# Development of an Analytical Method for Quantifying Nitrosamine Impurities in Metformin hydrochloride Using Liquid Chromatography-Mass Spectrometry

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***Abstract*—Nitrosamine-containing active pharmaceutical ingredients (APIs) have raised safety concerns due to their potential carcinogenic nature. Regulatory agencies such as the United States Food and Drug Administration (FDA) have established guidelines limiting nitrosamine impurities, including N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA), among others. To ensure compliance, this study presents an analytical method for detecting and quantifying nitrosamine impurities in Metformin hydrochloride API, utilizing liquid chromatography coupled with mass spectrometry (LC-MS/MS). A Waters XSelect High Strength Silica (HSS) pentafluoro phenyl (PFP) column was employed for chromatographic separation, using a mobile phase gradient composed of 0.1% methanoic acid in water and methanol. Under the optimized analytical conditions, the retention times for Metformin hydrochloride, NDMA, NDEA, NEIPA, NMPA, and NDBA were 8.47, 15.83, 19.35, 20.54, 22.11, and 24.85 minutes, respectively, demonstrating efficient separation with** good resolution **for all analytes.The linearity assessment showed that NDMA exhibited a linearity range of 0.019–0.135 ppm, while NDEA, NEIPA, NMPA, and NDBA each showed linearity within the range of 0.002–0.10 ppm. The correlation coefficients (r) were 0.9913 for NDMA, 0.9973 for NDEA, and 0.9967 for NEIPA, NMPA, and NDBA, confirming excellent linearity, with corresponding regression coefficients ($R^2$) of 0.9828, 0.9967, and 0.9934, respectively. The method demonstrated strong sensitivity, with LOD values of 0.0012 ppm (NDMA), 0.0056 ppm (NDEA), 0.0052 ppm (NEIPA), 0.0042 ppm (NMPA), and 0.0044 ppm (NDBA), and LOQ values of 0.0124, 0.0091, 0.0083, 0.0057, and 0.0067 ppm, respectively. Accuracy and recovery results were within the acceptable ICH limits, confirming the reliability of the method for quantitative analysis. Robustness evaluation, performed by varying critical parameters by ±10%, demonstrated consistent performance in accordance with ICH validation criteria. Furthermore, the developed method aligns with FDA guidelines for LOD and LOQ, ensuring suitability for routine analysis of nitrosamine impurities in pharmaceutical products. The approach also optimizes solvent consumption while maintaining essential sensitivity and specificity for detecting nitrosamine impurities in Metformin hydrochloride. Overall, the method meets ICH requirements, demonstrating high efficiency, sensitivity,** good resolution**, and reliability for regulatory and quality-control applications.**

***Index Terms*—Nitrosamine, Carcinogenic, Metformin hydrochloride, X select HSS PFP, LC-MS/MS**

Highlights

- A method using Select HSS PFP column was developed to quantify nitrosamine impurities in Metformin hydrochloride API
- Enhanced resolution between Metformin hydrochloride and nitrosamine impurities was achieved
- The developed method is applied for the routine analysis of Metformin hydrochloride in the pharmaceutical industry.
- To demonstrate regular sample analysis while minimizing the run time and reducing solvent consumption

## I. INTRODUCTION

Diabetes is classified into three types, and type 2 is the most common. This is a chronic state in which the body either does not use insulin properly (insulin resistance) or fails to produce enough to regulate blood sugar (glucose). In 1921, Frederick Banting and Charles Best in Canada found an insulin that saved millions of lives by revolutionizing the treatment of

diabetes. Diabetes is the largest prevalence in China, India, and the United States. Type 2 diabetes affects around 537 million adults globally, within the age range of 20 to 79 years. The first oral drug was Metformin hydrochloride, which was derived from the plant Galega officinalis (French lilac). Though its blood sugar-lowering properties were known for centuries, it was officially developed as a medication in the 1950s and became widely used in the 1970s [1].Various formulations, including immediate-release and extended-release versions, are available for therapeutic use[2, 3] .The first nitrosamine contaminants in drug products were discovered in 2018. The presence of NDMA was detected in Sartan medications, including valsartan, losartan, and irbesartan, which are commonly used to manage high blood pressure [4, 5]. Subsequent investigations in 2020 identified similar impurities in Metformin hydrochloride formulations, prompting regulatory actions from agencies such as the FDA and the European Medicines Agency (EMA) [6–9]This regulatory authority set strict limit controls on the NDMA level in medication. The permissible daily intake (ADI) for NDMA is 96 ng·day$^{-1}$[10] .The calculation of the NDMA limit based on the daily dose is determined by dividing the acceptable intake (AI) limit of nitrosamine impurity by the daily dose of Metformin hydrochloride**.** For example, if the maximum daily dose of Metformin hydrochloride is 2.0 grams**,** and AI for NDMA is 96 ng·day$^{-1}$, the acceptable NDMA limit would be 0.048 parts per billion (ppb**).** If the detected nitrosamine impurity exceeds the ADI value, the FDA has requested applicants to voluntarily recall the affected Metformin hydrochloride products [11, 12].The FDA has stipulated an ADI limit of 96 ng·day$^{-1}$ for NDMA and 26.5 ng·day$^{-1}$ for other nitrosamines. The structural representation of these impurities is provided in Figure 1.

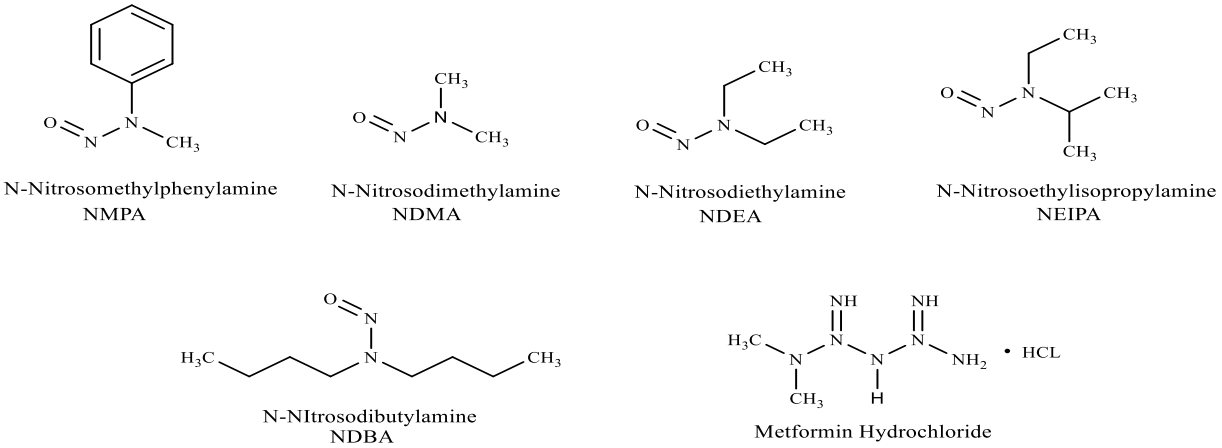


Figure 1. Presented five nitrosamine impurity structures and Metformin hydrochloride Hydrochloride

Nitrosamine impurities such as NDMA can form under acidic conditions when dimethylamine reacts with nitrite salts, during the synthesis of Metformin hydrochloride [13] .Figure 2.

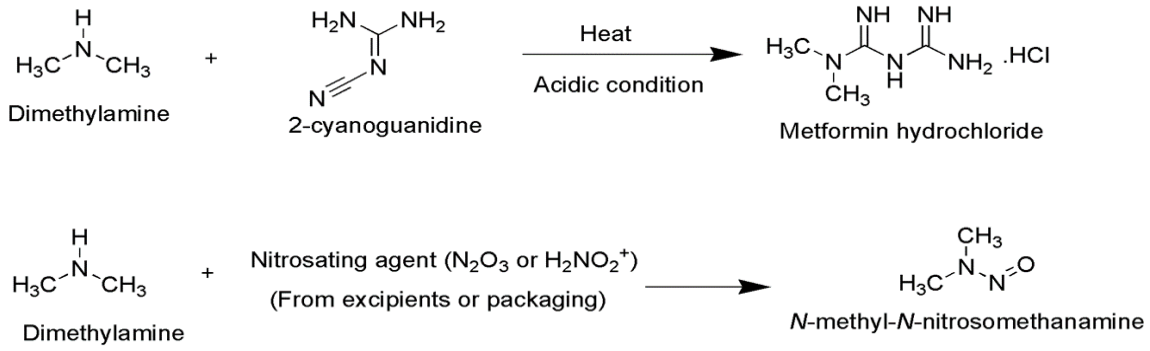


Figure 2. NDMA impurity formation during the manufacturing process of Metformin hydrochloride HCL

The most widely used and sensitive way to detect nitrosamine contaminants in medication and drug substances using instrumental techniques such as LC-MS/MS and GC-MS/MS are commonly used techniques, while Fourier Transform Infrared Spectroscopy (FTIR) and Ultraviolet-Visible Spectroscopy (UV-VIS) can serve as supplementary methods for preliminary screening. LC-MS/MS and GC-MS/MS are the most reliable ways to detect nitroimines, but each method has its own limitation [14–17].The limitations in LC-MS detection methods often result in undesirable peak shapes and poor resolution of analytes. This issue is particularly visible when NDMA is present in the drug product [18] .The main challenge in the quantitative evaluation of nitro impurities in Metformin hydrochloride is to achieve a good resolution between nitrosamine and nitrosamine impurities because of its short retention time. In addition, the choice of diluents such as acetonitrile and methanol greatly affects sensitivity and specificity. Quantitative analysis using the method of the internal reference standard is effective, but it is very expensive for the routine sample analysis. This study introduces a method designed to overcome these challenges. This method provides a foundation for further enhancements, enabling researchers to customize it for drug products, drug substances, and various dosage forms.

## II. METHODOLOGY

2.1. Analytical grade chemicals and solvents

Metformin hydrochloride API was sourced from Om Sales, while nitrosamine standards, including NDMA, NMPA, NEIPA, NDEA, and NDBA, were procured from Sigma-Aldrich LC/MS-grade solvents, such as acetonitrile and methanol, were utilized alongside high-purity methanoic acid and ammonium formate. Milli-Q water was used for sample preparation to maintain high analytical purity. The Metformin hydrochloride drug product, specifically Gliclazide and Metformin hydrochloride Hydrochloride Extended-Release Tablets (Cyblex M30), was purchased from the market, while the Metformin hydrochloride API was sourced from Deepen Drugs, Gujarat.

2.2. Preparation of standards and sample solution

Each nitrosamine impurity standard stock solution was prepared into a 100-ppm solution by diluting the required volume or amount with methanol. Mix 1.0 ml of each of the five nitroso impurities using the standard stock solution, and use the diluent to create a 5-ppm impurity stock solution. The preparation of linearity calibration standards using this impurity stock solution, the final concentrations of each nitrosamine impurity ranged from 20% to 150% of the required limits. This strategy ensured comprehensive technique validation throughout a broad dynamic range.

2.3. HPLC-MS/MS operating analytical condition

A Waters India High-Performance Liquid Chromatography (HPLC) system coupled with a Thermo LC Quantum triple quadrupole LC-MS/MS was utilized with electrospray ionization (ESI) instruments to separate the Metformin hydrochloride API and nitrosamine impurities.

HPLC Analytical Conditions:

Instrument: Waters HPLC coupled with Thermo LC Quantum MS/MS

Column: XSelect HSS PFP, 100 Å, 250 × 4.6 mm, 5 µm

Regent :- Methanoic acid

Mobile Phase A: 0.1% Methanoic acid in water

Mobile Phase B: 0.1% Methanoic acid in methanol

Flow Rate: 0.4 mL/min

Absorbance : 230 nm

Injection Volume: 20 µL

Run time : 40 min

Gradient Elution Mode: Optimized for effective separation

The needle is rinsed with an equal volume (1/1 v/v) mixture of water and methanol that was prepared. The elution modes of the gradient program were: The gradient program was as follows: at 0.00 minutes, the level is 10% B, remaining constant until 2.00 minutes. It then increases to 15% B at 4.00 minutes. A significant rise occurs at 12.00 minutes, reaching 70% B, followed by an increase to 90% B at 25.00 minutes and 95% B at 29.00 minutes. Shortly thereafter, at 29.10 minutes, the level drops back to 10% B, where

it remains until the end of the observation at 40.00 minutes. Multiple reaction mode (MRM) was used to operate the Thermo LC Quantum MS/MS in positive ESI mode. To enhance sensitivity, the source parameters were altered as follows: shield gas flow rate at 40 L/min, auxiliary gas flow rate at 10 L/min, and purge gas nitrogen flow rate at 0. The sweep gas flow rate was maintained constant at 0, the capillary temperature was maintained at 350°C, the spray voltage was set to 4800 V, and the lens was set to 68. The mass software Xcalibur regulated all parameters of the LC and MS systems.

2.4. Method Validation

The LC-MS/MS method was validated by evaluating key parameters, including specificity, precision, linearity, limit of quantification (LOQ), and limit of detection (LOD). Specificity was determined by comparing Metformin hydrochloride with the impurity spiked in a diluent consisting of 70% methanol and a methanoic acid (0.1%) aqueous mixture. Precision was evaluated at the 100% concentration level of each nitrosamine impurity using six standard solution injections, and linearity was demonstrated by constructing a six-point calibration curve over which each nitrosamine impurity was assessed within a concentration range of 20% to 150% of the target value. The LOD and LOQ for each analyte were determined based on the signal-to-noise (S/N) ratio approach, with thresholds set at 3:1 for LOD and 10:1 for LOQ. The suggested maximum daily dose of the drug is 1000 mg/day. This acts as a reference dose threshold for determining drug concentration limits.

2.5. Analysis of data

Analytical data processing and evaluation were performed using Xcalibur software (version 3) from Thermo, TSQ Quantum, LC solution form Shimadzu.

## III. ANALYTICAL METHOD DEVELOPMENT AND DATA INTERPRETATION

3.1. Liquid chromatography analytical method development

A method was developed using LC-MS/MS to detect nitrosamine impurities in Metformin hydrochloride. The investigation began with tackling the issue of retention time, followed by improving the MS/MS conditions. A 100-ppm stock solution containing nitrosamine impurities was prepared, and the LC conditions were adjusted with a UV detector. Screening various columns, including Hypersil C18 and Waters HSS PFP, for the initial screening of column selection, Various combinations of organic solvents were evaluated, and methanol was preferred due to its high polarity and improved NDMA retention time. To optimize initial conditions, mobile phases were supplemented with a 0.1% methanoic acid solution in acetonitrile or methanol utilized with the HSS PFP column; however, the solvent's high viscosity results in elevated backpressure. To minimize viscosity and enhance peak shape, Figure 3 presents the UV analysis data of nitrosamine impurities obtained using the optimized LC method. The HSS PFP column works well in acidic mobile phases because it supports pH between 2 and 8. Polar substances like Metformin hydrochloride does not ionize under acidic conditions, which reduces their polarity and makes them behave like non-polar substances. Because "like dissolves like," these non-ionized polar molecules could be more retained on the column. The PFP column's fluorinated phase (pentafluoro phenyl) separates polar compounds better than C18 alkyl phases[19].These polar contacts allow non-ionized polar molecules to engage with the PFP phase, promoting efficient separation. The PFP phase's increased selectivity is particularly helpful for separating active drugs like Metformin hydrochloride from structurally identical impurities like nitrosamines. This mixture contains a mobile acid, and the HSS PFP column is an excellent choice for this particular application because it combines an acidic mobile phase with a fluorinated stationary phase. Figure 3 shows the results

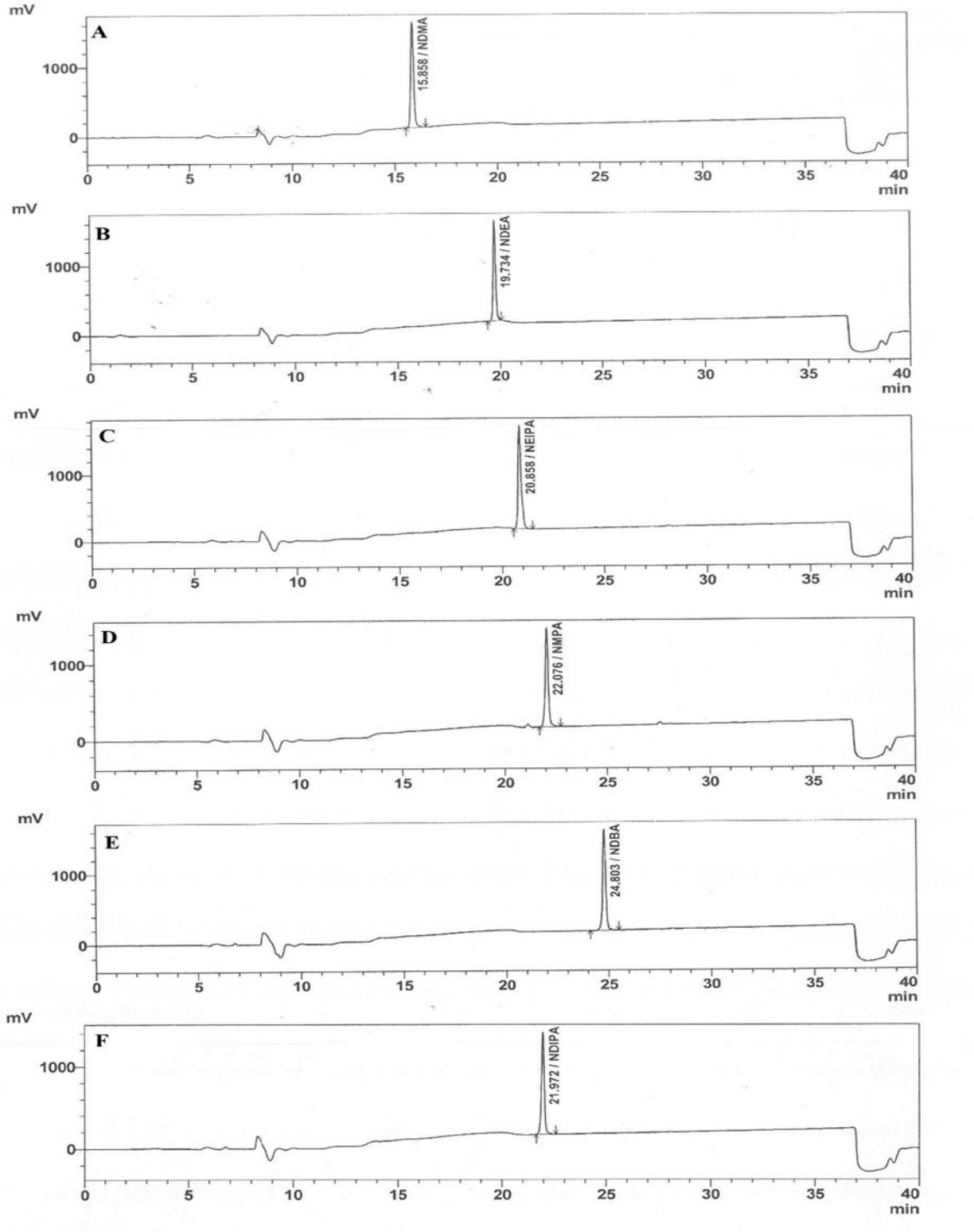


Figure 3. HPLC chromatograms of nitrosamine impurities: (A) NDMA (B) NDEA (C) NEIPA (D) NMPA (E) NDBA

3.2 Optimization of chromatography solvent system

Different mobile phase additives were tested to optimize signal sensitivity. Various mobile phase combinations were assessed in the study, including ammonium formate with an aqueous solution containing methanoic acid (0.1%) aqueous mixture with acetonitrile, and a methanoic acid (0.1%) aqueous mixture with methanol. Switching from acetonitrile to methanol in an aqueous solution containing 0.1% methanoic acid improved the resolution between Metformin hydrochloride and NDMA impurity. In the context of using electrospray ionization (ESI) mode for detection, nitrosamines show enhanced ionization when using methanoic acid. Selecting an appropriate diluent is crucial for method development and accurate quantification of nitroso impurities. Different mixtures of solvents and buffers, which include acetonitrile, methanol, ammonium bicarbonate, and ammonium formate, have been examined. The highest signal-to-noise ratio was achieved using a diluent of 70% methanol and a methanoic acid (0.1%) aqueous mixture, along with optimized mobile phases and additives.

3.2 Mass spectrometer optimization

The Thermo TSQ Quantum 2.3 LC-MS/MS system operated in electrospray ionization (ESI) mode, using a mass spectrometer detector to detect nitrosamine impurities at trace levels (ng range). This study was carried out using the nitrosamine impurities identified by the FDA. Each nitrosamine impurity was tuned on mass spectrometry using an impurity concentration of 1000 ng/ml. Following optimization of molecular masses, the MS2 experiment was used to identify product ions of nitrosamine impurities. Table 1 presents a detailed list of product ions. During MS tuning, product ions were generated and broken into impurity-specific ions.

Table 1. MS/MS tune parameter for nitrosamine impurities identification

| Analyte | Parent Ion | Product Ion | Coll.E (V) | Product Ion | Coll.E (V) | Tube.L |
|---|---|---|---|---|---|---|
| NDMA | 75.1 | 43.15 | 15 | 58.18 | 19 | 53.31 |
| NDEA | 103.1 | 27.23 | 20 | 74.16 | 14 | 76.34 |
| NEIPA | 117.1 | 75.11 | 33 | 75.11 | 8 | 53.06 |
| NMPA | 137.0 | 66.10 | 19 | 41.16 | 27 | 56.82 |
| NDBA | 159.1 | 41.15 | 18 | 57.18 | 13 | 60.57 |

- *Abbreviations: Coll. E (V) – Collision Energy (Volts), Tube L – Tube Lens Voltage*

## IV. ANALYTICAL METHOD VALIDATION

4.1. Specificity

The method specificity was confirmed by injecting Metformin hydrochloride API and five nitrosamine impurities at their corresponding specification levels. Better resolution was observed between Metformin hydrochloride and nitrosamine impurity (Figure 3). Table 2 represents a detailed list of retention times and concentrations of each analyte.

Table 2. Presents the specificity analytical parameters for the five nitrosamine impurities

| Analyst | RT (min) | RRT | T.Plate | T.Factor | Resolution |
|---|---|---|---|---|---|
| NDMA | 15.85 | 1.56 | 239831 | 1.11 | 7.80 |
| NDEA | 19.73 | 1.93 | 848112 | 1.10 | 14.10 |
| NEIPA | 20.87 | 2.04 | 749660 | 1.30 | 4.84 |
| NMPA | 22.06 | 2.15 | 443263 | 1.11 | 4.03 |
| NDBA | 25.09 | 2.54 | 919485 | 0.94 | 9.90 |

- *Abbreviations: T. Plate – Theoretical Plates, T. Factor – Tailing Factor*

4.2. Linearity

The method's linearity was assessed across a concentration range of 20% to 150% for each impurity at target level. The coefficient of determination ($R^2$) for all impurities was found to be $\leq 0.99$, and it demonstrates a good linear response as shown in Table 3.

4.3. Detection and quantification threshold

Detection and quantification threshold values for the six impurities were determined using S/N ratios of 3:1 and 10:1, respectively. Known standard concentrations of the nitrosamine impurities were injected, and LOD and LOQ were assessed using Xcalibur software (Table 3, Figure 4). Reproducibility was tested at the LOD level with three injections

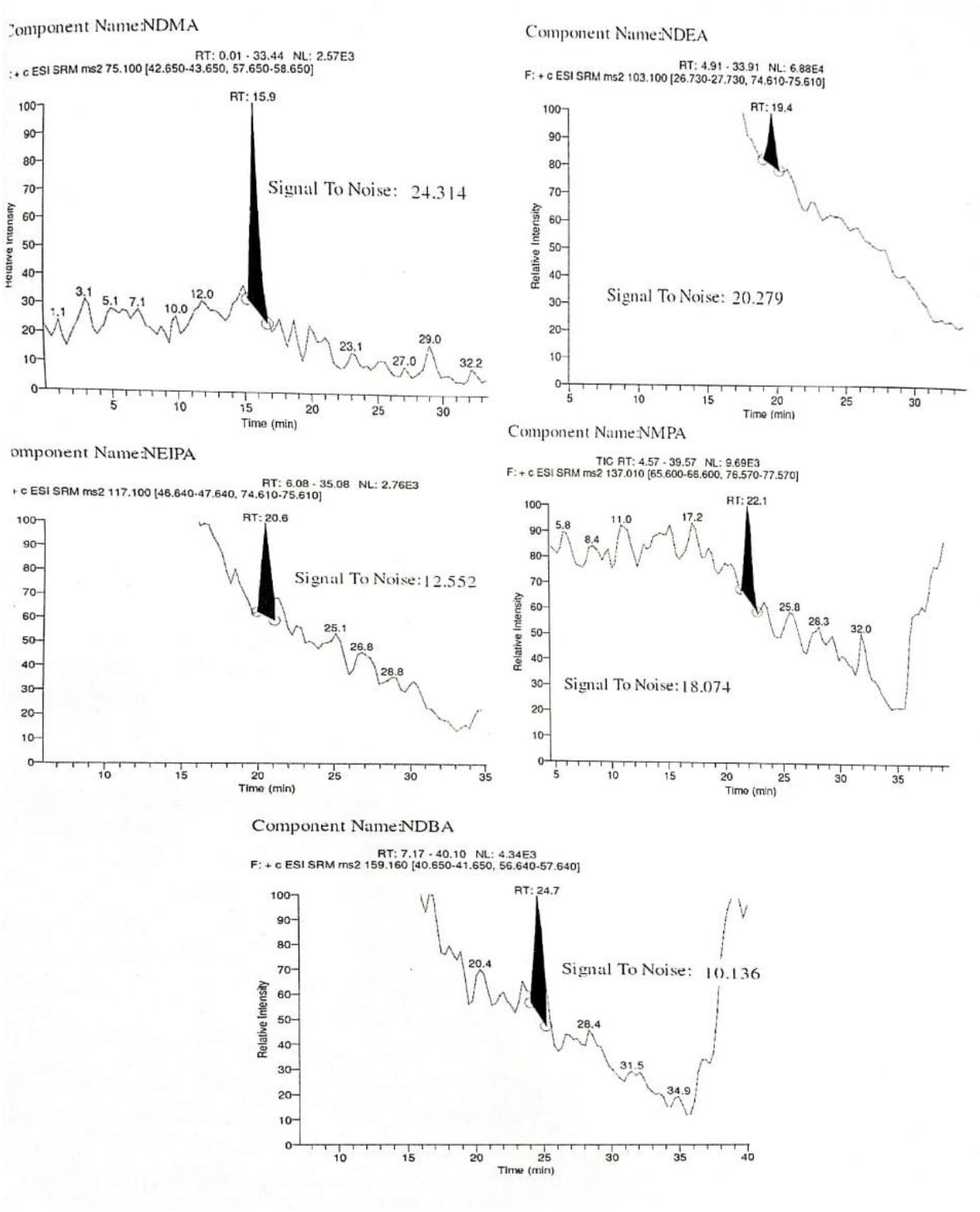


Figure 4. TIC of nitrosamine impurity at LOD

Table 3. Linearity, Recovery and precision analysis results for nitrosamine impurities

| Parameter | NDMA | NDEA | NEIPA | NMPA | NDBA |
|---|---|---|---|---|---|
| Linearity Range (ppm) | 0.019-0.135 | 0.002-0.10 | 0.002-0.10 | 0.002-0.10 | 0.002-0.10 |
| Correlation coefficient (r) | 0.9913 | 0.9973 | 0.9967 | 0.9967 | 0.9967 |
| Regression Coefficient ($R^2$) | 0.9828 | 0.9967 | 0.9934 | 0.9934 | 0.9934 |
| Intercept | 258680 | 8021 | 114973 | -85749 | -29306 |
| Slope | 20722 | 50468 | 52495 | 42137 | 50652 |
| LOD (ppm) | 0.0012 | 0.0056 | 0.0052 | 0.0042 | 0.0044 |
| LOQ (ppm) | 0.0124 | 0.0091 | 0.0083 | 0.0057 | 0.0067 |
| S/N | 15.94 | 12.70 | 12.55 | 18.07 | 10.13 |
| Precision (%RSD) | 7.16 | 8.15 | 5.87 | 3.45 | 3.41 |
| Intermediate precision (%RSD) | 2.22 | 4.35 | 3.84 | 3.10 | 1.69 |

4.4. Precision and Recovery

Method precision was evaluated by spiking impurity standard solutions at 100% of their target concentrations into the Metformin hydrochloride API, followed by replicate analyses. The relative standard deviation (RSD) values for nitrosamine impurities were found to be within the acceptable limit of 20%. Intermediate precision of the developed LC-MS/MS method was evaluated to demonstrate its robustness under normal laboratory variability. The study was performed by analysing Metformin hydrochloride API samples spiked with nitrosamine impurities at 100% of their target concentrations under varied conditions, including different days, analysts, and instruments. For each condition, six independent sample preparations were carried out and analysed following the established procedure. The results obtained across these varied conditions were assessed for consistency by calculating the relative standard deviation (RSD) values of the measured concentrations. The RSD values for all nitrosamine impurities remained within the predefined acceptance criteria (≤15% at the target level, ≤20% at the LOQ), confirming that the method provides reproducible results irrespective of changes in analyst, instrument, or day of analysis. These findings demonstrate that the method possesses adequate intermediate precision and is suitable for routine application in the determination of nitrosamine impurities in Metformin hydrochloride API. The validated method was subsequently applied to assess the presence of nitrosamine impurities in a commercially available Metformin hydrochloride drug product—(Gliclazide and Metformin hydrochloride Hydrochloride) Extended-Release Tablets (Cyblex M30). Method accuracy was evaluated through spiked recovery experiments at 50%, 100%, and 150% of the acceptable intake (AI) levels of each nitrosamine impurity. The sample was diluted with an appropriate diluent. The sample was spiked with six nitrosamine impurities, and the recovery results demonstrated the accuracy of the method (refer to Table 4 for details). No nitrosamine impurities were detected in the Cyblex M30 drug product.

Table 4 Recovery and accuracy results for five nitrosamine impurities

| Name | Recovery ( AI Target level) | | | % RSD of Recovery ( AI Target level) | | |
|---|---|---|---|---|---|---|
| | 50% | 100% | 150% | 50% | 100% | 150% |
| NDMA | 96-99 | 96-108 | 82-83 | 2.2 | 8.4 | 1.1 |
| NDEA | 106-116 | 89-92 | 97-109 | 6.7 | 2.4 | 8.0 |
| NIPEA | 109-110 | 84-85 | 111-113 | 0.5 | 1.2 | 1.3 |
| NMPA | 110-116 | 89-100 | 102-103 | 3.4 | 1.8 | 0.6 |
| NDBA | 111-118 | 99-101 | 100-105 | 4 | 1.2 | 3.0 |

4.5. obustness

The robustness of the method was evaluated by changing one parameter at a time: (1) varying the methanoic acid composition in mobile phase A and mobile phase B by ±10%, and (2) adjusting the flow rate by ±10% from the original method. Each robustness parameter was tested in a separate run. For each condition, six system suitability test (SST) injections were performed, followed by one injection of the as-such sample and one injection of the 100% spiked impurity standard. The recovery results were evaluated to confirm that all values remained within the acceptable ICH range of 80%–110%.

## V. CONCLUSION

According to regulatory guidelines, detecting nitrosamine impurities in pharmaceutical active ingredients is a significant global concern due to their high potency. Analytical method was developed in this study using a PFP reverse-phase column, methanoic acid as an additive, and ESI mode with multiple reaction monitoring. This method is capable of detecting nitrosamine impurities at LOD (0.0012 to 0.0056 ppm) and LOQ (0.0057 to 0.0124 ppm) levels while achieving good retention of both Metformin hydrochloride API and nitrosamine impurities. The method demonstrates acceptable accuracy, with percent recovery ranging from 80% to 110%, indicating suitability for trace-level quantification. To date, no method has been reported that utilizes a PFP column to achieve good retention of polar impurities, particularly NDMA and Metformin hydrochloride API, while reducing the consumption of LCMS-grade solvent and validated method as per ICH guidelines. The validated method can be used for routine quantification of nitrosamine impurities in Metformin hydrochloride API.

Declaration of Competing Interest

The authors declare no financial interests or personal relationships that could have influenced this study.

## VI. ACKNOWLEDGMENTS

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