peak shape. Optimization steps involved adjusting the sample pH using sodium hydroxide (1 N, freshly prepared), selecting an appropriate solvent system, and incorporating an internal standard to improve reproducibility [17, 18]. As a Internal standard, Dodecane with defined concentration was chosen for its stability and lack of interference with the analyte peak. Final GC-MS conditions were established through iterative testing of various temperature ramps, carrier gas flow rates, and split ratios. The optimized method resulted in sharp, well-resolved peaks with minimal matrix interference and consistent retention times.

Various critical parameters were considered during the method development for GC-MS (Gas Chromatography–Mass Spectrometry), including the choice of diluent (solvent), column selection, oven temperature programming, and other gas chromatographic conditions such as carrier gas flow rate, injector temperature, and detector temperature [19, 20]. In addition, mass spectrometric parameters were optimized [21, 22, 23].

The analytes of interest NEIPA, NDEA, and NDMA are volatile compounds. Therefore, GC-MS with liquid injection technique was selected to ensure the Mass and the concentration of Nitrosamines present in the subjected drug substance. The low detection limits can be achieved with this approach. The sample matrix consisted of 40 mg/mL. At such a high concentration, there is a risk of column damage, making it essential to protect the column from excessive sample load. This was addressed by selecting a solvent in which the active pharmaceutical ingredient (API) was insoluble, while the target analytes remained soluble. This approach minimized matrix interference from the API during analysis. Several solvents were evaluated during method development, including dichloromethane, methanol, isopropanol, and n-hexane. Based on criteria such as analyte recovery and minimization of matrix interference at the analyte retention time, a mixture of n-hexane and methanol was selected as the diluent for both standard and sample preparations. Various GC columns were tested during the development phase, including DB-5, DB-1, DB-624, and Rtx-1301, each with different dimensions. Based on chromatographic performance, specificity, and minimal baseline interference, the Rxi-1ms column (60 m length, 0.25 mm internal diameter, 0.25 µm film thickness) was found to be the most suitable for the analysis.

Conditions Pertaining to Chromatography: The analysis was performed using a gas chromatographic system equipped with an Rtx-5 capillary column (30 m × 0.53 mm I.D., 5.0 µm film thickness). The oven temperature program was initiated at 60°C with a 4-minute hold, ramped at 6°C/min to 130°C, then at 10°C/min to 220°C with a final hold of 5.33 minutes. The injector temperature was set at 180°C, and detection was carried out using a Flame Ionization Detector (FID) maintained at 250°C. Helium was used as the carrier gas at a constant pressure of 40 kPa. The injection volume was 2.0 µL with a split ratio of 1:3. The total run time for the analysis was 10 minutes.

Conditions Pertaining to Mass Spectrometry: The mass spectrometry conditions included an ion source temperature of 240°C, interface temperature of 250°C, and solvent cut time of 5 minutes. The acquisition was performed in Electron Ionization (EI) mode. Targeted analysis was conducted for nitrosamine impurities, with transitions monitored for NDMA (m/z 74), NDEA (m/z 102), and NEIPA (m/z 116).

Standard and Sample Solutions Preparations:

1N Sodium Hydroxide Solution: Accurately weighed approximately 8000 mg of Sodium Hydroxide pellets and transferred them into a 200 mL volumetric flask. Added approximately 50 mL of distilled water to dissolve the pellets completely. Once dissolved, diluted the solution to the 200 mL markwith distilled water, and mixed thoroughly.

Internal Standard Solution: Accurately weighed 700 mg of Dodecane and transferred it into a 25 mL volumetric flask containing approximately 15 mL of methylene chloride. Dissolved the dodecane completely, then diluted to the mark with methylene chloride and mixed thoroughly. To prepare a working solution, transfer 2.5 mL of this stock solution into a 500 mL volumetric flask and dilute to volume with methylene chloride, resulting in a final concentration of 140 mg/mL.

Preparation of Blank Solution: Transferred 3.0 mL of the internal standard solution into a 15 mL centrifuge tube. Added 4.0 mL of 1 N sodium hydroxide solution to the tube. Centrifuge the mixture at 3000 rpm for 5 minutes. Carefully collected the lower (methylene chloride) layer using an autopipette, and passed it through anhydrous sodium sulphate to remove any residual moisture.

Preparation of Standard Solution: Accurately weighed 21 mg of p-toluidine and transferred it into a 25 mL volumetric flask containing approximately 15 mL of the internal standard solution. Dissolved the compound completely and diluted to the volume with the internal standard solution. To

prepare a working solution, diluted 1.0 mL of this stock solution to 50 mL using the internal standard solution.Transferred 3.0 mL of the resulting standard solution into a 15 mL centrifuge tube, then added 4.0 mL of 1 N sodium hydroxide solution. Centrifuged the mixture at 3000 rpm for 5 minutes. Carefully collected the lower methylene chloride layer using an autopipette, and pass it through anhydrous sodium sulphate to remove residual moisture.

Preparation of Sample Solution: Accurately weigh 500 mg of the sample material into a 15 mL centrifuge tube. Add 4.0 mL of 1 N sodium hydroxide solution and shake the mixture for approximately 2 minutes using a mechanical shaker. Then, add 3.0 mL of the internal standard solution to the same tube. Shake the contents manually for an additional 2 minutes. Centrifuge the mixture at 3000 rpm for 5 minutes. Carefully collect the lower (methylene chloride) layer using an autopipette, and pass it through anhydrous sodium sulphate to remove any remaining moisture.

GC-MS/MS-Based Validation of a Quantitative Method for the Determination of N-Nitrosamines: Validation criteria for GC-MS/MS methods used in the detection of three N-nitrosamines include system suitability, specificity, sensitivity, linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy, precision, and solution stability [24, 25, 26]. The LOQ was determined as the lowest concentration with a signal-to-noise ratio of 10:1, while the LOD was defined as the concentration corresponding to a signal-to-noise ratio of 3:1. The matrix effect (ME) was assessed by means of equation [27, 28, 29, 30].

Specificity: Combining active pharmaceutical compounds with nitrosamine standards revealed analytical specificity. The lack of interference of the approach during nitrosamine retention permitted consistent difference of the target analyte from APIs and other sample components. Helping to find trace nitrosamine contamination in complex pharmaceutical matrices enhances the regulatory testing procedures.

Limit of Detection (LOD): The lowest routinely detectable concentration of N-nitrosamines is found using the limit of detection (LOD). Using the signal-to-noise (S/N) ratio, standard mixes with concentrations between 0.1 and 1.0 ng/mL were studied. The specified detection threshold was three S/N, therefore ensuring that the analyte signal at least three times greater than the background noise. The sensitivity of the method for trace N-nitrosamines was confirmed by LOD testing, therefore ensuring public health safety and regulatory requirements compliance.

Limit of Quantification (LOQ): Defined as the limit of quantification, the lowest concentration of N-nitrosamines that may be regularly identified based on adequate accuracy and precision. Standard mixes with concentrations between 0.2 and 1.0 ng/mL revealed a signal-to- noise ratio of 10, therefore establishing their quantitative acceptable standards.

The relative standard deviation (RSD) of sequential injections indicates that the procedure has accuracy less than 10%. The LOQ study suggests that in pharmaceutical research the strategy might assess low N-nitrosamine levels for regulatory compliance and quality control.

Range: The method specifically has a linear concentration range for N-nitrosamines. The Limit of Quantification (LOQ) defines the lower threshold; the highest concentration reachable free from instrument limitations such as detector saturation or column overload defines the upper limits of measurement. By means of the assessment of the process from the limit of quantification to the maximum detectable level across many concentrations, reliable data for regulatory compliance and pharmacological quality are guaranteed.

Linearity: Linearity guarantees proportional response of the detector to N-nitrosamine concentration. A calibration curve was constructed to demonstrate typical solutions with regard to peak area and concentration. The method shows linearity in the 0.5 to 100 ng/mL range with a R^2 value better than 0.99. Constant analyte quantification across a large range of concentrations is ensured by statistical validation of the slope and y-intercept. This validation ensures the operational accuracy for regulatory measurement and routine testing.

Accuracy and Precision: 5 and 10 ng/mL nitrosamine concentrations allow repeatability testing to assess accuracy and precision. Six consecutive injections with a relative standard deviation threshold of ≤10% helped one to find accuracy. Comparing concentrations to expectations helped to evaluate the method's consistency and accuracy. Crucially for regulatory compliance, these tests revealed that the method can provide consistent and reliable results at several dosages.

RESULTS AND DISCUSSION:

Results:

Mass Spectral Analysis: The peak of NEIPA elutes at 1.906 minutes. NDEA elutes at 5.92 minutes and NDMA elutes at 7.273 NEIPA mass spectra showed fragments at m/z 119. Similarly, NDEA showed fragments at m/z 103 and NDMA showed fragments at m/z 107 respectively. Spectra of both the components is compared and matched with NIST spectrum library. Refer spectra in **Fig. 2, 3 & 4.**

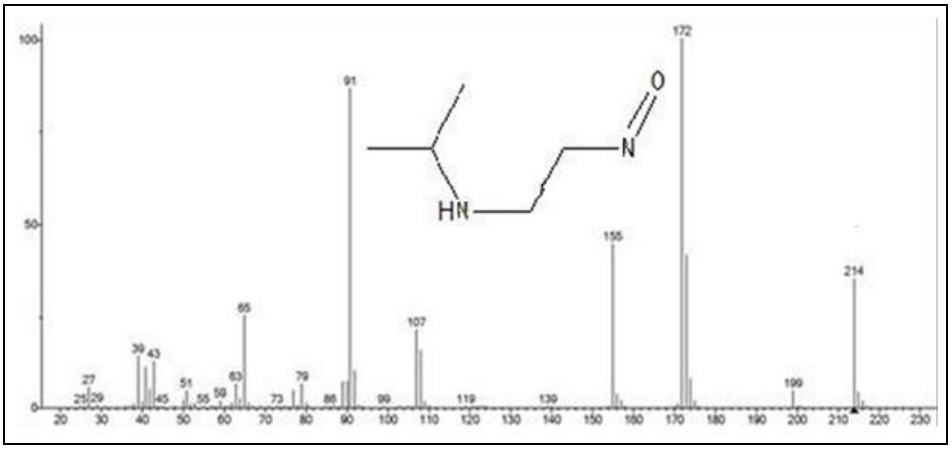

FIG. 2: SPECTRUM OF N-NITROSOETHYLISOPROPYLAMINE (NEIPA)

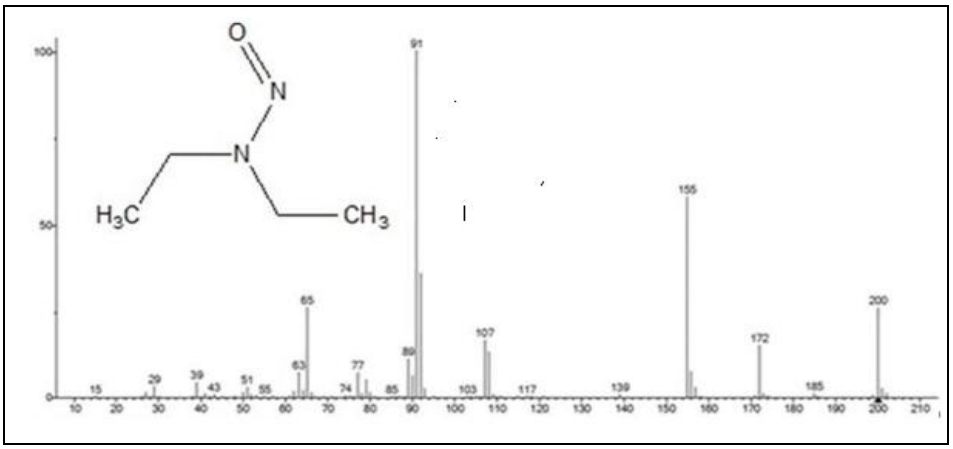

FIG. 3: SPECTRUM OF N-ETHYL-N-NITROSOETHANAMINE (NDEA)

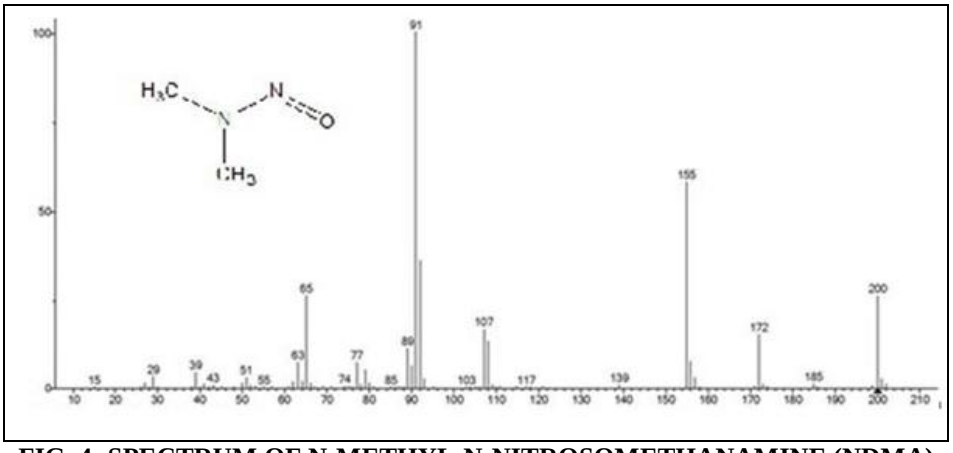

FIG. 4: SPECTRUM OF N-METHYL-N-NITROSOMETHANAMINE (NDMA)

Method Validation: Developed method is proposed for the complete validation to prove it's intended use. Validation planning was conducted on the basis of ICH guideline. Important validation parameters performed during the method validation were specificity, system suitability, sensitivity (LOQ, LOD), linearity, precision, accuracy.

System Suitability: Before every parameter, six injections of system suitability solution were injected into GC-MS to check the performance of the system as a system suitability solution.

Specificity: Specificity analysis was performed to confirm the absence of interference at the retention times (RT) of the target analytes. The observed retention times were 1.906 minutes for NEIPA, 5.92 minutes for NDEA, and 7.273 minutes for NDMA. No peaks were observed at these retention times in the blank solution, confirming the method's specificity and indicating that the analytes were free from interference.

Detection Limit (LOD) and Quantification Limit (LOQ) LOD-LOQ Prediction: The LOD-LOQ (Limit of Detection and Limit of Quantitation) prediction was based on the linear response of peak areas to increasing concentrations (µg/g) of NEIPA, NDEA, and NDMA. A consistent rise in detector response was observed with increasing concentration. For NEIPA, the peak area increased from 3116 at 2 µg/g to 50845 at 16 µg/g, showing a strong linear correlation. NDEA showed a progressive area response starting from 2148 at 1 µg/g to 27222 at 16 µg/g. NDMA demonstrated linearity with a peak area increasing from 4079 at 2 µg/g to 19321 at 8 µg/g. These results confirm the method's suitability for detecting and quantifying these nitrosamines at low concentrations, essential for impurity profiling.

Linearity: Linearity solutions were prepared after quantitatively diluting standard stock solution to obtain solutions in the range of LOQ and 150% level of the specification level and proved that method was linear.

Linearity of NEIPA: The linearity of NEIPA was evaluated across six concentration levels ranging from the limit of quantitation (LOQ) to 150% of the evaluation limit. The concentration levels tested were 0.17, 0.85, 1.36, 1.70, 2.04, and 2.55 µg/g, with corresponding mean area responses of 1904, 2254, 2592, 2756, 2908, and 3219, respectively. The calibration curve showed a strong linear relationship with a correlation coefficient (R^2) of 0.997, indicating excellent linearity. The slope and intercept of the regression line were 551.7 and -1808.3, respectively. The residual sum of squares (STEYX) was 470.39, suggesting a well linear method.

Linearity of NDEA: The linearity assessment for NDEA was performed over the concentration range of 0.16 to 2.4 µg/g. The mean area responses for concentrations 0.16, 0.80, 1.28, 1.60, 1.92, and 2.40 µg/g were found to be 1074, 1399, 2199, 2521, 2982, and 3214, respectively. The linear regression analysis yielded a slope of 1244.4 and an intercept of 462.15, with a correlation coefficient (R^2) of 0.9387. The residual sum of squares (STEYX) was 853.97, indicating moderate data scatter around the regression line.

Linearity of NDMA: NDMA showed linearity over a concentration range of 0.27 to 4.05 µg/g. The respective mean area responses for concentrations 0.27, 1.35, 2.16, 2.70, 3.24, and 4.05 µg/g were 527, 3650, 4954, 6656, 8412, and 10136. The regression analysis indicated a slope of 2525.4 and an intercept of -62.76. The linearity was found to be strong with a correlation coefficient (R^2) of 0.995. The standard deviation associated with the regression was 3448.56, supporting the reliability of the calibration model.

Precision (Repeatability): System Precision was evaluated by six replicate injections of standard solutions for NEIPA, NDEA, and NDMA. NEIPA showed a mean area of 30077.60, with an SD of 27.54 and %RSD of 0.09%.NDEA had a mean area of 16826.60, SD of 21.62, and %RSD of 0.13%.NDMA yielded a mean area of 3,658.60, SD of 29.90, and %RSD of 0.82%.All %RSD values are well below 2%, indicating excellent system precision and consistency of the instrument response.

Method Precision: Method precision was assessed by analyzing six independent sample preparations: For NEIPA, the mean concentration was 10.158 µg/g, with an SD of 0.0288 and %RSD of 0.28%.NDEA had a mean of 9.954 µg/g, SD of

0.08331, and %RSD of 1.50%.NDMA showed a mean of 1.3546 µg/g, SD of 0.0033, and %RSD of 0.24%.These results confirm that the method demonstrates good repeatability and reliability for quantitative analysis.

In conclusion, both system and method precision results comply with acceptable analytical standards, supporting the robustness of the developed method.

Accuracy: An accuracy i.e recovery study was conducted at three levels50%, 100%, and 150%to evaluate the accuracy and precision of the analytical method for NEIPA, NDEA, and NDMA. For NEIPA, the amount recovered ranged from 96% to 100% across all levels, with a mean recovery of 98%, a standard deviation (SD) of 1.05, and %RSD is 1.12%. This indicates consistent and accurate quantification at different concentrations. NDEA recovery ranged between 97% and 100%, showing slightly better precision, with a mean recovery of 99% with standard deviation of 0.75, and %RSD of 0.75%. NDMA showed the highest recovery consistency, with values ranging from 98% to 103%, a mean recovery of 100%, standard deviation of 1.32, and a %RSD of 1.32%.Overall, the method demonstrated high accuracy and reproducibility for all three analytes, supporting its suitability for routine analysis in pharmaceutical matrices. For spiked sample chromatogram refer **Fig. 5.**

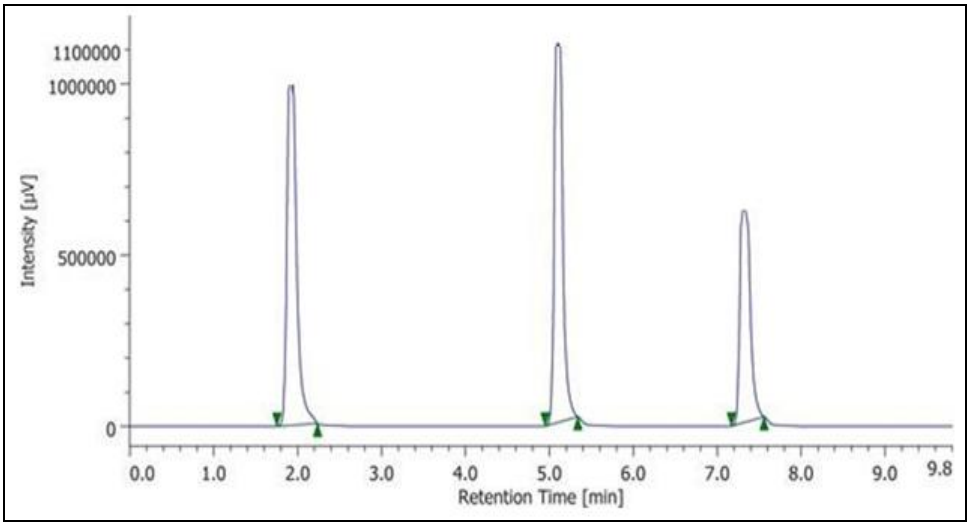

FIG. 5: CHROMATOGRAM OF SPIKED SAMPLE SOLUTION (RETENTION TIME: 1.906 MIN: NEIPA, 5.92 MIN: NDEA, 7.273 MIN: NDMA)

DISCUSSION: The validated GC-MS method developed in this study successfully meets the stringent analytical requirements for detecting genotoxic and carcinogenic impurities NEIPA, NDEA, and NDMA in Apixaban. The distinct retention times and unique mass spectral profiles of each analyte, confirmed through the NIST spectral library, ensured unambiguous identification.

The method displayed excellent sensitivity, with low LOD and LOQ values, enabling the detection of trace levels of impurities, well below the regulatory limits. System suitability studies demonstrated consistent and precise performance across multiple injections, confirming the method's reliability. Specificity assessments ruled out interference from excipients or co-eluting substances, underscoring the method's selectivity. Linearity studies showed excellent correlation coefficients, validating the method's capability for accurate quantitation over a broad concentration range. Additionally, precision and accuracy evaluations yielded low %RSD values and recovery rates within 96–103%, reinforcing the method's repeatability and reliability.

Chromatographic resolution of the impurities from the matrix further supports the robustness of the method. These findings confirm that the developed method aligns with ICH validation guidelines and provides a strong analytical foundation for routine quality control. The results, summarized in **Table 1**, emphasize that this GC-MS method is a robust and effective tool to safeguard the safety and quality of Apixaban by ensuring the reliable detection of potential contaminants.

TABLE 1:

Parameter	NEIPA	NDEA	NDMA
System Precision (%RSD)	0.09%	0.13%	0.82%
Method Precision (%RSD)	0.28%	1.50%	0.24%
LOD-LOQ Slope	276.34	138.14	242.87
LOD-LOQ Intercept	-4178.9	-513.49	24.75
LOD-LOQ STEYX	15833.41	8251.2	886.09
LOD-LOQ Correlation (r)	0.9995	0.9988	0.996
LOD (µg/g)	0.057	0.053	0.09
LOQ (µg/g)	0.174	0.16	0.27
Linearity Range (µg/g)	0.17 – 2.55	0.16 – 2.40	0.27 – 4.05
Linearity Slope	551.7	1244.4	2525.4
Linearity Intercept	-1808.3	462.15	-62.758
Linearity STEYX / SD	470.39	853.97	3448.56
Linearity Correlation (r)	0.997	0.9387	0.995
Accuracy – Mean Recovery	98.4%	99.4%	100.5%
Accuracy – SD	1.05	0.75	1.32
Accuracy – %RSD	1.12%	0.75%	1.32%

CONCLUSION: The developed GC-MS method demonstrated excellent sensitivity, specificity, precision, and accuracy for the detection of NEIPA, NDEA, and NDMA impurities in Apixaban. Distinct retention times and mass spectral fragments confirmed the reliable identification of each analyte.

Validation results, including low LOD and LOQ values, high linearity, and strong recovery rates, meet ICH regulatory standards. The method showed no interference from excipients, confirming its selectivity. System suitability and reproducibility were consistently achieved across replicate injections. Overall, this validated method provides a robust analytical tool to ensure the quality and safety of Apixaban by effectively monitoring potential genotoxic and carcinogenic impurities.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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