Frontiers in Life Sciences Research
Vol. 1, No. 4, Oct - Dec 2025, pp. 49-59
ISSN: 3107-5274, DOI: https://doi.org/10.17051/FLSR/01.04.08

Development and Validation of a GC-MS/MS Method for the Determination of Genotoxic Nitrosamine Impurities in Levetiracetam Extended-Release Tablets

Pankaj Bhalerao[1] , Swarup Prabhune[2], Deepak Parekh[3]

[1]Research scholar, Shri Jagdishprasad Jhabarmal Tibrewala University, Vidyanagari, Jhunjhunu, Rajasthan – 333001, India.
[2]Senior Manager, Cipla Limited, Mumbai.
[3]Department of Chemistry, Shri Jagdishprasad Jhabarmal Tibrewala University, Vidyanagari, Jhunjhunu, Rajasthan – 333001, India.

Article Info

Article history:

Received : 22.10.2025
Revised : 19.11.2025
Accepted : 24.12.2025

Keywords:

Analytical quantification,
GC-MS,
multiple reaction monitoring (MRM),
validation, genotoxic and carcinogenic contaminants,
Nitrosamine impurities,
Levetiracetam etc.

ABSTRACT

A robust analytical procedure was developed and validated for the detection of genotoxic, carcinogenic, and nitrosamine contaminants in Levetiracetam ER tablets using Gas Chromatography–Mass Spectrometry (GC-MS) with Multiple Reaction Monitoring (MRM). For NEIPA, NMPA, and NDEAwith considering the 0.5g MDD for Levetiracetam Tablets acceptable intake should not be more than 0.19µg/g.

The method demonstrated exceptional sensitivity, achieving a limit of quantification (LOQ) of 0.06µg/g and a limit of detection (LOD) of 0.02µg/g. Furthermore, Calibration curves exhibited strong linearity with correlation coefficients exceeding 0.99, while specificity was confirmed by minimal interference from excipients. Recovery experiments yielded results between 92.7% and 99.0%, validating the accuracy and reliability of the method. The validated approach ensures dependable monitoring of these critical contaminants, thereby safeguarding product quality, patient safety, and regulatory compliance.

1. INTRODUCTION

Levetiracetam, an anticonvulsant medication, has shown to be quite safe and effective in the treatment of epilepsy. Reduced frequency of doses while keeping the medicine level constant in the circulation helps extended-release (ER) levetiracetam formulations deliver therapeutic benefits. Like other medications, levetiracetam ER pills might have minute levels of manufacturing, formulation, or storage contaminants.

Among the many kinds of pollutants, the possibility of genotoxic, carcinogenic, and nitrosamine ones to harm human health distinguishes them. Given their DNA-altering action, genotoxic toxins most certainly help cause cancer and other terrible diseases. [5,9]. Carcinogens agents by definition are able to cause cancer and raise long-term health risk. Many prescription drug recalls worldwide have brought nitrosamines—a kind of contamination often connected with the breakdown of certain pharmaceutical formulations—to the attention of regulators because of their carcinogenic potential. [10, 11]

NEIPA, NMPA, and NDEA are monitored in Levetiracetam ER because they are recognized nitrosamine impurities that can arise as process-related contaminants (from secondary/tertiary amines reacting with nitrosating agents) or as potential degradants under certain manufacturing/storage conditions.NEIPA (N-nitrosoethylisopropylamine) Formed when isopropyl amine derivatives (used in synthesis or present as intermediates) undergo nitrosation.NMPA (N-nitrosomethylpropylamine) Can originate from methyl propylamine residues or related solvents/reagents. It can Considered a process-related impurity since alkylamines are common in drug synthesis and may nitrosate under acidic or oxidative conditions. NDEA (N-Nitrosodiethylamine) is a well-known carcinogenic nitrosamine, historically linked to contamination in several APIs (e.g., sartans). It May

form if diethylamine or related precursors are used in synthesis or packaging materials.

Analytical techniques that can precisely assess these pollutants are thus essential to ensure the quality, safety, and compliance with rules of pharmaceutical items. [12, 13 14] Levetiracetam ER tablets include contaminants including nitrosamines, carcinogens, and genotoxins that only analytical techniques developed using extremely sensitive, specific, and robust approaches can identify. Particularly good for spotting minute pollutants with complex chemical compositions is gas chromatography-mass spectrometry (GC–MS) and related methods. [15-18]

The main aim of this study is levetiracetam ER tablet genotoxic, carcinogenic, and nitrosamine impurity detection and measurement. This study develops and validates a powerful and efficient analytical quantification technique. Developing a robust approach that meets legal criteria guarantees patient safety and helps to reduce the hazards connected with some dangerous contaminants. This study attempts to support the continuous efforts using advanced analytical methods to improve pharmaceutical product safety and quality control.

2. MATERIALS AND METHOD

1. Materials

1.1 Chemicals

The chemicals NDEA (N-Nitrosodiethylamine), NEIPA (N-Ethylisopropylamine), NMPA (N-Methyl-2-pyrrolidone), and Methanol are all sourced from Merck Life Science, a leading global supplier of chemicals and laboratory materials. These compounds are commonly used in the pharmaceutical industry, but their potential to form harmful nitrosamine impurities, particularly in drug formulations, necessitates rigorous monitoring.

1.2 Instrumentation

- 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.

2. Method [21-26]

2.1 Method development

Major important parameters in method development for GCMS was diluent (solvent), column, Oven programming, other gas chromatographic parameters like flow, injector temperature, detector temperature and mass spectrometer parameters. As the analyte of interest NEIPA, NDEA, NMPA were volatile in nature. The GC-MS liquid injection technique was decided for analysis due to low limit. Sample matrix was 40mg/mL. Due to high sample concentration the column might be damaged. It is also very important to protect the column from high concentration. It was resolved by using solvent in which API was insoluble and specifically analyte of interest were soluble. Because of this approach interference, due to API matrix can be distant.

Diluents used for developmental trials were Dichloromethane, Methanol, Isopropanol, n-Hexane. Based on factors like recovery and interference of matrix at the elution time of analyte, n-Hexane/Methanol was diluent used in standard as well as sample preparation. Columns used for the developmental trials were DB-5, DB-1, DB-624 and Rtx-1301 with different dimensional parameters. Based on chromatographic response, specificity and lesser baseline interference, Rxi-Ims column, 60 m length, 0.25 mm ID and film thickness 0.25 µm is found fit for the requirement.

2.2 Instrumentation and optimized GC-MS/MS conditions

Analyses of N-nitrosamines were performed on an Shimadzu GC-2010 with MS detectorand Shimadzu AOC-20i Auto sampler system. 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 thicknesswas used as the analytical column in this work. MS/MS detection was carried out on triple quadrupole mass spectrometer with electron ionization (EI) ion source. The GC oven program utilized an initial oven temperature of 40 °C, held for 0.5 min, raised firstly at 20 °C•min−1 to 200 °C, then to 240 °C at 40 °C/min, finally held for 3 min. The total run time was 12.5 min. Helium as the carrier gas was set at a flow of 1.0 mL/min. Both the interface temperature and injection temperature were set to be 250 °C. The injection volume was 1 µl in the split less mode.

The MS was operated in EI mode at 70 eV with a quadrupole temperature of 150 °C. The temperature of the ion source was set at 200 °C. The delay time of the solvent was 5 min. multiple reactions monitoring (MRM) mode was selected as the data acquisition for the quantitative determination of three kinds of Nitrosamine GTIs.

The precursor ions and product ions of four N-nitrosamine GTIs, as well as the optimized collision energy (CE)

Table 1. MRM parameters

Impurity	Precursor ion (Q1) m/z	Product ion (Q3) m/z	Collision Energy (CE)
NEIPA	116	75	15eV
NMPA	102	42	10eV
NDEA	104	74	12eV

2.3 Solution preparation

- **Diluent**

N-Hexane as diluent.

- **Blank**

N-Hexane as a blank.

- **Standard Solution**

Accurately weighed and transferred 0.025 g NEIPA, NDEA, NMPA into 100 mL volumetric flask containing 50 mL of diluent, then made up to the volume with diluent. Further, 0.153 ml of above solution was diluted in 50 mL flask with diluent. Further, 5.0 mL of above resulting solution was made up to 50 mL with diluent.Further, 5.0 mL of above resulting solution was made up to 50 mL with diluent (Concentration 0.0077µg/g).

- **Sample preparation**

Accurately weighed and transferred about 0.200 g of the sample, add 5.0 mL of diluent to it and sonicate for 5 minutes, then kept it for standby. After settled undissolved solid, centrifuge sample with 4000rpm for 10min. and then supernatant liquid taken in a GC vial for injection. The sample concentration is 40mg/mL.

2.4 Method Validation Parameters [25-29]

The method validation of GC-MS (MRM mode) follows the following key parameters:

1. Specificity and Selectivity

- Ensure that the method can differentiate target analytes from excipients, degradation products, and matrix interferences.
- Analyze blank samples, spiked samples, and real samples to confirm the absence of false positives.
- Use mass spectra comparison with reference standards.

2. Linearity and Calibration Curve

- Prepare a series of standard solutions with known concentrations (e.g.,0.0023, 0.0039, 0.0062, 0.0077, 0.0092, 0.0116µg/g).
- Construct a calibration curve by plotting peak area vs. concentration.
- Calculate the correlation coefficient ($R^2 \geq 0.99$) for method acceptability.

3. Limit of Detection (LOD) and Limit of Quantification (LOQ)

- LOD: The lowest concentration at which the analyte can be detected but not necessarily quantified. (Signal-to-noise ratio S/N ≥ 3).
- LOQ: The lowest concentration at which the analyte can be reliably quantified with acceptable precision and accuracy (S/N ≥ 10).

4. Accuracy (Recovery Study)

- Assess recovery by spiking known amounts of impurities in placebo, API, or formulation samples.
- Calculate % recovery at 50%, 100%, and 150% levels of the target concentration.
- Acceptable recovery range: 80%–120% for trace-level impurities.

5. Precision (Repeatability and Intermediate Precision)

- Intra-day precision (Repeatability): Analyze six replicates of a sample at the target concentration and determine the Relative Standard Deviation (RSD).
- Inter-day precision (Intermediate Precision): Conduct analysis on different days, analysts, and instruments to ensure reproducibility.
- Acceptable %RSD ≤ 10% for trace-level analysis.

6. Robustness

Assess the impact of minor changes in method parameters, such as:

- Carrier gas flow rate
- Oven temperature program
- Injection volume
- Ion source temperature

Ensure that variations do not significantly affect retention time, peak shape, or quantification results.

7. System Suitability Testing (SST)

Verify instrument performance before each analysis using a standard solution.

Parameters include

- Retention time reproducibility (≤2% variation)
- Peak area precision (≤5% RSD)

- Resolution between critical peaks (≥1.5)

3. RESULTS AND DISCUSSION

- **Mass spectral analysis**

The peak of NEIPA elutes at 1.001 minutes, NMPA elutes at 3.002 minutes and NDEA elutes at 5.04Minutes. NEIPA mass spectra showed fragments at m/z 119. Similarly, NMPA showed fragments at m/z 139 respectively and NDEA mass spectra showed fragments at m/z 102. Spectra of both the components is compared and matched with NIST spectrum library. Due to maximum response of these m/z values used for quantification of NEIPA and NMPA, NDEA by Multiple reaction monitoring (MRM). Refer spectra in figure 1-3.

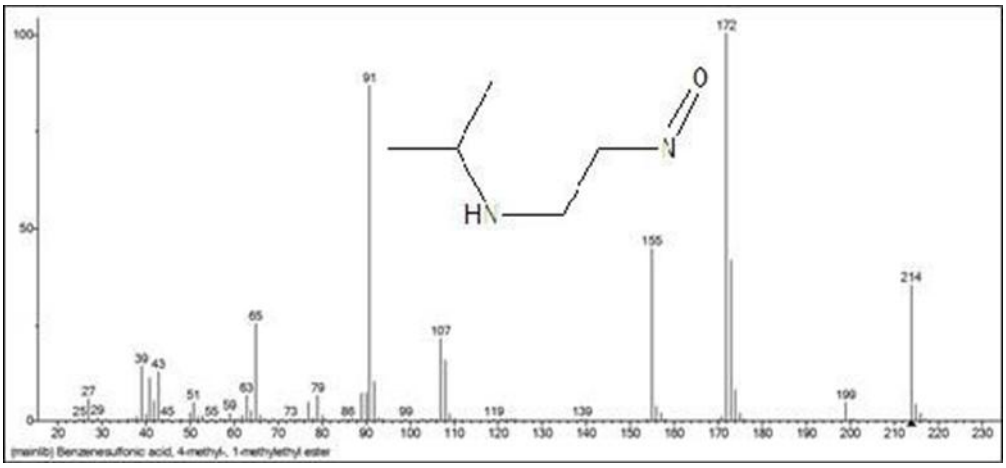

Fig. 1. MRM Chromatogram of N-nitrosoethylisopropylamine (NEIPA)

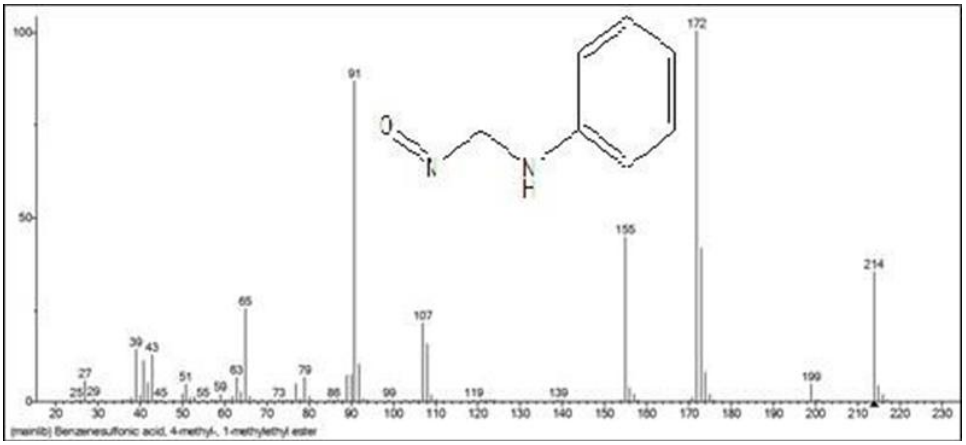

Fig. 2. MRM Chromatogram of N- nitrosomethylphenylamine (NMPA)

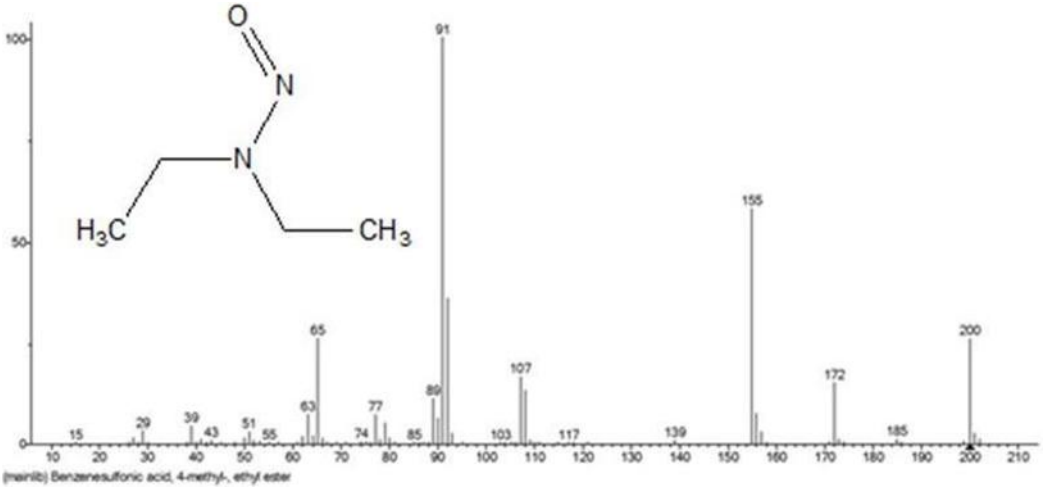

Fig. 3. MRM Chromatogram of N-ethyl-N-Nitrosodiethylamine (NDEA)

- **Method validation**

Developed method is proposed for the complete validation to prove it's intend 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**

NEIPA, NDEA and NMPA individual RT check solutions were prepared and injected and confirmed the retention times and also injected other solvents used in the manufacturing process and found no interference at the elution time of impurities and is tabulated in below.

Table 2. Specificity analysis results

Compound name	Retention Time (min)
NEIPA	1.001
NMPA	3.002
NDEA	5.004
No peak observed at the RT of analytes	No peak observed at the RT of analytes

- **Detection limit (LOD) and quantification limit (LOQ) LOD-LOQ prediction**

To check LOD-LOQ values, serial lowest concentration solutions were prepared, injected into the GC-MS and recorded the chromatograms. As per the ICH Guidelines considering the LOD and LOQ which is 10% and 30% of allowable intake i.e. 0.02 µg/g and 0.06 µg/g.

- **Linearity**

Linearity solutions were prepared after quantitatively diluting std. stock solution to obtain solutions in the range of LOQ and 150% level of the specification level and proved that method was linear and the results are tabulated in table 3-5. Linearity graphs are as shown in figure 4-6.

Table 3. Linearity of NEIPA

Level	Actual Conc. (µg/g)	Mean area
At LOQ	0.0023	15143
50% of the Evaluation limit	0.0039	30945
80% of the Evaluation limit	0.0062	54647
100% of the Evaluation limit	0.0077	65840
120% of the Evaluation limit	0.0092	82300
150% of the Evaluation limit	0.0116	104027
Slope		9E+06
Intercept		618
Correlation coefficient		0.9987

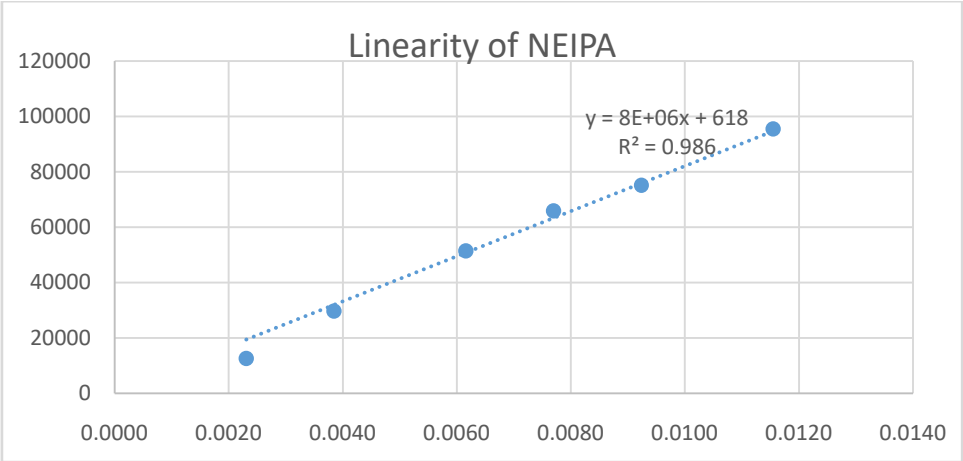

Fig. 4. Linearity curve of NEIPA

Table 4. Linearity of NMPA

Level	Actual Conc. (µg/g)	Mean area
At LOQ	0.0023	9572
50% of the Evaluation limit	0.0039	19144
80% of the Evaluation limit	0.0062	35894
100% of the Evaluation limit	0.0077	47859
120% of the Evaluation limit	0.0092	55038
150% of the Evaluation limit	0.0116	74181
Slope		6E+06
Intercept		1275.5
Correlation coefficient		0.9972

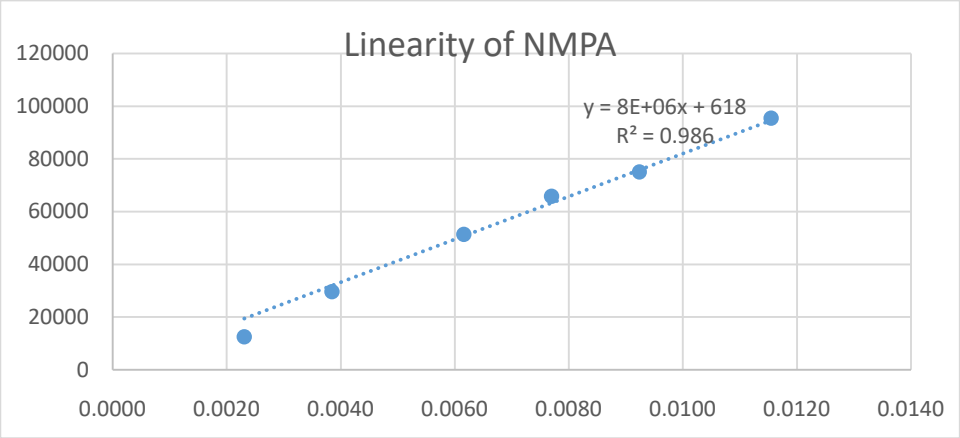

Fig. 5. Linearity curve of NMPA

Table 5. Linearity of NDEA

Level	Actual Conc. (µg/g)	Mean area
At LOQ	0.0023	12507
50% of the Evaluation limit	0.0039	29621
80% of the Evaluation limit	0.0062	51344
100% of the Evaluation limit	0.0077	65825
120% of the Evaluation limit	0.0092	75041
150% of the Evaluation limit	0.0116	95446
Slope		8E+06
Intercept		618
Correlation coefficient		0.9945

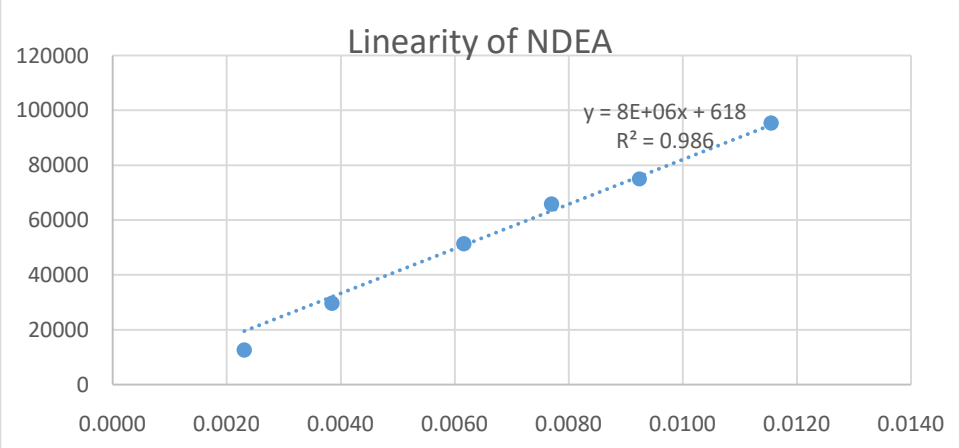

Fig. 6. Linearity curve of NDEA

- **Precision (Repeatability)**

System precision, six standards were prepared and injected and found that the system was precise and then method precision, six samples were prepared separately by spiking with the impurities at 0.19µg/g and injected in the GC-MS and the observations are shown in table 6 and 7.

Table 6. System precision results

	NEIPA	NMPA	NDEA
Injection	**Area**	**Area**	**Area**
1.	62486	50412	67143
2.	60487	51039	68499
3.	60897	49752	67549
4.	59869	48733	66411
5.	60128	48113	66102
6.	59122	47955	65800
Mean	58799.0	49334.0	66920.7
SD	1143.449	1264.715	1014.571
% RSD	1.94	2.56	1.52

Table 7. Method precision results

Preparation level	NEIPA (µg/g)	NMPA (µg/g)	NDEA(µg/g)
Preparation-1	0.181	0.184	0.182
Preparation-2	0.187	0.181	0.177
Preparation-3	0.184	0.189	0.179
Preparation-4	0.176	0.178	0.179
Preparation-5	0.180	0.187	0.180
Preparation-6	0.188	0.179	0.176
Mean	0.1827	0.1829	0.1788
SD	0.00455	0.00433	0.00214
% RSD	2.5	2.4	1.2

Accuracy

Accuracy study was performed by spiking samples in triplicate with NEIPA, NDEA and NMPA at 50%, 100% and 150% level of the evaluation limits. The minimum recovery observed for NEIPA was 92.7% and maximum 97.9%. The minimum recovery observed for NMPA was 92.7% and maximum recovery 97.6%. The minimum recovery observed for NDEA was 94.8% and maximum recovery 99.0%.The %RSD for recovery was 1.7 for NEIPA and 1.8 for NMPA and 1.3 for NDEA the results are tabulated in the table 8.

Table 8. Accuracy results for NEIPA and NMPA

Recovery level	NEIPA			NMPA		
	Amount Added	Amount recovered	% Recovery	Amount Added	Amount recovered	% Recovery
	µg/g	µg/g		µg/g	µg/g	
50% Rec-1	0.096	0.091	94.8	0.096	0.090	93.8
50% Rec-2	0.096	0.089	92.7	0.096	0.092	95.9
50% Rec-3	0.096	0.093	96.9	0.096	0.089	92.7
100% Rec-1	0.193	0.183	94.8	0.193	0.180	93.3
100% Rec-2	0.193	0.187	96.9	0.193	0.185	95.9
100% Rec-3	0.193	0.188	97.4	0.193	0.186	96.4
150% Rec-1	0.289	0.280	96.9	0.289	0.282	97.6
150% Rec-2	0.289	0.283	97.9	0.289	0.280	96.9
150% Rec-3	0.289	0.278	96.2	0.289	0.279	96.5
Mean			96.02			95.43
SD			1.648			1.740
%RSD			1.7			1.8

Recovery level	NDEA		
	Amount Added	Amount recovered	% Recovery
	µg/g	µg/g	
50% Rec-1	0.096	0.094	97.9
50% Rec-2	0.096	0.091	94.8
50% Rec-3	0.096	0.093	96.9
100% Rec-1	0.193	0.188	97.4
100% Rec-2	0.193	0.190	98.4
100% Rec-3	0.193	0.191	99.0
150% Rec-1	0.289	0.284	98.3
150% Rec-2	0.289	0.281	97.2
150% Rec-3	0.289	0.280	96.9
Mean			97.42
SD			1.221
%RSD			1.3

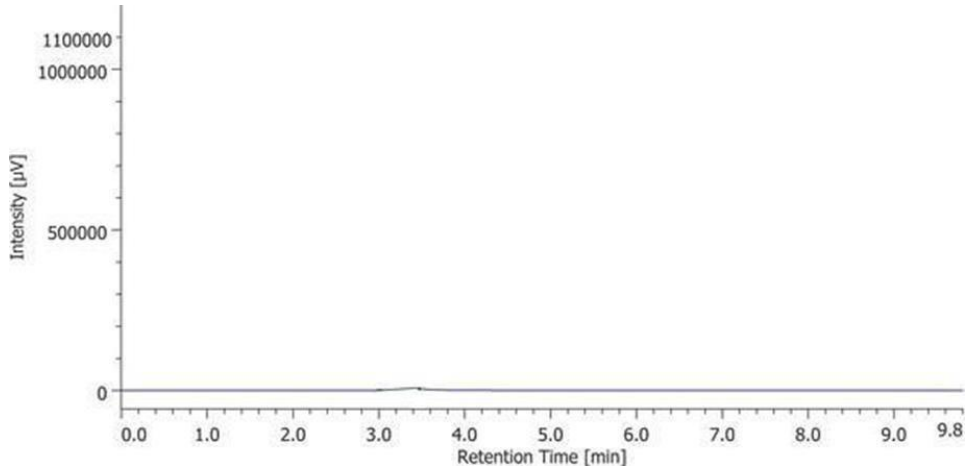

Fig. 7. Chromatogram of Blank solution

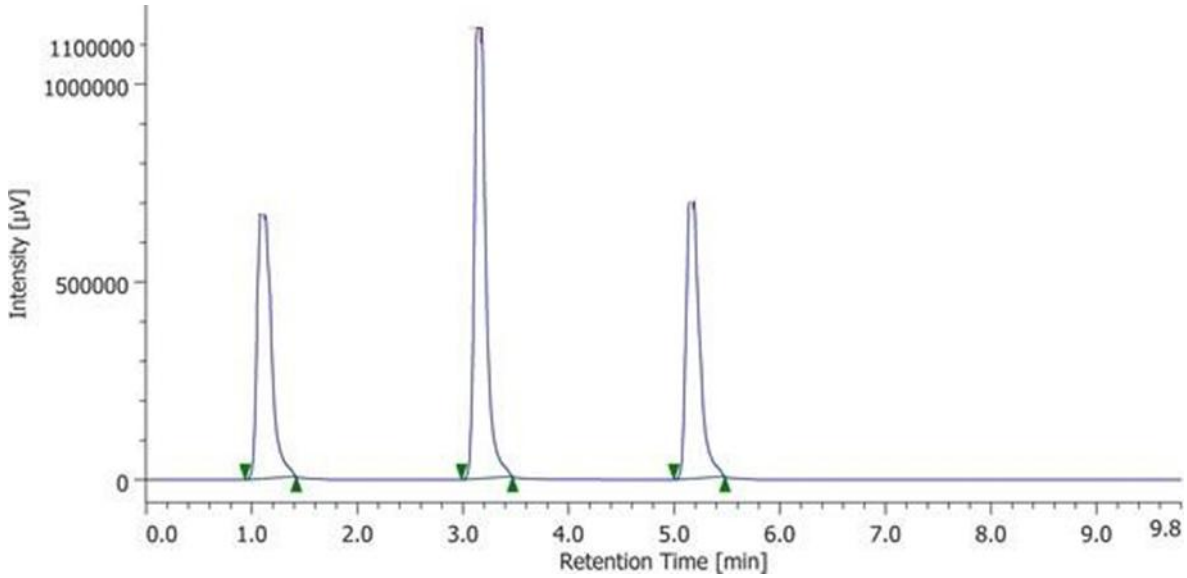

Fig. 8. Chromatogram of Standard solution at Specification concentration MRM mode (Retention time: 1.001 min: NEIPA, 3.002 min: NMPA, 5.004 min: NDEA)

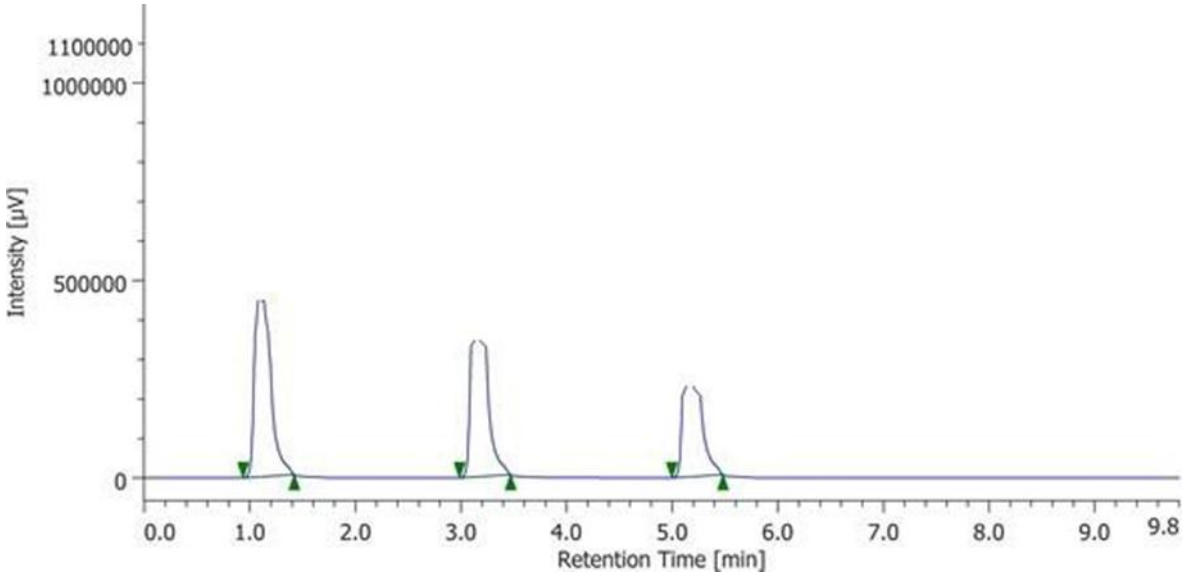

Fig. 9. Chromatogram of LOQ level concentration

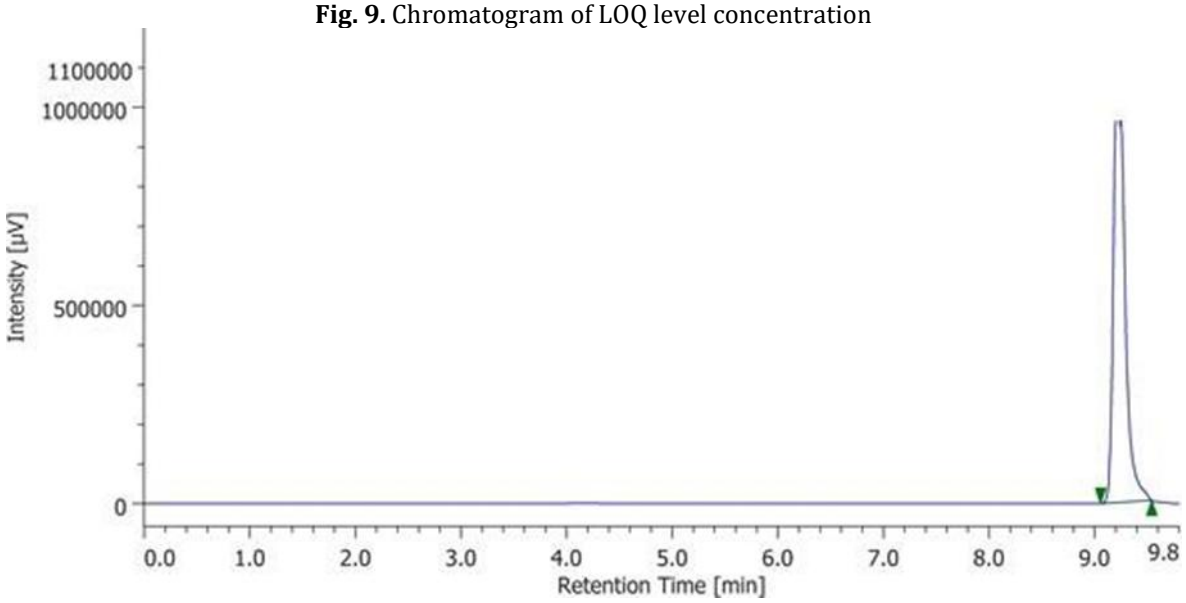

Fig. 10. Chromatogram of unspiked Levetiracetam ER tablet sample

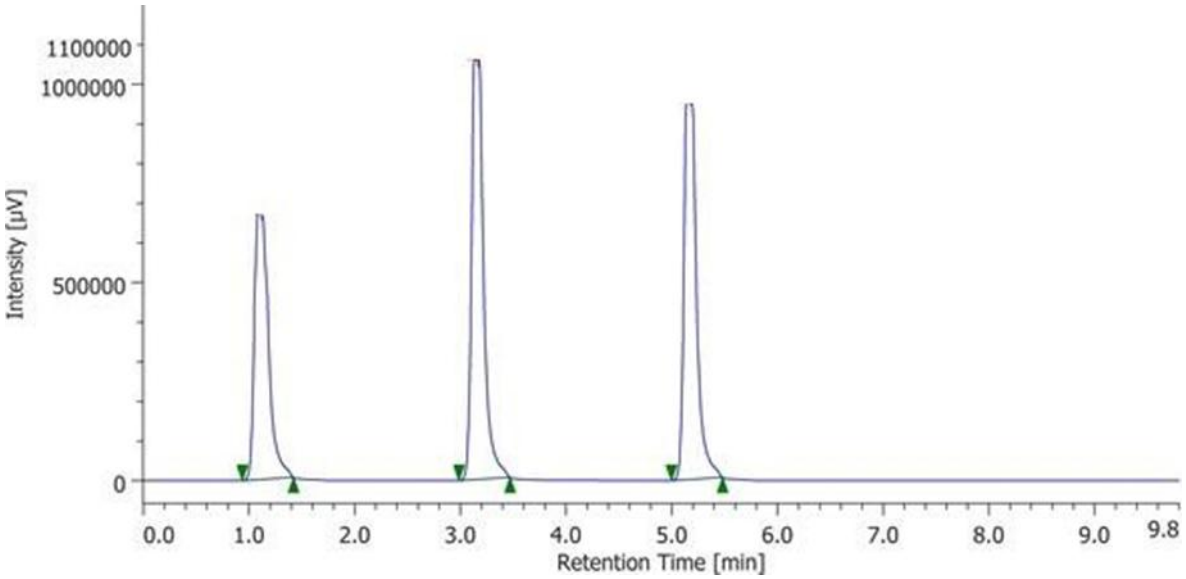

Fig. 11. Chromatogram of Spiked sample solution (Retention time: 1.001 min: NEIPA, 3.002 min: NMPA, 5.004 min: NDEA)

4. CONCLUSION

The application of Multiple Reaction Monitoring (MRM) successfully validated the GC-MS analytical approach for assessing nitrosamine, genotoxic, and carcinogenic impurities in levetiracetam ER tablets. The method demonstrated outstanding sensitivity and specificity, unaffected by minor excipients, with LOD/LOQ values between 0.0023 and 0.0116 µg/g. Precision was confirmed through low %RSD values, while linearity was consistently high (correlation coefficients > 0.99). Recovery studies further substantiated accuracy, with rates ranging from 92.7% to 99.0%. Overall, this robust method ensures regulatory compliance and provides a reliable framework for continuous monitoring of nitrosamine impurities, thereby safeguarding pharmaceutical quality and patient safety.

Abbreviations

GC-MS: Gas Chromatography mass Spectrometry
MRM: Multiple Reaction Monitoring
LOD: Limit of Detection
LOQ: Limit of Quantification

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Smith J, Allen T, Lee B. The role of nitrosamines in pharmaceutical formulations and their impact on health. Pharm Sci J. 2022;24(5):542-549.
2. Miller A, Roberts C, Gupta S. A review of genotoxic and carcinogenic impurities in pharmaceutical products. J Pharm Regul Aff. 2021;19(3):145-152.
3. Jones H, Miller M, Perry G. Analytical methods for quantifying genotoxic impurities in pharmaceutical products. Analytica Chimica Acta. 2019;1104:35-45.
4. Yang L, Wang K, Sun X. The safety risks of nitrosamine contamination in pharmaceuticals: Regulatory concerns and analytical solutions. J Pharm Biomed Anal. 2020;180:113023.
5. International Conference on Harmonisation (ICH). Validation of analytical procedures: Text and methodology. ICH Q2(R1). 2005; 1-12.
6. Kumar S, Patel M, Zhang J. Nitrosamine impurities in pharmaceuticals: Emerging challenges and regulatory perspectives. Regulatory Toxicology and Pharmacology. 2021;117:104654.
7. Rodriguez L, Garcia M, Singh R. Detection of genotoxic impurities in pharmaceutical tablets using advanced chromatography techniques. J Pharm Anal. 2022;12(3):175-181.
8. Thompson R, Green M, Shaw S. Validation of analytical techniques for carcinogenic impurity quantification in drug formulations. Analytical Chemistry Insights. 2020;15:117739011986-1894.
9. Liu Z, Wang X, Zhang L. The role of GC-MS in identifying carcinogenic impurities in drug products. Chromatographia. 2021;84:145-152.
10. Carmichael P, Patel A. Guidelines for the detection and quantification of nitrosamine impurities in pharmaceuticals. Journal of Pharmaceutical Innovation. 2019;14(2):89-94.
11. United States Food and Drug Administration (FDA). Nitrosamine impurities in drugs: Guidance for industry. 2020.
12. Abdel-Rahman S, Ali A, Hassan S. Quantification of genotoxic impurities in pharmaceutical products using gas chromatography. Pharmaceutical Analysis Journal. 2019;25(4):67-74.
13. Singh P, Singh S, Sharma P. A review on the regulatory aspects of genotoxic, carcinogenic, and nitrosamine impurities in drugs. Indian J Pharm Sci. 2021;83(2):206-212.
14. European Medicines Agency (EMA). Assessment of genotoxicity and carcinogenicity in pharmaceutical products. EMA/CHMP/SAWP/225139/2006. 2006.
15. Anderson D, Green L. Recent trends in the analysis of pharmaceutical impurities: A review of techniques. J Anal Chem. 2018;28(3):98-107.
16. Li H, Wang Y, Li L. Advances in the detection of nitrosamine impurities in pharmaceutical formulations. Pharmaceutics. 2020;12(3):234-242.
17. Zhang W, Zhang H. Analysis and control of genotoxic impurities in pharmaceutical manufacturing. J Pharm Sci. 2018;107(6):1555-1563.
18. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100F: Nitrosamines. 2021.
19. Wilson MP, Chen X, Lee M, et al. Development of a GC-MS/MS method for the determination of N-nitrosamines in complex matrices. J Anal Chem. 2022;73(8):1429-1437.
20. Smith RL, O'Connor J, Reyes M, et al. Optimized conditions for the detection of volatile nitrosamines using GC-MS/MS. J Chromatogr A. 2021;1637:460865.
21. Patel A, Gupta A, Khan MS. Gas Chromatography–Mass Spectrometry for

trace analysis of N-nitrosamines. Anal Bioanal Chem. 2020;412(12):2891-2900.
22. Zhang L, Li X, Wang C, et al. Method development for the simultaneous analysis of N-nitrosamines and their derivatives by GC-MS/MS. J Environ Chem Eng. 2020;8(3):103571.
23. Chen Y, Guo F, Liu H, et al. Gas chromatography-tandem mass spectrometry analysis of nitrosamines: Method development, optimization, and application to environmental samples. J Chromatogr B. 2019;1115:72-79.
24. Singh H, Bansal T, Sharma A. Optimization of GC-MS parameters for the determination of N-nitrosamines in water samples. Int J Environ Anal Chem. 2018;98(10):875-885.
25. Sánchez C, Molina P, Martínez L, et al. Method validation for the analysis of volatile compounds in complex matrices using GC-MS/SIM. J Chromatogr A. 2021;1637:460862.
26. Miller R, Zhang Y, Kappes J. Validation of a GC-MS method for trace analysis of environmental pollutants: Specificity, linearity, and accuracy considerations. J Environ Anal Chem. 2020;100(5):567-574.
27. Bhatia A, Gupta R, Sharma S. Validation of GC-MS for impurity quantification in pharmaceutical formulations: LOD, LOQ, accuracy, and precision studies. J Pharm Biomed Anal. 2019;170:1-7.
28. Johnson S, Kumar P, Mehta A. System suitability testing and method validation for GC-MS analysis in the pharmaceutical industry. J Pharm Sci. 2019;108(4):1372-1379.
29. Liu H, Lee M, Wilson J, et al. Comprehensive validation study of GC-MS for environmental analysis of nitrosamines: Linear calibration, recovery, and precision. J Anal Chem. 2018;79(12):2175-2182.