

## Quantitation of N-Nitroso-Propranolol in Drug Substance using LC-MS/MS

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### Abstract

N-Nitrosamines (nitrosamines) can be potentially mutagenic and carcinogenic. Since 2018, nitrosamines have been discovered in several classes of pharmaceuticals. There have been concerted efforts to mitigate the presence of nitrosamines in all marketed medicines while still ensuring continued safe access to vital medications.

Nitrosamine drug substance related impurities (NDSRIs) have been detected in multiple drug products. NDRSI formation occurs due to presence of susceptible structural properties, such as a secondary or tertiary amine, that allows for the addition of a nitroso group under certain chemical conditions, including the presence of nitrites from excipients.

Recently, both the EMA and the FDA provided revisions on how acceptable intake values (AI) are determined. The revisions introduced an expanded structure activity (SAR) approach with different potency categories based on carcinogenicity data derived from known nitrosamines (Carcinogenic Potency Categorization Approach, CPCA). In 2022, propranolol, a beta-blocker, was the subject of a recall due to the detection of the nitrosated impurity, N-nitroso-propranolol in drug product. This study describes the analysis of N-nitroso-propranolol in drug substance using Ultra-Performance Liquid Chromatography (UPLC) with electrospray detection (ESI) and a Xevo™ TQ-S micro Tandem Quadrupole Mass Spectrometer. Analytical methods used for the detection of NDSRIs, are required to have a lower limit of quantitation (LOQ) at 10% of the limit derived from the AI and the

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active pharmaceutical ingredients (API) maximum daily dose (MDD). Assuming a MDD of 320 mg, the assay exceeded the regulatory requirements according to the revised AI of 1500 ng/day for N-nitroso-propranolol. The method demonstrated good linearity over the concentration range of 0.01–100 ppm for N-nitroso-propranolol with less than 15% concentration deviations. The  $R^2$  was greater than 0.998. The method recovery ranged from 89.3–104.6% and the accuracy was within +/- 10% of the true value.

## Benefits

- Trace level detection beyond the required regulatory limits as defined by new CPCA approach for the analysis of N-nitroso-propranolol using the Xevo TQ-S micro Tandem Quadrupole Mass Spectrometer in MRM acquisition mode
- Accurate and reproducible methodology for quantitative analysis of N-nitroso-propranolol in drug substance within the required recovery range
- Chromatographic resolution between propranolol, N-nitroso-propranolol and N-formylpropranolol

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## Introduction

Nitrosamines can be potentially mutagenic and carcinogenic.<sup>1-2</sup> Since 2018, Nitrosamines have been discovered in several classes of pharmaceuticals.<sup>3-5</sup> There have been concerted efforts to mitigate the presence of nitrosamines in all marketed medicines while still ensuring continued safe access to vital medications.<sup>6</sup>

Nitrosamine drug substance related impurities (NDSRIs), a term used to indicate the structural relationship between the active pharmaceutical ingredient (API) and its nitrosated impurity, have been detected in multiple drug products. NDRSI formation occurs due to presence of susceptible structural properties, such as a secondary or tertiary amine, that allows for the addition of a nitroso group under certain conditions, including the presence of nitrites from excipients.<sup>2</sup>

Recently, both the EMA and the FDA provided revisions on how acceptable intake values (AI) are determined.<sup>7-8</sup> The revisions introduced an expanded structure activity (SAR) approach with different potency categories based on carcinogenicity data derived from known nitrosamines (Carcinogenic Potency Categorization Approach, CPCA). The calculation of a potency score aids in the assignment of the revised AI limits.<sup>9</sup> The current potency categories range from 18 ng/day (EMA) and 26.5 ng/day (FDA) to 1500 ng/day. Flexibility in instrument

sensitivity is an important feature to enable accurate measurements to be made for nitroso impurities across all potency categories. Tandem Quadrupole Mass Spectrometer analysers offer the best performance characteristics for quantitative measurements in complex matrices such as drug products due to their ease of use, robustness, sensitivity, and the assay selectivity afforded through selection of precursor and product ions in multiple reaction monitoring (MRM) experiments.

In 2022, propranolol, a widely used beta-adrenergic receptor blocker (beta-blocker) used in the treatment of hypertension, abnormal heart rhythms, and other cardiovascular disorders, was the subject of a recall due to the detection of the nitrosated impurity, N-nitroso-propranolol in drug substance using Ultra-Performance Liquid Chromatography (UPLC™) with electrospray detection (ESI) and a Tandem Quadrupole Mass Spectrometer. During the study, one of the API samples tested was found to contain N-formylpropranolol which has  $m/z$  288 and fragments that in the absence of chromatographic separation can lead to signal overlap in some of the MRM transitions of N-nitroso-propranolol.

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## Experimental

### LC Conditions

|                     |  |
|---------------------|--|
| LC system:          | ACQUITY Premier Binary with an FTN                               |
| Detection:          | PDA 210–400 nm: 230 nm single wavelength                         |
| Vials               | TruView LC/MS (p/n: 186005663CV)                                 |
| Column:             | Xbridge® BEH C <sub>8</sub> 2.5 µm 3.0 x 100 mm (p/n: 186006047) |
| Column temperature: | 45 °C  |
| Sample temperature: | 5 °C   |
| Injection volume:   | 10 µL  |

|                 |   |
|-----------------|---|
| Flow rate:      | 0.50 mL/min                                       |
| Mobile phase A: | 0.1% formic acid in water                         |
| Mobile phase B: | 0.1% formic acid in methanol                      |
| Extension loop: | Extension Loop, 50- $\mu$ L, HPS (p/n: 700012825) |

## MS Conditions

|  |                       |
|--|-----------------------|
| Ionisation mode:                         | Electrospray positive |
| Capillary voltage (kV):                  | 1.0                   |
| Cone voltage (V):                        | Table2                |
| Collision energy (eV):                   | Table 2               |
| Source temperature ( $^{\circ}$ C):      | 130                   |
| Desolvation temperature ( $^{\circ}$ C): | 500                   |
| Desolvation gas flow (L/hr):             | 1000                  |
| Cone gas flow (L/hr):                    | 100                   |

## Sample Preparation

### Standards and Reagents

Authentic standards of N-nitroso-propranolol were purchased from Toronto Research Chemicals (Toronto, Ontario). Propranolol hydrochloride was purchased from Sigma Aldrich (St. Louis, MO). N-Formylpropranolol was purchased from BOC Sciences (Shirley, NY). Optima LC/MS grade solvents and formic acid were purchased from Fisher Scientific. Primary stock solutions of propranolol (1 mg/mL), N-nitroso-propranolol and N-

formylpropranolol at 10 mg/mL were used to prepare the working solutions.

## Recovery, Accuracy and Precision Studies

Propranolol ( $C_{16}H_{21}NO_2$ ) constitutes 87.8% of propranolol hydrochloride ( $C_{16}H_{21}NO_2 \cdot HCl$ ). Aliquots of propranolol hydrochloride (5.7 mg = 5.005 mg of propranolol) were weighted into 5 mL centrifuge tubes (Eppendorf). Spiking solutions were prepared in methanol at 2.5  $\mu\text{g/mL}$ , 250  $\text{ng/mL}$  and 25  $\text{ng/mL}$  in glass scintillation vials. The spiking solutions were used to prepare three concentrations at which the recovery was evaluated.

Pre-spikes: 10  $\mu\text{L}$  of each spiking solution concentration was pipetted into 6 tubes each containing 5.7 mg of propranolol hydrochloride. The samples were allowed to equilibrate for 30 min before 5 mL of methanol was added to make final concentrations of 5  $\text{ng/mL}$ , 0.5  $\text{ng/mL}$  and 0.05  $\text{ng/mL}$  ( $n=6$  at each concentration level). The centrifuge tubes were vortex mixed (1 min).

Post-spikes: Post spiked samples were prepared by weighing 5.7 mg of propranolol hydrochloride into 5 mL centrifuge tubes, 5 mL of methanol was then added. The three spiking solutions were used to prepare 6 replicates at each concentration level by adding 10  $\mu\text{L}$  to the methanol to make 5  $\text{ng/mL}$ , 0.5  $\text{ng/mL}$  and 0.05  $\text{ng/mL}$  concentrations. The centrifuge tubes were vortex mixed (1 min).

Matrix blanks: Matrix blanks were prepared by adding 5 mL of methanol to 6 tubes containing 5.7 mg of propranolol hydrochloride. The centrifuge tubes were vortex mixed (1 minute).

Standard solutions: Standard solutions at each test concentration level (5  $\text{ng/mL}$ , 0.5  $\text{ng/mL}$  and 0.05  $\text{ng/mL}$ ) ( $n=6$ ) were prepared in 5 mL centrifuge tubes using 10  $\mu\text{L}$  of the spiking solutions in 5 mL of methanol. The centrifuge tubes were vortex mixed (1 minute).

## Calibration Curve Preparation

### Authentic Standard Calibration Curve

An authentic standard of N-nitroso-propranolol (10  $\text{mg/mL}$ ) in methanol was sequentially diluted to create a calibration curve ranging from 0.005  $\text{ng/mL}$  to 100  $\text{ng/mL}$ .

### Matrix Calibration Curve

Propranolol hydrochloride (21.34 mg) was weighted into a 20 mL glass scintillation vial. A stock solution of 1  $\text{mg/mL}$  in propranolol was made up by dissolving the propranolol hydrochloride in 18.7 mL of methanol. This solution was used as the diluent for the N-nitroso-propranolol matrix calibration curve. An authentic standard of N-nitroso-propranolol was sequentially diluted using the 1  $\text{mg/mL}$  propranolol solution to create a calibration

curve ranging from 0.005 ppm to 100 ppm.

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## Results and Discussion

### Chromatographic Separation

Photodiode array detector (PDA) data was collected simultaneously with the MRM data. The chromatographic resolution of the API, as well as other impurities detected in the UV, from the trace level impurities detected in the MRM data were evaluated based on the retention times ( $t_R$ ) observed. To avoid saturation of the MS the first 6.5 minutes of the chromatographic run was diverted to the waste using the integrated solvent divert valve. The separation between the propranolol API and the N-nitroso-propranolol was optimized on a  $C_8$  stationary phase (Table 1 and Figure 2). Chromatographic resolution of the API from the trace level impurities is important to avoid any potential matrix effects that could occur due to the proximity of the high levels of API present in the samples.

The MRM transitions were tuned using the Intellistart autotune feature present in the MassLynx™ software.

Multiple MRM transitions can be useful for additional specificity if there is increased noise due to the matrix. Two of the optimized MRM transitions are shown in Figure 2, one of the confirmation transitions (289>259) and the quantifier transition (289>72).

| Time (min) | Flow (mL/min) | %A | %B | Curve |
|------------|---------------|----|----|-------|
| 0.00       | 0.50          | 85 | 15 | 6     |
| 0.50       | 0.50          | 85 | 15 | 6     |
| 3.00       | 0.50          | 50 | 50 | 6     |
| 9.00       | 0.50          | 40 | 60 | 6     |
| 10.00      | 0.50          | 5  | 95 | 6     |
| 12.00      | 0.50          | 5  | 95 | 6     |
| 12.10      | 0.50          | 85 | 15 | 1     |

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Table 1. Gradient program.

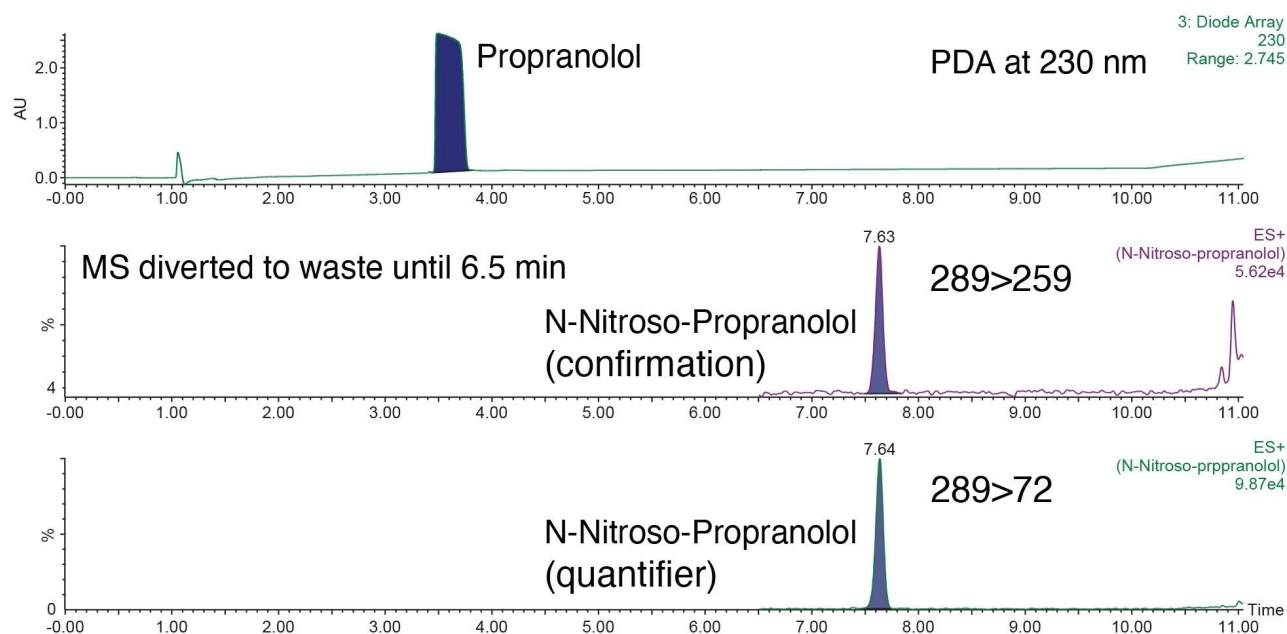


Figure 2. PDA chromatogram at 230 nm (top) resulting from the analysis of propranolol API at 1 mg/mL spiked with N-nitroso-propranolol at 0.1 ppm, 10  $\mu$ L inj. in methanol. Confirmation and quantifier MRM chromatograms shown beneath.

### Separation of N-formylpropranolol and N-nitroso-propranolol

Several API samples were tested during the study. In one sample, the N-formylpropranolol impurity with its structure shown in Figure 1, was detected. The identity of N-formylpropranolol was verified using an authentic standard. N-Formylpropranolol has an  $[M+H]^+$  of  $m/z$  288, N-nitroso-propranolol has an  $[M+H]^+$  1 amu higher at  $m/z$  289. Two of the optimized MRM transitions for N-formylpropranolol, 288>144 and 288>102 are one amu less in both the precursor and the product ion masses when compared to the confirmatory transitions of N-nitroso-propranolol (Table 2). It follows that the  $^{13}C$  isotope of N-formylpropranolol will give rise to a signal in two of the MRM transitions used for N-nitroso-propranolol 289>145 and 289>103 since the  $^{13}C$  will be one amu higher. Figure 3 shows a chromatographic peak at the same  $t_R$  for N-formylpropranolol (7.14 min) in the 289>145 MRM transition for N-nitroso-propranolol. Consequently, to avoid signal overlap of these MRM transitions, chromatographic resolution is recommended. Using the proposed method, it is possible to resolve N-formylpropranolol from N-nitroso-propranolol (Figure 3).



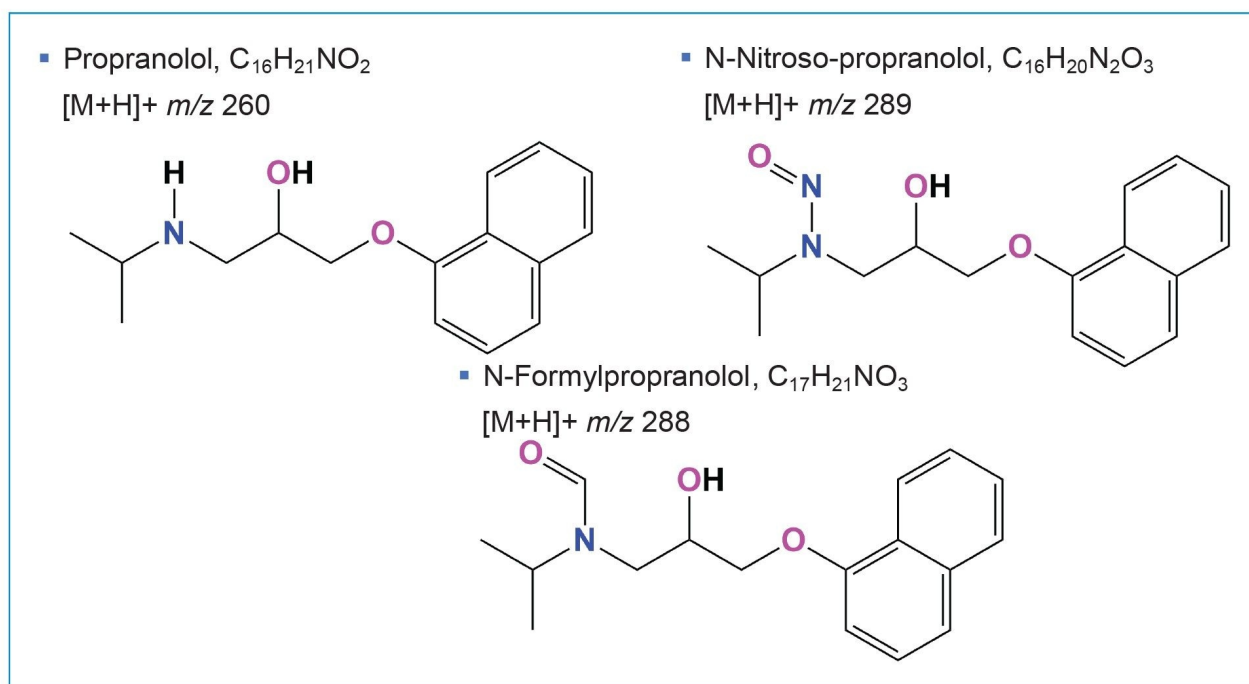


Figure 1. Structures of propranolol, N-nitroso-propranolol and N-formylpropranolol.

| Compound name         | Precursor Ion (m/z) | Product ion (m/z)       | Cone voltage (V) | Collision energy (eV) |
|-----------------------|---------------------|-------------------------|------------------|-----------------------|
| Propranolol           | 260.12              | 72.08 (quantifier)      | 34               | 22                    |
|                       |                     | 74.06 (confirmation 1)  | 34               | 22                    |
|                       |                     | 116.11 (confirmation 2) | 34               | 16                    |
| N-Nitroso-propranolol | 289.15              | 71.98 (quantifier)      | 28               | 12                    |
|                       |                     | 145.00 (confirmation 1) | 28               | 8                     |
|                       |                     | 102.97 (confirmation 2) | 28               | 22                    |
| N-Formyl-propranolol  | 288.12              | 144.04 (quantifier)     | 30               | 10                    |
|                       |                     | 101.90 (confirmation 1) | 30               | 22                    |
|                       |                     | 58.00 (confirmation 2)  | 30               | 36                    |

Table 2. Quantification and confirmatory MRM transitions, cone voltage and collision energy settings used for propranolol, N-nitroso-propranolol and N-formylpropranolol.

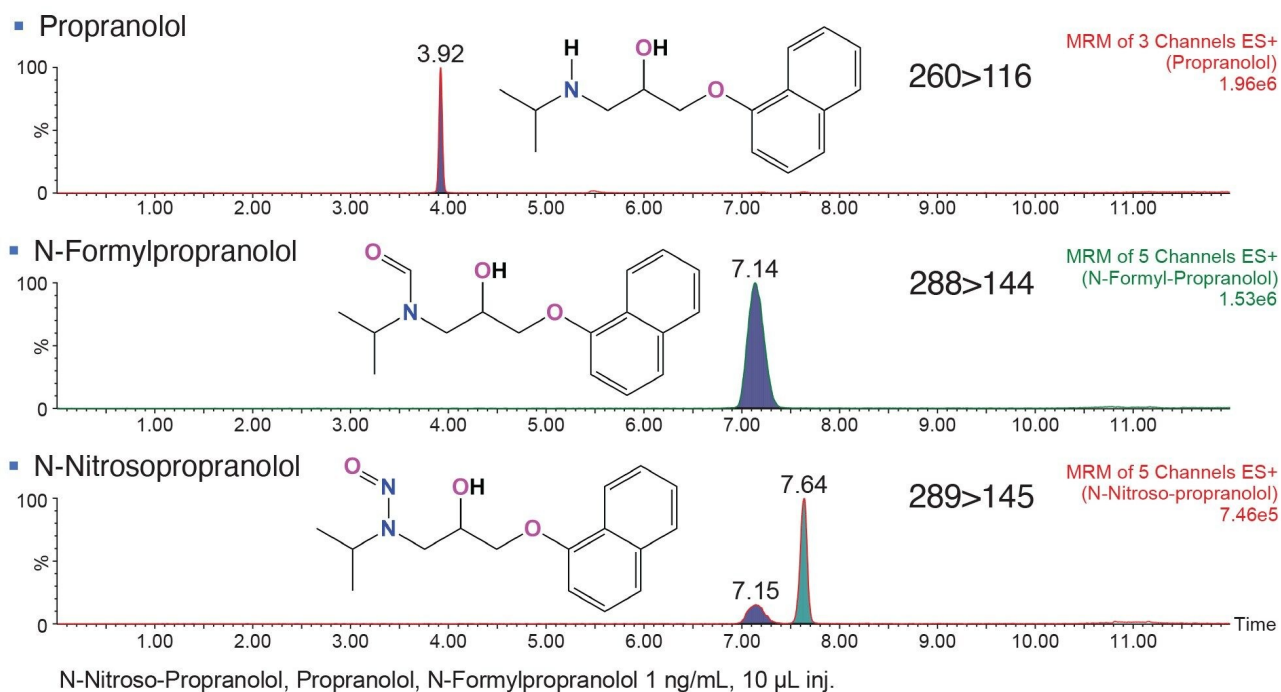


Figure 3. MRM chromatogram resulting from the analysis of an authentic standard mix of propranolol, N-formylpropranolol and N-nitroso-propranolol at 1 ng/mL, 10  $\mu$ L inj. in methanol. A peak at the same  $t_R$  of N-formylpropranolol is visible in the 289>145 MRM transition of N-Nitroso-propranolol.

### Chromatographic Peak Shape

An injection solvent containing high levels of organic can lead to deleterious solvent effects resulting in degradation of the chromatographic peak shape. The injection solution of 100% methanol used for this assay leads to peak shape distortion. However, the peak shape can be dramatically improved by adding some pre-column volume to the flow path. An extension loop (50  $\mu$ L volume, p/n: 700012825) was added to port 6 of the Sample Manager valve allowing the preservation of the impurity peak shape (Figure 4).

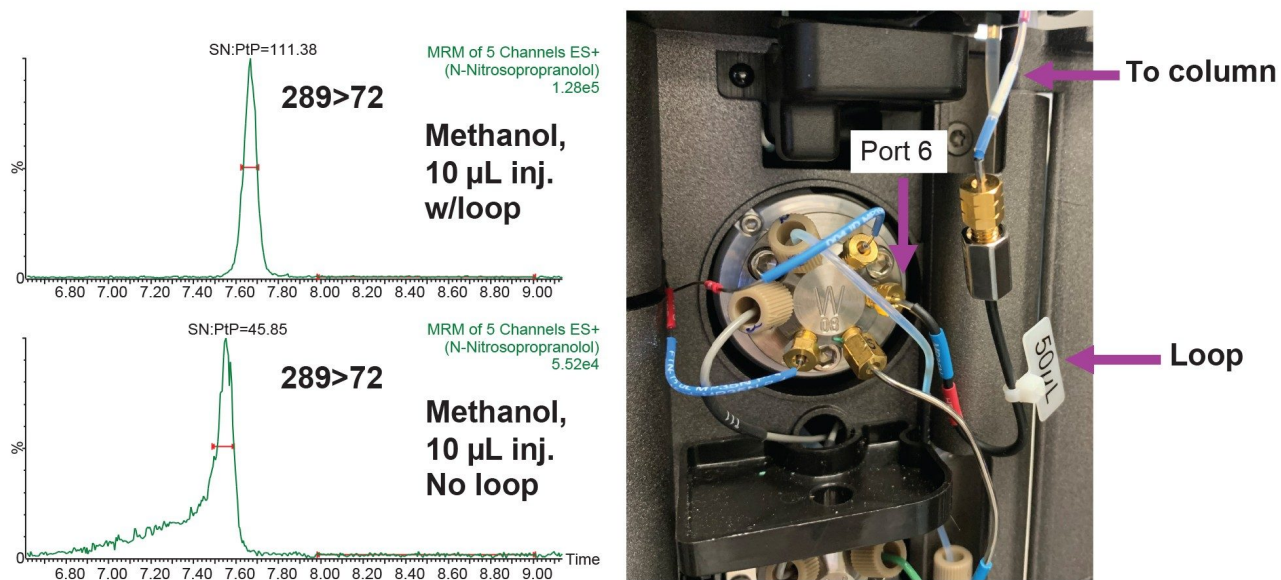


Figure 4. MRM chromatograms showing the comparison of peak shape when a 50 mL extension loop is included in the flow path (top) and excluded from the flow path (beneath). Propranolol at 1 mg/mL containing N-nitrosopropranolol at 0.1 ppm, 10 µL inj. in methanol.

### Limit of Detection (LOD), Limit of Quantitation (LOQ) and Linear Dynamic Range

The quantitative limits of the assay were initially established using authentic standards of N-nitroso-propranolol. The LOD and LOQ based on 3:1 and 10:1 signal-to-noise (S/N) respectively, are shown in figure 5. The LOD and LOQ for an authentic standard of N-nitroso-propranolol were found to be 0.005 ng/mL and 0.01 ng/mL respectively.

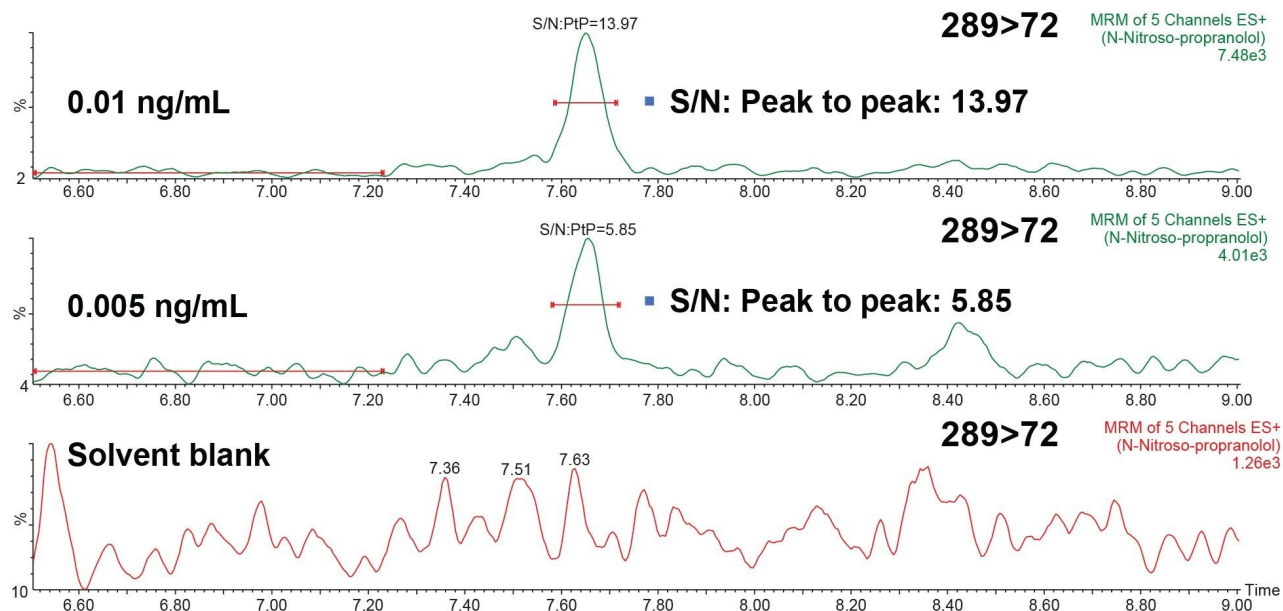


Figure 5. The S/N was measured using the Peak-to-peak (PtP) algorithm at the LOD (0.005 ng/mL) and LOQ (0.01 ng/mL) in an authentic standard of N-nitroso-propranolol, 10  $\mu$ L inj. in methanol.

Establishing the LOD and LOQ of N-nitroso-propranolol in the propranolol API was complicated by the presence of endogenous levels of the impurity in each of the propranolol API samples tested. The lower levels of the calibration curve made up in 1 mg/mL propranolol are shown in Figure 6.

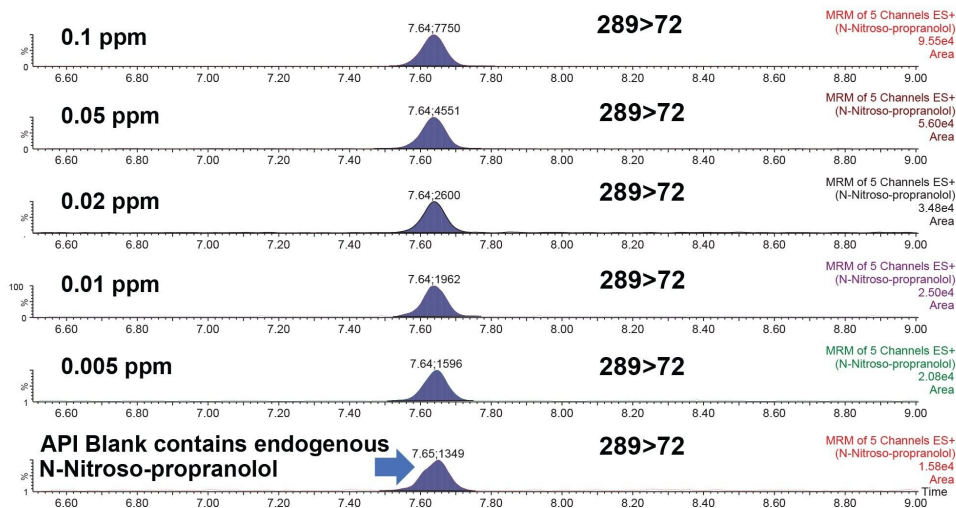


Figure 6. MRM chromatograms from the analysis of the lower calibration levels of N-nitroso-propranolol in 1 mg/mL propranolol. The response of the peak in the matrix blank (unspiked API).

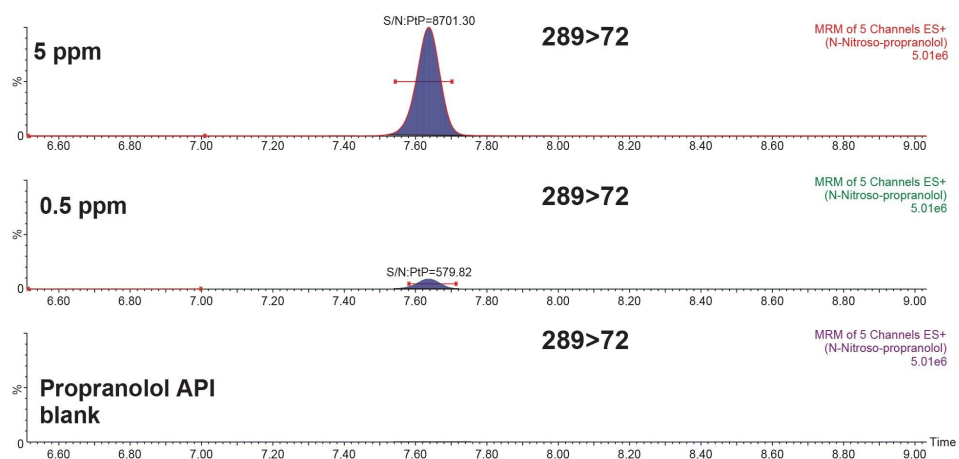
Table 3 summarizes the average peak area responses obtained for 6 replicate injections of the API samples (1 mg/mL propranolol) spiked at 0.005 ppm and 0.01 ppm with N-nitroso-propranolol. The average peak area responses for authentic standards of N-nitroso-propranolol at the LOD of 0.005 ng/mL and LOQ 0.01 ng/mL are also shown. The responses for the N-nitroso-propranolol in the spiked API samples were corrected for the endogenous level of impurity using the average peak response of the N-nitroso-propranolol present in the API (n=6). The corrected peak area response of the spiked samples was then compared with the response of the authentic standards. The corrected responses at the LOD and LOQ in the API are within 10% of the responses observed in an authentic standard at the same concentration levels.

| Concentration (ppm) | API sample average response (n=6); SD | Corrected API sample average response- Average matrix response | Standard average response (n=6); SD | % Difference |
|---------------------|---------------------------------------|--|-------------------------------------|--------------|
| 0.005               | 1594.16 (104)                         | 264.67   | 253.33 (29)                         | 104.47       |
| 0.01                | 1937.33 (57)                          | 607.83   | 555.5 (55)                          | 109.42       |

SD = standard deviation  
Average endogenous response and SD: 1329.50 (31)

*Table 3. Comparison of the peak area responses for the API samples spiked with N-nitroso-propranolol, the corrected responses of the spiked samples, and the response of the authentic standard samples at the LOD (0.005 ppm) and LOQ (0.01 ppm).*

The threshold level of N-nitroso-propranolol is 4.69 ppm, 10% of the threshold level is 0.469 ppm. The response obtained for N-nitroso-propranolol spiked at 5 ppm and 0.5 ppm in 1 mg/mL of propranolol, and the API matrix blank are shown in Figure 7 along with the S/N calculated using the PtP algorithm, illustrating the ability of the method to exceed the sensitivity required at the regulatory threshold levels.



*Figure 7. MRM chromatograms from the analysis of N-nitroso-propranolol spiked at 5 ppm and 0.5 ppm in 1 mg/mL propranolol, the API blank and the PtP S/N is also displayed.*

An authentic standard of N-nitroso-propranolol was used to determine the linear dynamic range before

evaluating the N-nitroso-propranolol in the presence of the API. The curve, when injected in triplicate was linear from 0.005-100 ng/mL with an  $R^2$  of 0.998 and <10% concentration deviations across the range (data not shown).

The calibration curve for the N-nitroso-propranolol in 1 mg/mL of the API is shown in Figure 8. The  $R^2$  was 0.998 and the concentration deviations were less than 15% over the range of 0.01 to 100 ng/mL (4 orders of magnitude) using 1/X weighting.

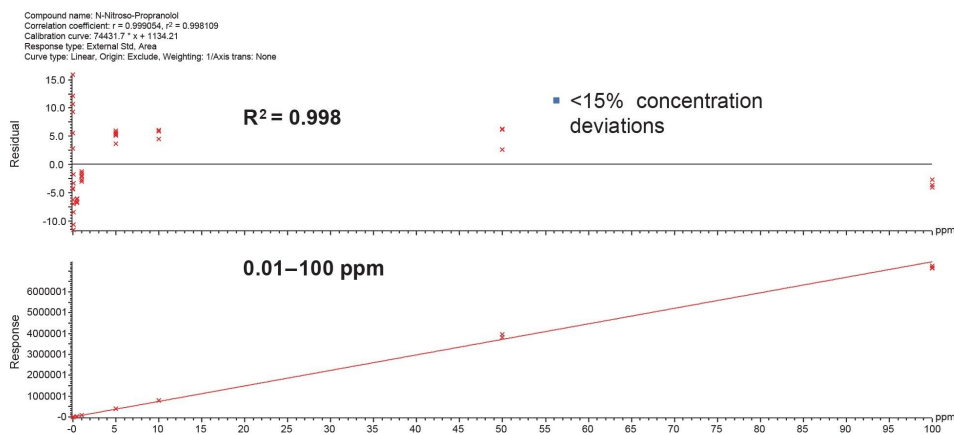


Figure 8. Linear range for N-nitroso-propranolol 0.01-100 ng/mL in 1 mg/mL of propranolol, and residuals <15% across the calibration range tested, injected in triplicate.

## Recovery, Precision and Accuracy

The recovery experiments were performed at 0.05 ppm, 0.5 ppm and 5 ppm (n=6). The results are summarized in Table 4. Due to the presence of the endogenous level of N-nitroso-propranolol in the API, the recovery calculations were based on the corrected responses for the pre-spiked API samples using the average response for the N-nitroso-propranolol peak present in the API blank (n=6). The average response for the peak in the API was subtracted from each of the responses in the pre-spiked samples. The recovery was calculated using the following formula:

$$\% \text{ Recovery} = (\text{Response Pre-spike corrected} / \text{Standard Response}) * 100\%$$

The calculated recoveries were between 89.3-104.6%. The %RSD for the recoveries at each concentration level

were less than 5%.

| Concentration (ppm) | Average (n=6) | Standard deviation | %RSD | Range %    |
|---------------------|---------------|--------------------|------|------------|
| 0.05                | 98.50         | 4.10               | 4.16 | 92.6–104.6 |
| 0.5                 | 96.873        | 0.98               | 1.01 | 96.0–98.5  |
| 5                   | 92.0          | 3.15               | 3.43 | 89.3–97.8  |

Table 4. Summary of the method recovery at 0.05 ppm, 0.5 ppm and 5 ppm in 1 mg/mL API (n=6).

Method precision and accuracy was evaluated at 0.5 ppm and 5 ppm (Table 5). The precision of the assay was measured by the %RSD of 6 replicate measurements made at 0.5 ppm and 5 ppm. The %RSD were less than 2% for the levels tested. The accuracy was measured as the percentage deviation from the nominal value and was accurate to within 10%.

| Concentration (ppm) | Average (n=6); SD | %RSD | Accuracy% |
|---------------------|-------------------|------|-----------|
| 0.500               | 0.454 (0.0046)    | 1.01 | 91        |
| 5.000               | 5.51 (0.07)       | 1.31 | 110       |

SD = standard deviation

■ Measured in 1 mg/mL Propranolol API

Table 5. Summary of the precision and accuracy at 0.5 ppm and 5 ppm.

Matrix effects were assessed at 0.05 ppm, 0.5 ppm and 5 ppm by comparing the response obtained in neat standards to the corrected response for the post spiked samples. The matrix effects were found to be <10% for all levels tested.



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## Conclusion

In the presented study, a UPLC-MS/MS method was developed for the quantitation of N-nitroso-propranolol in drug substance. The method can perform high sensitivity quantitative analysis, with good precision, and accuracy within the required recovery range to meet regulatory guidelines. In addition, the impurity, N-formylpropranolol can be chromatographically resolved from N-nitroso-propranolol avoiding the overlap of the signals from the <sup>13</sup>C isotopes in the N-nitroso-propranolol MRM transitions (289>145 and 289>103). The chromatographic resolution is important to retain specificity of the assay thus reducing the risk of misreporting impurity levels.

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