

DEVELOPMENT AND VALIDATION OF A SENSITIVE AND STABILITY-INDICATING LC-MS/MS METHOD FOR TRACE-LEVEL DETERMINATION OF N-NITROSO OXCARBAZEPINE IMPURITY IN OXCARBAZEPINE DRUG SUBSTANCE

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ABSTRACT

Nitrosamine impurities have received wide attention after their discovery in the valsartan drug in 2018. Studies also confirmed that drug substances can be contaminated with nitrosamines during synthesis and long-term storage. Hence, validated analytical procedures are in great demand to determine nitrosamine impurities in pharmaceuticals within the acceptable threshold limits. The present study reported a sensitive LC-MS/MS method for N-nitroso oxcarbazepine determination in oxcarbazepine drug substance. The impurity was separated on a Zodiac C18 (150 x 4.6 mm, 5.0 μ m) column using two mobile phases (mobile phase A: 0.1% formic acid in water, mobile phase B: 0.1% formic acid in methanol) in gradient elution mode with a flow rate of 0.5 mL/min. A triple quadrupole mass spectrometer in positive-ion mode was used for the quantification of impurity. The method achieved an LOD of 0.0156 ppm and an LOQ of 0.0312 ppm. The linearity was found excellent through the coefficient of determination ($r^2 > 0.99$), and the recovery of analyte was found between 87.48 and 97.00% across the tested concentration range. The validation data confirmed the method's reliability for N-nitroso oxcarbazepine impurity analysis in oxcarbazepine following the current regulatory standards. This study contributes to Sustainable Development Goal 9 by promoting advanced technologies and quality infrastructure for pharmaceutical manufacturing.

Keywords: Nitrosamines, LC-MS/MS, Method Validation, Quality Assurance, Drug Substances.

RASĀYAN J. Chem., Vol. 19, No.4, 2026

INTRODUCTION

Oxcarbazepine is an antiepileptic drug widely used to treat partial seizures and focal epilepsy in adults as well as pediatric patients. It was developed to overcome the metabolic and safety limitations associated with carbamazepine. The drug produces 10-monohydroxy derivatives when it undergoes rapid hepatic reduction, which is primarily responsible for its therapeutic action. The drug has gained significant clinical importance in long-term epilepsy management owing to its improved tolerability profile and reduced potential for drug-drug interactions. The recommended maximum dosage of oxcarbazepine for adults is 1200 mg/day.¹ In recent years, nitrosamine (NA) impurities in pharmaceuticals have emerged as a critical global regulatory concern due to their known human carcinogenic and mutagenic potential. As a result, USFDA and EMA have mandated stringent control strategies for NA impurities in drug substances and finished formulations.^{2,3} NA impurities may arise during the synthesis, storage, or packaging when secondary or tertiary amines interact with nitrosating agents under suitable conditions. Even the small concentrations of NAs in finished products have led to widespread recalls of several drug substances worldwide, considering the patient safety. The detection of NAs such as N-nitroso dimethylamine (NDMA) and N-nitroso diethylamine (NDEA) in various pharmaceuticals has triggered the global

regulatory concerns due to their extreme carcinogenicity and mutagenicity.^{4,5,6} Though the oxcarbazepine drug does not contain any nitrosating functional group, its structural features and synthetic routes may form NAs under certain manufacturing or storage conditions.⁷ In this context, validated analytical procedures are required to analyse NA impurities in oxcarbazepine to ensure its compliance with regulatory limits. In recent times, extensive research was carried out to develop highly sensitive analytical methods that can determine potentially mutagenic NA impurities in distinct drug substances at permissible levels.⁸⁻¹⁴ For instance, a LC-HRMS allowed for the concurrent measurement of 13 NA impurities in different pharmaceuticals.⁸ Another study demonstrated a supercritical fluid chromatography for the determination of various NA impurities in APIs.⁹ In addition to this, a GC-MS technique was optimised and validated for the analysis of 12 low-molecular-weight NAs in pharmaceutical formulations.¹⁰ Since oxcarbazepine is thermally labile, GC-based analysis is not a suitable option for the quantification of NAs. Instead, LC-based techniques are commonly employed because it combines high analytical sensitivity with low sample consumption.^{11,12} As the number of drugs affected by NAs continues to expand, the existing analytical methods cannot be universally applied in all cases. Consequently, the development of sensitive analytical techniques is essential for the determination of potential NA impurities in oxcarbazepine active pharmaceutical ingredients (APIs)/drug substances. In this regard, the current study presents the development and validation of a simple LC-MS/MS method for oxcarbazepine analysis in accordance with the current regulatory guidelines. As the method was established using a triple-quadrupole MS/MS detector, it is readily suitable for routine analytical assessments. The method demonstrated high sensitivity and robustness for the determination of N-nitroso oxcarbazepine impurity at trace levels (LOQ - 0.0312 ppm), making it well suited for rapid risk-screening applications. The outcome of this work is expected to support regulatory compliance and reinforce the safety profile of oxcarbazepine drug substances. The chemical structures of the N-nitroso oxcarbazepine impurity and oxcarbazepine are shown in Fig.-1.

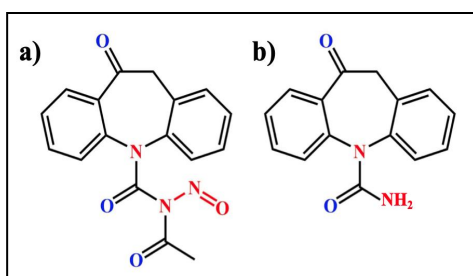


Fig.-1: The Chemical Structures of a) N-Nitroso Oxcarbazepine Impurity, and b) Oxcarbazepine Drug Substance

EXPERIMENTAL

Chemicals and Reagents

N-nitroso oxcarbazepine impurity and oxcarbazepine API were received from SynZeal (Ahmedabad, Gujarat, India). LC-MS grade acetonitrile, methanol, and water were purchased from Honeywell (Mumbai, India), while formic acid of LC grade was sourced from Biosolve Lab Chemicals (Indore, India).

Instrumentation and Chromatography Conditions

The analysis was carried out on a TSQ Quantis Plus LC-MS/MS system (Thermo Scientific) configured with a triple quadrupole mass analyser and electrospray ionisation (ESI) interface with ion-focusing capability. The precursor and fragment ion scans were conducted for N-nitroso oxcarbazepine impurity, and the corresponding quantitative and confirmatory SRM transitions were determined through systematic optimisation of collision energy, vaporiser temperature and ion transfer tube temperature. The optimised SRM transition for the quantification of the selected impurity is presented in Table-1.

Chromatographic separation of the selected impurity was carried out on a Zodiac 100 C18 column, while maintaining the column temperature at 40 °C and a mobile phase flow of 0.5 mL/min. The total chromatographic run time was set to 20 min, and the injection volume was fixed at 25 µL. The elution was performed with a gradient program as follows: 0-3.0 min 70% A, 4.0-9.0 min 40% A, 9.5-15 min

10% A, 15.5-20 min 70% A, for equilibration. After every injection, the needle was rinsed with methanol-water (90:10, v/v) solution.

Table-1: Selective Reaction Monitoring (SRM) Transition of N-nitroso Oxcarbazepine Impurity

Compound	Polarity	Precursor ion (m/z)	Product ion (m/z)	Collision energy (V)	RF Lens (V)	Source fragmentation
N-nitroso oxcarbazepine	Positive	253.217	223.05	10.8	95	0

Preparation of Standard Solutions

5.0 mg of N-nitroso oxcarbazepine was dissolved in 5.0 mL of methanol to prepare 1000 ppm standard stock solution-I. Then, 0.1 mL of the stock solution-I was diluted to 10 mL with methanol to prepare the standard stock solution-II. The standard stock solution-III was prepared by adding 0.16 mL of stock solution-II to 20 mL of methanol. The 50 mg of oxcarbazepine API was dispersed in 5.0 mL of diluent and vortex-mixed for 2.0 min to aid complete dissolution for the preparation of the test sample. All the prepared solutions were kept in a refrigerator at 4 °C until further analysis.

Method Validation

The method validation for N-nitroso oxcarbazepine impurity analysis was performed following ICH Q2(R2) guidelines, i.e., '*Validation of Analytical Procedures*', to determine the linearity, LOD, LOQ, specificity, precision, accuracy, and robustness.¹⁵

System Suitability

Prior to sample analysis, system suitability tests were performed to confirm the performance and reliability of the analytical system. System suitability was assessed by injecting the prepared solutions, and the %RSD of the resulting peak areas was used as the acceptance criteria.

Specificity

The specificity was established by analysing blank and spiked samples to ensure the absence of interference at the retention time and SRM transition of N-nitroso oxcarbazepine. Peak purity was assessed using spectral correlation analysis to ensure chromatographic separation from oxcarbazepine and other potential degradation products. The response of any interfering peaks should be below 5% with respect to the corresponding standard solution.

Linearity and Sensitivity

The method linearity was evaluated by injecting standard solutions of N-nitroso oxcarbazepine impurity at five concentration levels, viz., LOQ, 50%, 100%, 125%, and 150% levels with respect to the specification limit. The calibration curve plotted between peak area response and analyte concentrations determined the least-squares regression with the coefficient of determination (r^2). Method sensitivity was further assessed through the determination of LOD and LOQ following the recommendations of the ICH guidelines for analytical procedure validation.¹⁵ The analytical sensitivity was characterised by estimating the LOD and LOQ at S/N ratios of approximately 3 and 10, respectively. At the LOQ level, acceptable precision was confirmed by evaluating replicate injections in terms of %RSD.

Accuracy and Precision

The accuracy was performed by spiking N-nitroso oxcarbazepine impurity into the sample at LOQ, 100% and 150% specification levels. Precision tests were performed in terms of repeatability and intermediate precision. Both accuracy (% recovery) and precision (%RSD) were evaluated at three concentration levels ranging from LOQ to 150% levels. To determine intraday precision, three separately prepared samples at each concentration level were analysed within a single day, with one injection performed for each sample (n = 3). Inter-day precision was assessed by analysing three independently prepared samples over different days at each concentration level.

Robustness and Ruggedness

The robustness was evaluated by keeping deliberate changes in selected chromatographic parameters and assessing their impact on method performance. The parameters considered for the robustness evaluation

include column oven temperature (38 °C & 42 °C), mobile phase flow (0.45 mL/min & 0.55 mL/min), and filter compatibility using 0.22 µm nylon and 0.22 µm PTFE syringe filters. The impact of the variations on chromatographic method performance was examined to confirm the method robustness. The method ruggedness was established through intermediate precision performed at the LOQ level of the N-nitroso oxcarbazepine impurity. The study was conducted by two different analysts under similar experimental conditions to assess analyst-to-analyst variability. The calculation of %RSD of six replicate determinations was examined to demonstrate the acceptable precision at trace-level concentrations.

Stability of Analytical Solutions

Solution stability was performed with respect to the standard and spiked sample solutions prepared at 100% specification level and stored at the autosampler temperature. The stability of the solutions was monitored for a period of up to 12 h. For the spiked sample solution, stability was determined by calculating the percentage difference in analyte content at each time point relative to the initial preparation. The standard solution stability was evaluated from the calculated %RSD of the responses obtained at different time intervals with respect to the initial standard solution.

RESULTS AND DISCUSSION

The developed analytical method was validated for the determination of N-nitroso oxcarbazepine in oxcarbazepine drug substance following the ICH Q2(R2) guidelines.

Optimisation of Chromatographic Conditions

Initially, the validation was started by following the chromatographic parameters described in USP Procedure 3 of General Chapter (1469) for the method development procedure. Due to the structural similarity between the selected impurity and the drug substance, the impurity co-eluted with the oxcarbazepine drug substance and exhibited poor peak shape. As a result, different column chemistries (C18 and phenyl columns) were tried to achieve the separation of N-nitroso oxcarbazepine impurity from oxcarbazepine drug substance. Out of all the columns screened, the Zodiac 100 C18 (150 x 4.6 mm, 5 µm) column showed promising separation due to a highly inert, end-capped C18 surface and functionalized silica chemistry compared to other columns.

Table-2: LC and MS Operating Conditions Applied for the Analysis of N-nitroso Oxcarbazepine Impurity

Parameter	Conditions		
<u>LC conditions</u>			
Column temperature	40 °C		
Flow rate	0.5 mL/min		
Run time	20 min		
<u>MS conditions</u>			
Positive ion	5000 V		
Vaporizer temperature	300 °C		
CID gas (mTorr)	1.5		
Scan mode	SRM		
Gradient program	Run Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
	0.00	70	30
	3.00	70	30
	4.00	40	60
	9.00	40	60
	9.50	10	90
	15.0	10	90
	15.5	70	30
	20.0	70	30
Divert valve position	MS	Waste	
1-2	NA	0 - 12 min	
1-6	12- 17 min	NA	
1-2	NA	17.0 - 20.0 min	

Therefore, the Zodiac 100 C18 column was selected for the optimisation of other method parameters, and the optimised method parameters are presented in Table-2. Further, a divert valve program was implemented to protect the mass spectrometer from contamination by high-concentration sample injections. While optimising the chromatographic conditions, ESI in positive mode was selected as the ionisation source due to its superior ionisation efficiency and sensitivity for nitrosamines, along with reduced susceptibility to matrix effects, enabling reliable and selective ion detection. Also, preliminary tests suggested higher signals for the selected impurity, and hence it was chosen as the ionisation source in this study.

Method Validation

System suitability requirements were met for the analysis of N-nitroso oxcarbazepine in oxcarbazepine drug substance. The %RSD for six replicate standard injections was 8.8% (acceptance criterion $\leq 10.0\%$), and the cumulative %RSD, including bracketing injections, remained within 15.0%. These results confirmed the acceptable system performance and method reliability.

Specificity

The method specificity was demonstrated using a mixture of N-nitroso oxcarbazepine impurity with oxcarbazepine drug substance. Figure-2 shows the distinct separation of the impurity peak from the drug peak at the optimised conditions. Further, injections of the drug sample were performed to confirm the absence of matrix interference at the analyte retention time. As shown in Fig.-2, no drug-related components were eluted at the retention time of the impurity. An evaluation of the blank confirmed the absence of interference in the SRM transitions of the impurity.

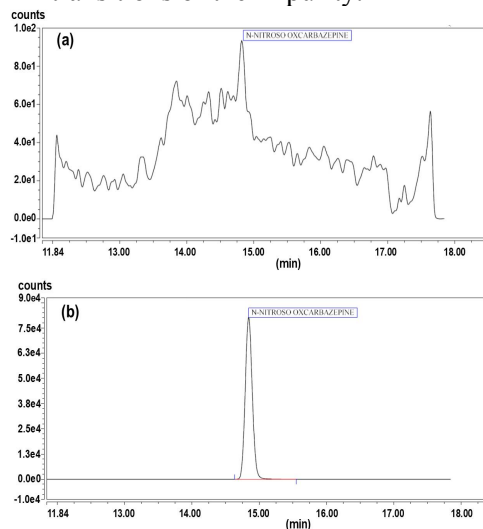


Fig.-2: Specificity Chromatogram of a) Blank, and b) N-nitroso Oxcarbazepine Impurity

Linearity and Sensitivity

The calibration solutions were prepared at five concentration levels corresponding to the LOQ, 50%, 100%, 125%, and 150% of the specification limit. The solutions were injected individually, and the corresponding chromatographic responses were recorded. A calibration graph was plotted for peak area responses against the impurity concentrations. The linearity was assessed by least-squares regression analysis, from which the slope, intercept, and coefficient of determination (R^2) were derived. The R^2 of ≥ 0.99 confirmed the excellent linearity between the analyte concentration and instrument response (Fig.-3).

The sensitivity of the developed method for N-nitroso oxcarbazepine impurity analysis was evaluated in terms of LOD and LOQ values. The determined LOD and LOQ were found to be 0.0156 ppm and 0.0312 ppm, respectively. The method sensitivity was verified at a concentration of 0.0312 ppm, where the impurity exhibited a signal-to-noise ratio (S/N) ≥ 10 . Hence, the method sensitivity was determined to be 0.0312 ppm, ensuring accurate quantification at trace levels relevant for regulatory compliance. The

representative chromatograms for LOD and LOQ concentrations are shown in Fig.-4, illustrating a well-defined and detectable peak with acceptable S/N characteristics.

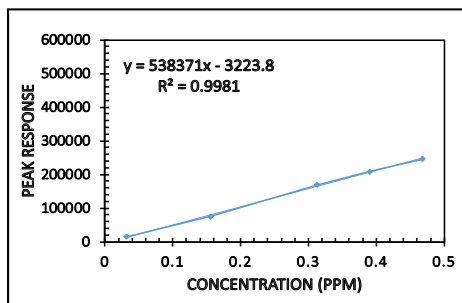


Fig.-3: Linearity and Regression Parameters for N-nitroso Oxcarbazepine Impurity

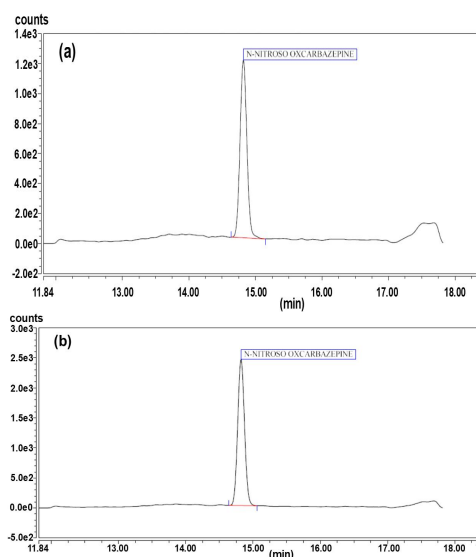


Fig.-4: Representative Chromatograms of N-nitroso Oxcarbazepine at a) LOD and b) LOQ Concentrations

Accuracy and Precision

The method accuracy was established through recovery analysis at three spiked concentrations (LOQ level, 100% level and 150% level). At all tested levels, the per cent recovery was within the specification limits of 80 to 120% (Table-3).

Table-3: Validation Data for the Accuracy and Precision of N-nitroso Oxcarbazepine Impurity Analysis

Concentration	Accuracy (n=3)			Intraday precision (n=3)			Interday precision (n=3)		
	Recovery (%)	Std. Dev.	%RSD	Recovery (%)	Std. Dev.	%RSD	Recovery (%)	Std. Dev.	%RSD
LOQ (0.0314 ppm)	90.98	3.180	3.495	88.85	0.001	3.082	92.03	0.001	3.930
100 % specification level (0.3142 ppm)	90.71	1.689	1.862	89.72	0.003	1.057	91.91	0.001	0.510
150% specification level (0.4713 ppm)	91.86	4.132	4.498	92.04	0.005	1.131	90.00	0.015	3.608

Also, the method precision was confirmed through repeatability assessments performed at three concentration levels. For both intraday and interday evaluations, the %RSD values at all concentration levels were below 5.0%, indicating acceptable precision. The method exhibited %RSD between 0.51 and

3.60% for both the precisions. Also, the cumulative method precision was calculated by injecting six replicate samples at the 100% specification level. The results demonstrated excellent method consistency, with recoveries ranging from 88.13% to 100.51% and an associated %RSD of 4.586, confirming the method's suitability for routine analysis of the impurity. The accuracy chromatograms at LOQ, 100% and 150% levels are presented in Fig.-5.

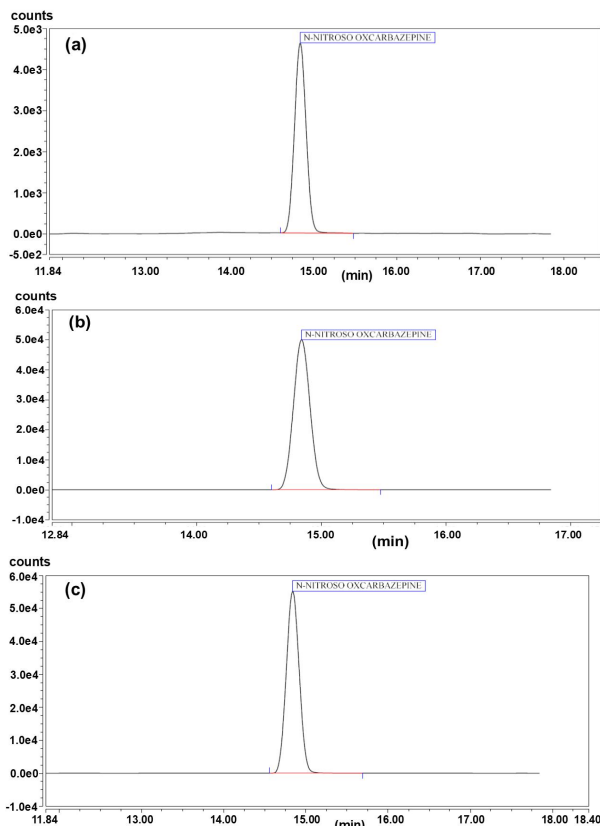


Fig.-5: Representative Chromatograms of N-nitroso oxcarbazepine at (a) LOQ, (b) 100%, and (c) 150% Concentration Levels

Ruggedness

The ruggedness of the method was evaluated through intermediate precision performed at the LOQ level of N-nitroso oxcarbazepine impurity. The study was conducted by two different analysts under similar experimental conditions to assess analyst-to-analyst variability. For the second analyst, the %RSD of six replicate determinations was found to be $\leq 1.0\%$, demonstrating excellent precision at trace-level concentrations. When the results from both analysts were combined (total of 12 determinations), the overall RSD was $\leq 1.0\%$, confirming the reproducibility of the method across different analysts. These results confirmed the satisfactory performance of the method at such a low concentration of nitrosamine impurity (Table-4).

Robustness

The method robustness was examined by altering the key parameters including column temperature, filter compatibility and mobile phase flow. The column oven temperature was deviated $\pm 2^\circ\text{C}$ from its optimised temperature (40°C), mobile phase flow rate was altered $\pm 0.5\text{ mL}$ from its optimised flow of 0.5 mL/min , and filter compatibility was checked by using $0.22\text{ }\mu\text{m}$ nylon and $0.22\text{ }\mu\text{m}$ PTFE syringe filters. The results demonstrated that the small variations in method parameters did not impact either the performance or sensitivity. Furthermore, the differences in analyte response or recovery between the samples filtered through nylon and PTFE syringe filters is not significant and confirmed the compatibility of both filter types for sample preparation (Table-4). Overall, the robustness study confirmed that the developed method maintains consistent performance under small, intentional variations in

chromatographic conditions and sample handling, supporting its reliability for routine analysis of N-nitroso oxcarbazepine impurity.

Table-4: Ruggedness and Robustness Assessment of the LC-MS/MS Method Under Deliberate Variations in Analytical Conditions

Validation parameter		Mean recovery (%)	Std. Dev.	%RSD
Ruggedness	Analyst 1	90.98	3.180	3.49
	Analyst 2	90.28	3.158	3.49
Robustness	Column flow	92.83	0.008	2.87
	Temperature	88.12	0.004	1.59
	Filter type	90.86	0.006	2.16

Standard deviation calculated from triplicate analysis.

Solution Stability

The sample solutions' stability was assessed using the samples spiked at 100% specification level and maintained at autosampler temperature. The analysis was carried out at different time intervals, and the % difference in content for the sample spiked at the specification level with that of the initial preparation. The % difference for N-nitroso oxcarbazepine impurity obtained from the standard solution at initial and predetermined time intervals did not exceed 10% even after 12 h of observation.

Analysis of Authentic Samples

The applicability of the developed method for real samples was ensured by the analysis of selected impurity in oxcarbazepine API. The assay results obtained for the marketed formulations were found to be within the specified acceptance criteria, demonstrating the method's compatibility for routine quality control analysis. However, no impurity was detected in injected test samples. The test solution chromatogram is presented in Fig.-6.

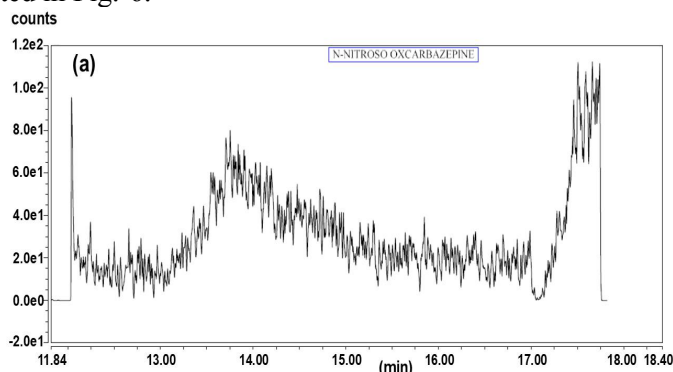


Fig.-6: Representative Chromatogram for Oxcarbazepine API Samples

CONCLUSION

The present study reported a validated LC-MS/MS method for N-nitroso oxcarbazepine analysis in oxcarbazepine drug substance. The proposed method has shown excellent performance and specificity in both screening and qualification of N-nitroso oxcarbazepine impurity. The method was found sensitive and robust for the quantification of selected impurity at low levels (LOQ at 0.0312 ppm) in oxcarbazepine drug substance. Also, the solution stability was demonstrated for 12 h in the standard and spiked sample solutions, with all remaining stable over this period. Overall, the proposed method not only confirmed its ability for the analysis of selected NA impurity but also serves as a general screening approach for NA impurities in other pharmaceutical formulations, requiring minimal optimisation of method conditions. This work contributes to Sustainable Development Goal 9 through the promotion of advanced analytical technologies and resilient quality infrastructure for the pharmaceutical industry.

ACKNOWLEDGMENTS

The authors are thankful to GITAM University, Visakhapatnam, for extending technical support, and Caponex Labs Private Ltd., Hyderabad, for providing the instrumentation to conduct this research.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-9: Industry, Innovation, and Infrastructure*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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Cite this article as: S. Batna *et al.*, *Rasayan J. Chem.*, 19(4), 2224-2232(2026), <https://doi.org/10.31788/RJC.2026.1949901>

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