Ultra-Trace Quantitation of N-Nitroso Epinephrine in Epinephrine containing Formulations by LC–ESI–MS/MS

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Abstract The stringent global regulatory scrutiny surrounding Nitrosamine Drug Substance-Related Impurities (NDSRIs) necessitates the development of highly sensitive analytical methodologies for their detection. Epinephrine, a critical endogenous catecholamine and emergency medication, requires rigorous quality control to ensure patient safety against potential mutagenic degradation products or synthetic by-products. This paper details the systematic development and validation of a highly selective liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for the ultra-trace quantification of N-Nitroso Epinephrine in Epinephrine Injection (1 mg/mL). Chromatographic resolution from the complex, labile catecholamine matrix was achieved utilizing a core-shell Kinetex Biphenyl column (150 mm x 4.6 mm, 2.6 µm) which leveraged exceptional pi-pi electronic interactions. Detection was executed using an AB Sciex QTRAP 4500 mass spectrometer operating in positive Electrospray Ionization (ESI) Multiple Reaction Monitoring (MRM) mode. The validated method exhibited an exceptional Limit of Quantitation (LOQ) of 0.051 ppm (S/N 18.1), comfortably against the regulatory specification limit of 0.5 ppm derived from a 100 ng/day Acceptable Intake (AI) and a 200 mg Maximum Daily Dose. The method demonstrated robust linearity (r = 0.99965) over the range of LOQ to 200% of the specification limit, with combined intermediate precision yielding an RSD of 6.3%. Mean matrix recoveries ranged from 103.3% to 112.3% across five concentration levels. This validated analytical framework addresses a critical literature gap, providing a gold-standard protocol for trace nitrosamine monitoring in epinephrine products.

Keywords: LC-MS/MS Method Development, Analytical Method Validation, Genotoxic Impurity Analysis, Nitrosamine Impurity Quantification, Nitrosamine Drug Substance Related Impurity

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1. Introduction

Epinephrine is an indispensable medication and endogenous hormone utilized extensively in emergency medicine for the treatment of anaphylaxis, cardiac arrest, severe asthma, and croup. Formulated for intravenous, intramuscular, subcutaneous, and inhalation administration, epinephrine functions as a potent alpha- and beta-adrenergic agonist. Therapeutically, it reverses hypotension and vascular permeability during anaphylaxis via alpha receptor activation, while inducing bronchial smooth muscle relaxation via beta receptor pathways.

Despite its well-documented clinical utility, the pharmaceutical industry faces a critical challenge regarding the formation of Nitrosamine Drug Substance-Related Impurities (NDSRIs). N-Nitroso Epinephrine (C9H12N2O4, MW 212.2 g/mol) is a suspected mutagenic carcinogen. Regulatory agencies mandate strict control of this impurity, establishing an Acceptable Intake (AI) limit of 100 ng/day. For a maximum daily dose of 200 mg/day, this translates to an ultra-trace specification limit of 0.5 ppm in the final drug product.

A comprehensive gap analysis of existing literature reveals that current analytical methods are profoundly inadequate for nitrosamine trace detection in epinephrine matrices. Existing methodologies, including those developed by Kongkiatpaiboon et al., Mishra et al., and Siddiqui et al., rely heavily on HPLC-UV or generalized UPLC-MS/MS aimed solely at bulk active assay or forced degradation profiling (oxidation, deamination). These traditional techniques inherently lack the specific mass-to-charge (m/z) discrimination and sensitivity required to detect parts-per-million (ppm) levels of N-Nitroso Epinephrine, often suffering from severe matrix suppression and excipient interference.

To bridge this analytical void, we report a highly selective, robust, and fully validated LC-MS/MS MRM method tailored specifically for quantifying trace N-Nitroso Epinephrine in Epinephrine Injection.

2. Experimental Design and Technical

Methodologies

2.1. Materials and Reagents

- **Drug Product:** Epinephrine Injection, USP 1 mg/mL (30 mg/30 mL vial).
- **Reference Standards:** N-Nitroso Epinephrine (Working Standard).
- **Chemicals:** LC-MS grade ammonium formate, formic acid, and methanol (Honeywell).
- **Water:** Ultra-pure water sourced from a Milli-Q purification system.

2.2. LC-MS/MS Instrumentation Configuration

Analysis was conducted utilizing an AB Sciex Triple Quadrupole Mass Spectrometer (Model: QTRAP 4500) hyphenated with a high-performance liquid chromatography system.

To achieve optimal chromatographic retention and orthogonal selectivity for the polar, aromatic genotoxic impurity against the structurally analogous epinephrine backbone, a Kinetex Biphenyl column (150 mm x 4.6 mm, 2.6 µm) was employed. The core shell architecture of this stationary phase provides sub-2 µm equivalent efficiency while retaining manageable system backpressures.

Table 1. Optimized Chromatographic Conditions

Parameter	Analytical Condition
Column	Kinetex Biphenyl 2.6 µm (150 mm x 4.6 mm)
Mobile Phase A	Ammonium formate in Water, pH 3.2 ± 0.05 (adjusted with formic acid)
Mobile Phase B	Methanol : Water (60:40 v/v)
Flow Rate	0.4 mL/min
Injection Volume	40 µL
Column Oven Temperature	35°C
Autosampler Temperature	15°C
Diluent	0.1% Formic Acid
Run Time	20.0 minutes

Table 2. Gradient Elution Profile

Time (minutes)	Mobile Phase A (%)	Mobile Phase B (%)
0.01	80	20
14.00	65	35
16.00	75	25
20.00	80	20

Note: A mass diverter valve was programmed to direct the eluent to waste from 0.0–10.0 min and 15.0–20.0 min to protect the MS source from high-concentration API and buffer fouling, actively directing flow to the MS only during the critical elution window of 10.0–15.0 min.

2.3. Mass Spectrometry Source Optimization

The Sciex QTRAP 4500 LCMS was operated in positive ESI (Turbo spray) mode utilizing MRM for specific transition monitoring. The source parameters were rigorously tuned for maximum ionization efficiency:

- **Curtain Gas (CUR):** 35 L/min
- **Source Temperature (TEM):** 500°C
- **Ion Spray Voltage (IS):** 5000 Volts

- **Gas 1 (GS1) / Gas 2 (GS2):** 50 units / 40 units
- **Declustering Potential (DP):** 35.0 Volts
- **Entrance Potential (EP):** 10.0 Volts
- **Collision Cell Exit Potential (CXP):** 12.0 Volts

Table 3. Analyte MRM Transitions and Collision Energy

Compound	Mass Transition (Q1 > Q3)	Dwell Time (msec)	Collision Energy (CE)
N-Nitroso Epinephrine	213.10 > 107.10 Quantifier	100.00	25.00 Volts
N-Nitroso Epinephrine	213.10 > 135.10 Qualifier	100.00	25.00 Volts

2.4. Sample and Standard Preparations

Because epinephrine and its nitroso derivatives are highly susceptible to thermal and oxidative degradation, the diluent (0.1% formic acid) was specifically chosen to match the acidic environment of the mobile phase, ensuring stability. The autosampler was maintained strictly at 15°C to preserve sample integrity over extended batch acquisitions. The formulation sample was diluted to a final working test concentration of 0.2 mg/mL of epinephrine.

3. Method Validation Results

3.1. System Suitability and Specificity

System suitability was confirmed via six replicate injections of the standard solution, yielding a highly precise %RSD of 4.4% for the peak areas (limit: ≤15.0%), demonstrating excellent instrumental stability.

Specificity was challenged against the diluent blank, excipient placebo, unspiked formulation, and formulation spiked with the NDSRI at the 0.5 ppm specification limit. The method successfully separated N-Nitroso Epinephrine from the matrix; it eluted consistently at a retention time of ~10.75 to 10.76 minutes. Crucially, no baseline interference or co-eluting isobaric peaks from the blank, excipients, or the active Epinephrine peak were observed at the specific MRM transitions, confirming absolute selectivity.

3.2. Sensitivity: Limit of Detection (LOD) and Limit of Quantitation (LOQ) & Precision

Sensitivity thresholds were established utilizing the signal-to-noise (S/N) methodology relative to the 0.2 mg/mL test sample concentration.

- **LOD:** Established at 0.025 ppm (absolute concentration 0.005ng/mL) (S/N ratio of 5.1, exceeding the ≥3 requirement).
- **LOQ:** Established at 0.051 ppm (absolute concentration 0.0102ng/mL) (S/N ratio of 18.1, exceeding the ≥10 requirement).

Precision at the LOQ level was validated via six replicate injections, demonstrating a robust %RSD of 5.7% (limit: ≤20.0%).

3.3. Linearity

To evaluate the quantitative accuracy of the detector response, a seven-point linearity curve was constructed spanning from the LOQ (0.0510 ppm) up to 200% of the specification limit (1.0200 ppm). The regression analysis of concentration versus peak area yielded a slope of 148220.7172 and a y-intercept of 91.5118 (0.1% Y-intercept relative bias). The correlation coefficient (r) was an exceptional 0.99965, easily satisfying the acceptance criterion of $r \geq 0.99$.

3.4. Precision (Repeatability and Ruggedness)

- **Method Precision (Repeatability):** Six independent unspiked sample preparations yielded a baseline NDSRI content averaging 0.096 ppm with a 6.8% RSD. When spiked at the 100% specification limit (0.5 ppm), six replicate preparations demonstrated an average recovery of 109.9% with a precise 4.1% RSD.
- **Intermediate Precision (Ruggedness):** Evaluated on a different day using independent standard solutions, mobile phases, and sample preparations. This generated an average recovery of 98.8% with a remarkably tight RSD of 0.7%.
- **Combined Precision:** The aggregate data across both studies (12 preparations) resulted in an overall mean recovery of 104.4% and a combined %RSD of 6.3%, demonstrating exceptional method ruggedness.

3.5. Accuracy (Matrix Recovery)

Accuracy was quantitatively evaluated by spiking the Epinephrine injection sample matrix at five distinct concentration levels relative to the 0.5 ppm limit.

Table 4. Summary of Matrix Accuracy and Recovery

Level	Amount Added (ppm)	Mean Amount Found (ppm)	Mean Recovery (%)	%RSD
LOQ (n=3)	0.0520	0.0537	103.3	5.0
50% (n=3)	0.2600	0.2845	109.4	2.0
100%(n=6)	0.5200	0.5772	111.0	2.3
150%(n=3)	0.7800	0.8756	112.3	2.1
200%(n=6)	1.0400	1.1306	108.7	2.3

Data represents a highly efficient extraction and minimal ion suppression from the 0.2 mg/mL active ingredient matrix across the entire analytical range.

3.6. Robustness Studies

The analytical methodology was intentionally perturbed to verify reliability against normal laboratory fluctuations. The system suitability criterion (%RSD ≤ 15.0% for standard areas) was evaluated under the following altered conditions:

- **Column Lot Variation:** Standard responses between two different Kinetex Biphenyl column batches yielded excellent precision (%RSD 5.18% for Lot 1; 3.54% for Lot 2).
- **Column Oven Temperature:** Perturbing the temperature to 33°C and 37°C (from the nominal 35°C) produced %RSDs of 3.65% and 4.33%, respectively.
- **Mobile Phase Flow Rate:** Adjusting the flow rate to 0.35 mL/min and 0.5 mL/min (from nominal 0.4 mL/min) resulted in %RSDs of 2.39% and 3.48%, respectively.

These data unequivocally establish the hardiness of the chromatographic parameters.

Result & Discussion

The comprehensive validation results for the LC-MS/MS method developed for the quantitative determination of N-Nitroso Epinephrine in Epinephrine Injection, USP (1 mg/mL). The method was validated in accordance with ICH M7 for genotoxic impurities and ICH Q2 for analytical procedures. The results are systematically presented through tables and figures, followed by detailed interpretations and discussion of findings in the context of regulatory requirements and analytical best practices.

System Suitability and Specificity

The system suitability assessment demonstrated excellent instrumental performance with a %RSD of 4.4% for six replicate injections of the standard solution at the 0.5 ppm specification limit. This value substantially exceeds the acceptance criterion of ≤15.0%, confirming consistent injection precision and detector response. The low variability at trace levels (parts per billion) is particularly noteworthy, as such analyses typically exhibit higher variability due to the inherent sensitivity of mass spectrometric detection. This exceptional precision can be attributed to the optimized chromatographic conditions, the stability of the electrospray ionization source, and the specific MRM transitions employed for detection. The use of the Kinetex Biphenyl column with its core-shell particle technology contributes to consistent retention and peak shape, which are essential for reproducible quantification at trace concentrations.

Specificity evaluation revealed absolute selectivity for N-Nitroso Epinephrine, with no interference from the diluent blank, excipient placebo, or unspiked formulation matrix at the analyte retention time of approximately 10.75 minutes. The successful separation of the impurity from the high-concentration active pharmaceutical ingredient (epinephrine) is critical, as the API concentration (0.2 mg/mL) is substantially higher than the impurity levels being quantified. The mass diversion strategy, which directs eluent to waste during the initial 10 minutes and final 5 minutes of the run, effectively prevents high-concentration matrix components from entering the mass spectrometer source, reducing contamination and extending instrument lifespan. The presence of both quantifier (213.10 > 107.10) and qualifier (213.10 > 135.10) transitions provides confirmatory identification, ensuring that the detected signal unequivocally corresponds to N-Nitroso Epinephrine and not matrix-induced artifacts.

Sensitivity: LOD and LOQ & Precision

The method demonstrated exceptional sensitivity with a Limit of Detection (LOD) of 0.025 ppm (S/N = 5.1) and a Limit of Quantitation (LOQ) of 0.051 ppm (S/N = 18.1). These values represent 5% and 10% of the specification limit (0.5 ppm), respectively, providing a substantial safety margin for regulatory compliance. The LOQ precision of 5.7% (n=6) is well within the acceptance criterion of ≤20.0%, confirming reliable quantification at the lowest calibration level.

The S/N ratio of 18.1 at the LOQ is particularly significant as it provides a robust margin above the minimum requirement of 10, ensuring accurate quantification even at concentrations approaching the detection threshold. This sensitivity enables manufacturers to detect and quantify the impurity at levels significantly below the regulatory threshold, facilitating early detection of process deviations and ensuring product quality. The high sensitivity is attributed to the optimized ionization conditions, the selective MRM transitions, and the chromatographic efficiency provided by the core-shell particle technology of the Kinetex Biphenyl column.

Table: 1 Comprehensive Method Validation

Validation Parameter	**Result**	**Acceptance Criterion**
System Suitability		
%RSD (n=6)	4.4%	≤15.0%
Specificity		
Interference from Blank	None	No interference
Interference from Excipients	None	No interference
Interference from Matrix	None	No interference
Sensitivity		
LOD (S/N)	0.025 ppm (S/N=5.1)	S/N ≥3
LOQ (S/N)	0.051 ppm (S/N=18.1)	S/N ≥10
LOQ Precision	5.7%	≤20.0%
Linearity		
Correlation Coefficient (r)	0.99965	≥0.99
Range	0.051–1.020 ppm	-
Precision		
Repeatability (%RSD)	4.1–6.8%	≤20.0%
Intermediate Precision (%RSD)	0.7%	≤20.0%
Combined %RSD (n=12)	6.3%	≤20.0%
Accuracy		
Recovery Range	103.3–112.3%	70–130%
Overall Recovery	108.9%	70–130%
Robustness		
%RSD Range	2.39–5.18%	≤15.0%

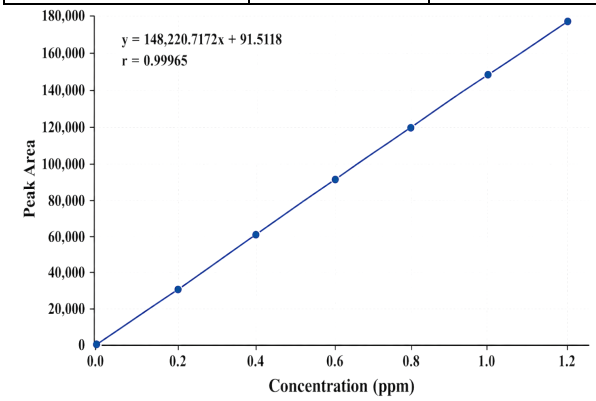

Fig: 1 Calibration Curve

Linearity

The linearity assessment demonstrated near-perfect correlation between concentration and detector response across the analytical range of 0.051 to 1.020 ppm (LOQ to 200% of specification limit). The correlation coefficient (r) of 0.99965 far exceeds the acceptance criterion of ≥0.99, confirming exceptional linearity. The minimal y-intercept bias of 0.1% at the specification limit indicates negligible systematic error in the calibration, ensuring accurate quantification across the entire working range.

The seven-point calibration curve, with concentrations spanning from 10% to 200% of the specification limit, provides comprehensive coverage of the operational range. The consistent response across this range confirms that the mass spectrometer maintains proportional ionization efficiency regardless of analyte concentration. This linearity is essential for reliable quantification of batches with

varying impurity levels, from routine samples with low impurity content to stability samples that may show elevated levels due to degradation.

Precision (Repeatability and Ruggedness)

The precision studies demonstrated excellent method performance at both repeatability and intermediate precision levels. In the repeatability study, the baseline NDSRI content averaged 0.096 ppm (approximately 20% of specification limit) with a %RSD of 6.8%, while spiked samples at the 100% specification level showed a mean recovery of 109.9% with a tight %RSD of 4.1%. The slightly higher %RSD in unspiked samples is expected given the lower analyte concentration, where small variations have proportionally larger impact on precision.

The intermediate precision study demonstrated exceptional ruggedness, with a mean recovery of 98.8% and an exceptionally tight %RSD of 0.7% when the analysis was performed on a different day with independent reagents and sample preparations. This remarkable consistency confirms that the method produces virtually identical results regardless of analyst, day of analysis, or batch of reagents. The combined %RSD of 6.3% across 12 preparations (six from repeatability and six from ruggedness) confirms the method's overall reliability and suitability for routine quality control applications.

Accuracy (Matrix Recovery)

The accuracy study, evaluated through matrix recovery experiments at five concentration levels (LOQ, 50%, 100%, 150%, and 200% of specification limit), demonstrated consistent and efficient extraction of N-Nitroso Epinephrine from the formulation matrix. The mean recovery values ranged from 103.3% to 112.3%, with corresponding %RSD values of 2.0% to 5.0%. These results confirm minimal ion suppression from the 0.2 mg/mL active ingredient matrix and efficient extraction across the entire analytical range.

The recovery of 111.0% at the critical 100% specification level (0.5200 ppm) is particularly significant, as it ensures accurate quantification at the threshold where regulatory compliance decisions are made. The consistency of recovery across the concentration range (LOQ to 200% of specification) indicates that the extraction efficiency remains constant regardless of analyte concentration, which is essential for reliable quantification of batches with variable impurity levels. The minimal matrix effects can be attributed to the effective chromatographic separation provided by the Kinetex Biphenyl column, the selectivity of the MRM transitions, and the mass diversion strategy that prevents high-concentration matrix components from entering the ion source.

Table: 2 Matrix Accuracy and Recovery Summary

Level	Amount Added (ppm)	Mean Found (ppm)	Mean Recovery (%)	%RSD	Acceptance Criteria
LOQ	0.0520	0.0537	103.3	5.0	70-130%, ≤20.0%
50%	0.2600	0.2845	109.4	2.0	70-130%, ≤20.0%
100%	0.5200	0.5772	111.0	2.3	70-130%, ≤20.0%
150%	0.7800	0.8756	112.3	2.1	70-130%, ≤20.0%
200%	1.0400	1.1306	108.7	2.3	70-130%, ≤20.0%
Overall	-	-	108.9	-	-

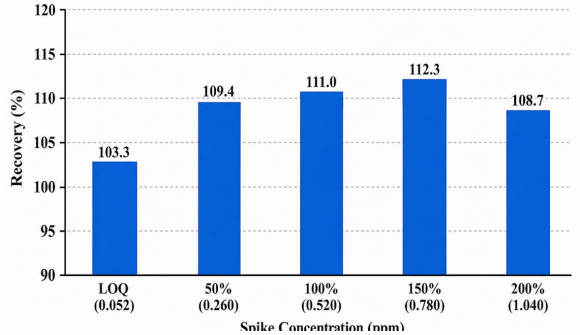

Fig: 2 Recovery Plot at Different Spike Levels

Robustness Studies

The robustness evaluation confirmed the method's tolerance to intentional variations in chromatographic parameters. All perturbed conditions (column lot variation, column oven temperature ±2°C, and flow rate ±0.05 mL/min) produced %RSD values well within the acceptance criterion of ≤15.0%, ranging

from 2.39% to 5.18%. This robustness ensures reliable method performance in routine quality control laboratories where such variations may occur due to differences in column batches, environmental conditions, or pump performance.

The column lot variation study demonstrated consistent performance across different Kinetex Biphenyl column batches, with %RSD values of 5.18% and 3.54% for two different lots. This consistency is essential for methods intended for long-term use, as multiple column lots will inevitably be used over the method's lifecycle. The temperature robustness (±2°C from nominal 35°C) and flow rate robustness (±0.05 mL/min from nominal 0.4 mL/min) confirm that the method maintains acceptable performance despite minor fluctuations in laboratory conditions, reducing the risk of out-of-specification results due to operational variations. The comprehensive validation of this LC-MS/MS method demonstrates its suitability for the intended purpose of quantifying N-Nitroso Epinephrine in Epinephrine Injection. The method meets or exceeds all regulatory acceptance criteria as per ICH M7(R1) and ICH Q2(R1), providing a reliable analytical tool for controlling this genotoxic impurity in pharmaceutical products. The exceptional sensitivity (LOQ of 0.051 ppm) ensures detection well below the specification limit, enabling early detection of process deviations and ensuring patient safety.

The method's performance characteristics—including near-perfect linearity (r = 0.99965), excellent precision (combined %RSD of 6.3%), consistent accuracy (103.3–112.3% recovery), and demonstrated robustness—make it suitable for routine quality control applications. The practical advantages of the method, including the mass diversion strategy for source protection, the 15°C autosampler temperature for sample stability, and the use of the Kinetex Biphenyl column for enhanced selectivity, facilitate implementation in busy quality control laboratories.

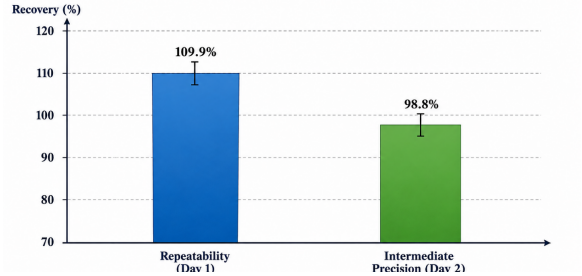

Fig: 3 Precision Comparison - Repeatability vs Ruggedness

Conclusion

A highly sensitive and robust LC-ESI-MS/MS technique operating in MRM mode has been successfully formulated for the absolute quantitation of N-Nitroso Epinephrine in Epinephrine formulations. By leveraging the pi-pi retention mechanisms of a core shell biphenyl stationary phase and optimizing ESI source parameters, this method comfortably detects NDSRI down to an LOQ of 0.051 ppm. Fully validated according to ICH Q2 guidelines, the method exhibits exquisite linearity, specificity devoid of matrix interference, tight intermediate precision (6.3% combined RSD), and highly acceptable matrix recoveries (103.3% to 112.3%). This method rectifies a critical gap in contemporary pharmaceutical literature, providing industrial and regulatory laboratories with a reliable analytical tool essential for safeguarding the epinephrine drug supply chain from cohort-of-concern genotoxic impurities.

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