

Note d'application

High Sensitivity Quantitation of Nitrosamine Genotoxic Impurities: LC-MS Analysis of Ranitidine Drug Product using the Waters ACQUITY UPLC I-Class/Xevo TQ-XS Tandem Quadrupole Mass Spectrometer

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Abstract

This application note presented herein, provides practical considerations for optimization of LC-MS conditions to achieve sensitive and robust simultaneous quantification of several nitrosamine GTIs (NDMA, NDEA, NEIPA, NDIPA, NDBA, and NMBA).

Benefits

- A simple and reproducible method for detection and quantification of multiple nitrosamine impurities
- Use of the UPLC HSS T3 Column for excellent reversed-phase chromatographic retentivity of NDMA, and resolution from the drug product ranitidine
- Highly sensitive and accurate quantification using the ACQUITY UPLC I-Class PLUS for separation and Xevo TQ-XS Mass Spectrometer for nitrosamine detection
- Nitrosamine quantification achieving LLOQs of 0.025–0.1 ng/mL

Introduction

Ranitidine is a histamine-2 blocker, which decreases the amount of acid created by the stomach and is approved for multiple indications, including treatment and prevention of stomach and intestinal ulcers, as well as treatment of gastroesophageal reflux disease.¹ Ranitidine is manufactured by many pharmaceutical and generic companies and is available over the counter (OTC) and by prescription. In 2019, reports appeared that the N-nitrosamine impurity, N-nitrosodimethylamine (NDMA) was found to be present in ranitidine drug products and resulted in recalls of this product.^{2,3}

N-nitrosamines, as a class, are known environmental contaminants with suspected carcinogenic/genotoxic effects in animals and humans.^{4,5} In response to public concern, regulatory agencies have issued guidance for allowable limits of these genotoxic impurities (GTIs) with an acceptable daily intake limit of 96 ng/day (0.32 ppm) for NDMA in ranitidine and a proposed limit in the future of 0.03 ppm. Information on how to assess and control these impurities can be found in the ICH M7 (R1) guideline.⁷

Due to the regulatory guidance's low safety threshold levels for these compounds, there exists a strong need for LC-MS methods that can accurately quantify them at low ppm levels. Developing such methods is challenging due to the chemical diversity of nitrosamines, poor chromatographic retention, MS ionization, and fragmentation, often limiting sensitivity and selectivity. This work presented herein, provides practical considerations for optimization of LC-MS conditions to achieve sensitive and robust simultaneous quantification of several nitrosamine GTIs (NDMA, NDEA, NEIPA, NDIPA, NDBA, and NMBA). A list of these impurities, including their chemical information, is shown in Table 1. The developed analytical method employs ultra performance liquid chromatography (UPLC) and tandem quadrupole MS-MS detection. Using the low dispersion ACQUITY UPLC I-Class PLUS and reversed-phase (UPLC-RP) separation with a sub-2- μ m C₁₈ column designed specifically for retention and separation of polar compounds coupled to a high sensitivity tandem quadrupole MS, lower limits of quantification (LLOQ) between 0.025–0.1 ng/mL (<1 pg on column) in ranitidine drug substance and product were achieved. This method was used to analyze a ranitidine drug product tablet, achieving an LLOQ of 0.1 ng/mL (0.0025 ppm based on a 30 mg/mL dose) and determining the concentration of NDMA in the tablet to be 29.0 ng/mL, or 1 ppm relative to the ranitidine API.

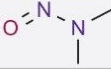
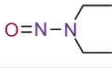



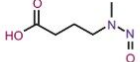
Impurity	Common name	Empirical formula	Chemical structure
NDMA	N-nitrosodimethylamine	C ₂ H ₆ N ₂ O MM: 74.05	
NDEA	N-nitrosodiethylamine	C ₄ H ₁₀ N ₂ O MM: 102.8	
NEIPA	N-nitrosoethyl isopropylamine	C ₅ H ₁₂ N ₂ O MM: 116.09	
NDIPA	N-nitrosodiisopropylamine	C ₆ H ₁₄ N ₂ O MM: 130.11	
NDBA	N-nitrosodibutylamine	C ₈ H ₁₈ N ₂ O MM: 158.14	
NMBA	N-nitroso-N-methyl-4-aminobutyric acid	C ₅ H ₁₀ N ₂ O ₃ MM: 146.07	

Table 1. List of nitrosamine impurities with common names and chemical information.

Experimental

Preparation of samples and calibration standards

NDMA, NDEA, and NMBA were obtained from Sigma-Aldrich (St. Louis, MO, USA). NDBA, NEIPA, and NDIPA were obtained from Toronto Research Chemicals (Ontario, Canada). Individual stock solutions (5.0 mg/mL) of the nitrosamines were prepared in methanol. Using the 5 mg/mL individual nitrosamines stock solutions, a combined working stock solution (250 µg/mL) of the 6 nitrosamines was prepared in methanol. Stock solutions containing 30 mg/mL ranitidine drug substance (DS) or drug product (DP) were prepared in water. The age, expiry, and storage conditions of the ranitidine drug tablet were unknown. Calibration curve standards (0.025–100 ng/mL) were prepared by spiking the working solution of the nitrosamine impurities into the prepared ranitidine DS and DP solutions. The prepared samples (30 µL) were then analyzed using the described LC-MS method in a previously published application (Application Note 720006751EN) using the ACQUITY UPLC I-Class PLUS (A) and Xevo TQ-XS Tandem Quadrupole Mass Spectrometer.

Results and Discussion

Mass Spectrometry

Detection and quantification of the nitrosamine impurities was performed using atmospheric pressure chemical ionization (APCI) MS operating in the positive ion mode using the Xevo TQ-XS Tandem Quadrupole Mass Spectrometer. A previous proof of concept application (Application Note 720006751EN) for MS nitrosamine impurity quantification provides detailed MS conditions, including the nitrosamine impurity MRM transitions. The multiple reaction monitoring (MRM) transitions and conditions chosen for nitrosamine analysis were optimized using MassLynx IntelliStart Software and confirmed with manual infusion. Representative MS spectra of the MH⁺ precursors for the 6 nitrosamines (10 µg/mL), using a combined infusion, is highlighted in Figure 1a, while an example of product ion spectra generated for NDMA, using optimal collision energies (CEs) for the 43.1 and 58.1 NDMA fragments is demonstrated in Figure 1b.

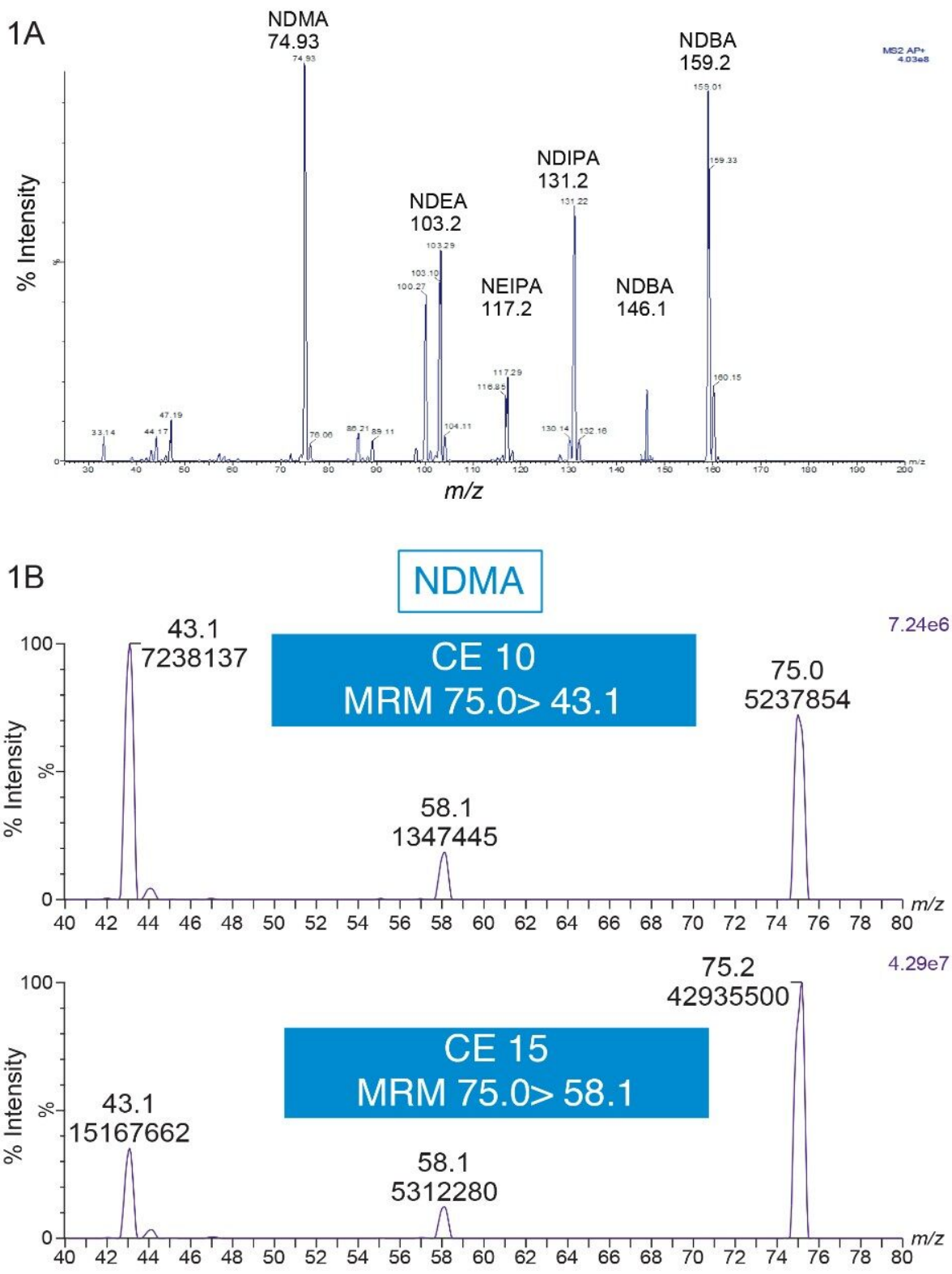


Figure 1. Representative MS precursor MH^+ spectra for the nitrosamine impurities (A) and representative

product ion spectra for the NDMA nitrosamine (B), identifying the primary fragments of 43.1 and 58.1 with optimal collision energies of 10 and 15, respectively.

During MS method development, use of an APCI probe over the more common electrospray ionization (ESI) probe provided 10X better sensitivity. This is illustrated in Figure 2 for the NDMA (A) and NDEA (B) nitrosamines. APCI is a soft ionization method well-suited for polar and relatively less polar thermally stable compounds with small molecular weights. Additionally, use of soft transmission/ionization mode within the experimental method further minimized in-source fragmentation, aiding in improved MS signal performance (peak area/height) for NEIPA, NDIPA, and NMBA (data not shown).

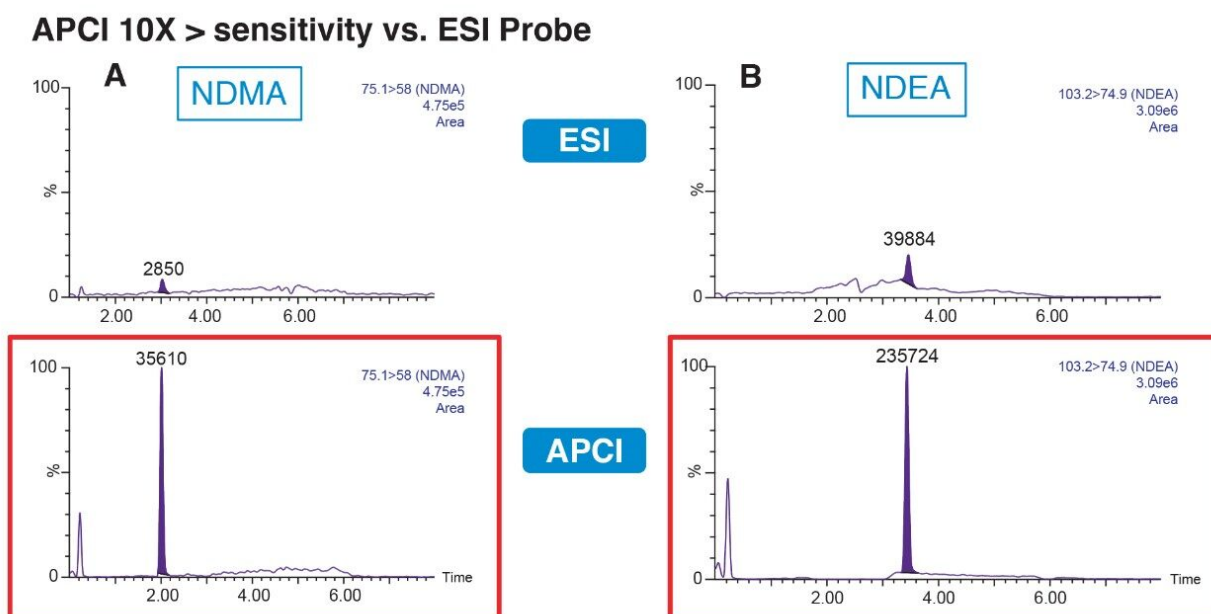


Figure 2. Comparison of APCI and ESI MS performance for the nitrosamines, NDMA (A) and NDEA (B). Use of the IonSABRE APCI probe provided a 10X improvement in analyte response vs. the ESI probe.

An additional improvement in MS signal (peak area/height) for the nitrosamines was achieved by decreasing probe and source temperatures (250/130 °C). This improvement is highlighted in Figure 3. Use of short dwell times (<30 msec.) for each MRM transition and fast scan time of the Xevo TQ-XS Mass Spectrometry system allowed for the simultaneous acquisition of all compounds with ≥ 10 data points for each nitrosamine. Final MS conditions are provided in Figure 4.

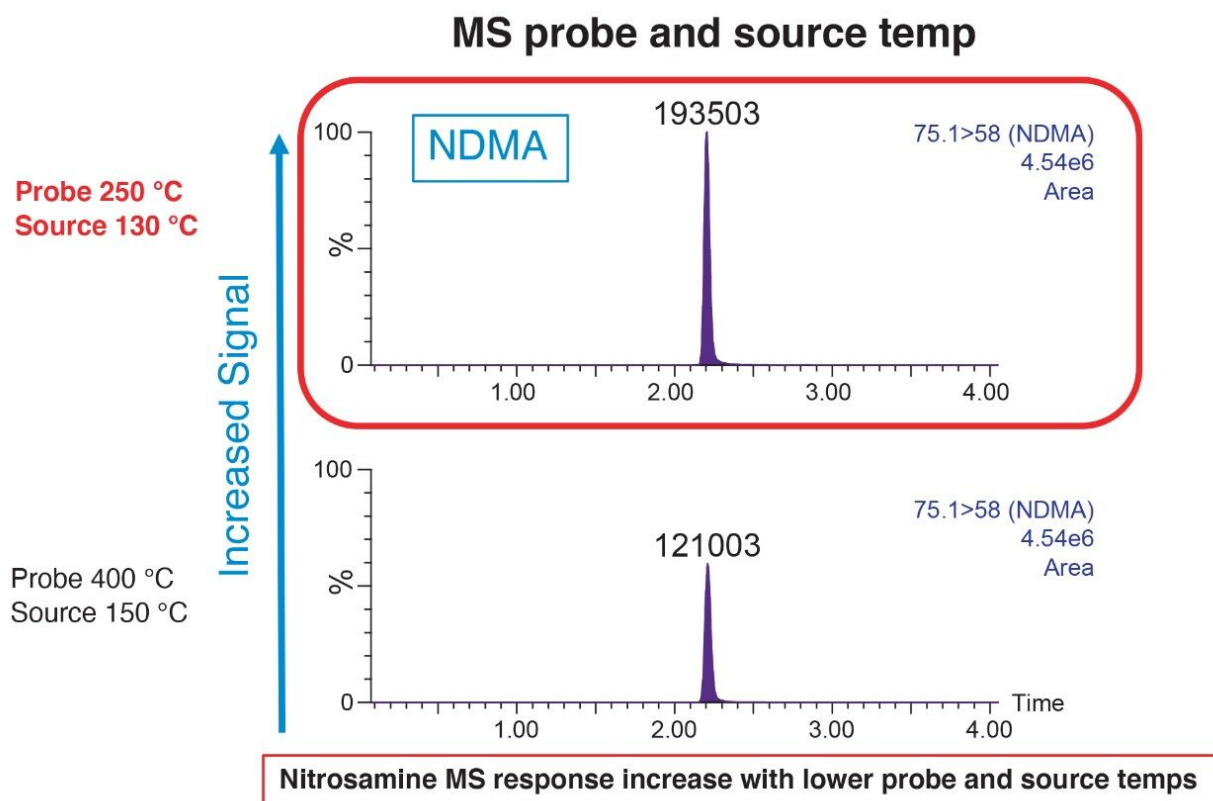


Figure 3. Demonstration of improved nitrosamine impurity analyte MS response with probe and source temperatures.

MS system	Xevo TQ-XS Tandem Quadrupole
Source	APCI +
Corona	1.3 μ A
Nebuliser	3.5 bar
APCI probe temp.	250 $^{\circ}$ C
Desolvation flow	1000 L/Hr
Cone gas flow	150 L/Hr
Cone voltage	30 V
Source temp.	130 $^{\circ}$ C
Data management:	Instrument control software: MassLynx (v4.2) Quantification software: TargetLynx

Figure 4. Xevo TQ-XS Mass Spectrometer final optimized instrument conditions detection, and quantification of nitrosamine impurities from ranitidine drug substance and product.

UPLC Chromatography

During method development, both reversedphase (RP) and reversed-phase/anion exchange columns (RP-AX) were evaluated for overall chromatographic performance (e.g., assessment of retention, peak shape, influence of diluent composition, area counts, and signal to noise). While the ACQUITY CSH Phenyl Hexyl and Atlantis PREMIER BEH C₁₈ AX columns provided adequate retention for the six nitrosamines and ranitidine API during method development, best overall chromatographic performance for the most polar nitrosamine, NDMA, and ranitidine was achieved using the ACQUITY HSS T3 column (Figure 5). The HSS T3 column not only provided significantly better retention for NDMA and ranitidine, but also facilitated resolution from the closely eluting NMBA nitrosamine impurity.

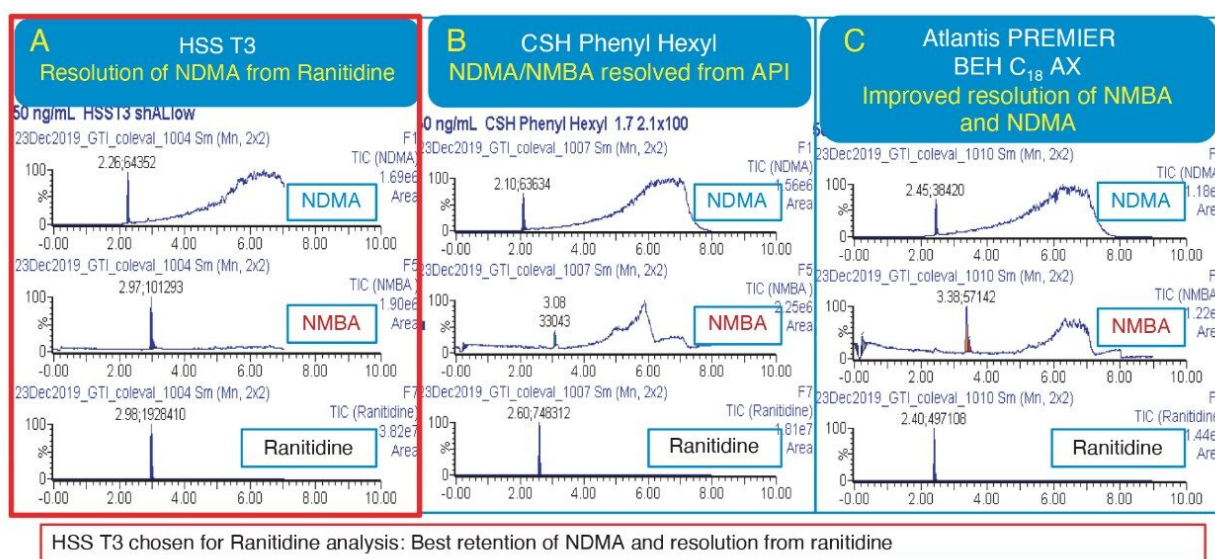


Figure 5. Comparison of chromatographic performance for the NDMA and NMBA nitrosamine impurities and ranitidine API in water: methanol neat solution (80:20) using the ACQUITY UPLC HSS T3 (A), CSH Phenyl Hexyl (B), and Atlantis PREMIER BEH C₁₈ AX (C), 2.1 mm × 100 mm columns. The HSS T3 provided best retention for NDMA and facilitated resolution from ranitidine and the closely eluting NMBA nitrosamine impurity.

Full UPLC chromatographic separation for all nitrosamines and ranitidine is illustrated in application note 720006751EN. Separation of the API from the impurities is critical, as it allows use of the divert valve to send the API to waste during analysis, minimizing impact of large quantities of the API (mg/mL) from interfering in the trace analysis (pg/mL) of the nitrosamine impurities. Use of ammonium formate buffer improved analyte performance (peak area/height) and minimized baseline noise, further improving levels of detection of the nitrosamine impurities in this assay (data not shown). While one of the benefits of using a low dispersion LC system and sub-2- μ m chemistry is use of high flow rates for fast analysis, in this assay it was determined that a lower flow rate of 0.35 mL/min further improved analyte intensity (peak area/intensity).

Quantitative Performance

The quantitative performance using the optimized LC-MS method was excellent, achieving LLOQs between 0.025–0.1 ng/mL for the nitrosamine impurities in drug substance (DS) with S/N ratios ≥ 10 . Relative to load on column with a 30 μ L injection, this would be equivalent to 0.75–3 pg/mL for a 0.1 ng/mL LLOQ. Calibration curves were linear ($R^2 \geq 0.99$) with accuracies between 85–115% for all points on the curve (Table 2), meeting recommended method validation guidelines for LC-MS quantitative analysis. Representative

chromatographic performance of the 0.025, 0.05, and 0.1 ng/mL over-spiked DS samples as compared to the blank is illustrated in Figure 6. Relative to the ranitidine API concentration (30 mg/mL), these LLOQs (<0.003 ppm) exceed the recommended regulatory limits of nitrosamine impurity detection of 0.3 ppm.

Nitrosamine quantification performance (neat solution)				
Nitrosamine	Std curve range (ng/mL)	Weighting	Linear fit (R ²)	MRM transition
NDMA	0.1-100	1/x	0.99	75.1>58.0 75.1>43.1
NDEA				103.2>74.9 103.2>46.9
NDBA				159.2>103.2 159.2>57.1
NMBA				147.1>117.1 147.1>44
NEIPA				117.2>74.9 117.2>43.1
NDIPA				131.2>89.1 131.2>47.1

Table 2. Calibration curve performance of the nitrosamine impurities spiked in a neat solution of water:methanol (80:20) using a 30 µL injection of prepared sample.

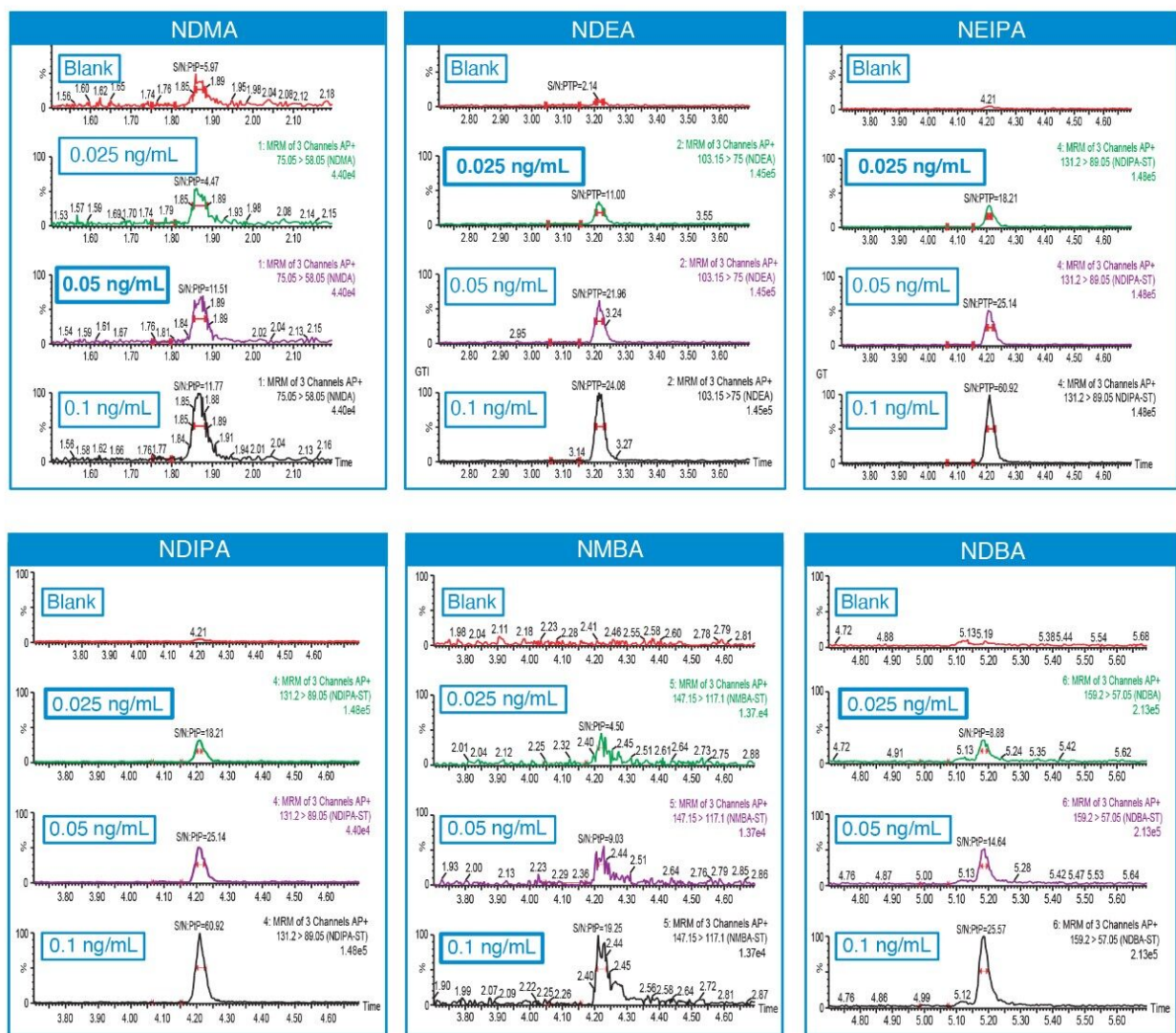


Figure 6. Representative chromatographic performance of the nitrosamine impurities spiked in a neat solution of water:methanol (80:20) at concentrations of 0.025, 0.05, and 0.1 ng/mL.

Analysis of the nitrosamine impurities in drug product (DP) also resulted in excellent quantitative performance with linear dynamic range of the calibration curves from 0.1–100 ng/mL. Representative chromatograms for NDMA (A), NDEA (B), NDBA (C), and NDIPA (D), over-spiked in drug product (0.5 ng/mL) as compared to the blank DP sample are illustrated in Figure 7, while the representative calibration curves are highlighted in Figure 8. It is important to highlight the use of multiple MRMs for each nitrosamine impurity, to ensure adequate sensitivity and selectivity. During MS optimization, the 75.1>58.1 MRM fragment of NDMA provided the best overall peak intensity and reduced baseline. However, during analysis of ranitidine DP and DS over-spiked with the nitrosamine impurities, it was found that the NDMA MRM

75.1>43.1 transition was more intense than the 75.1>58.1 MRM transition. This is illustrated in Figure 9 for ranitidine DP (A) and DS (B).

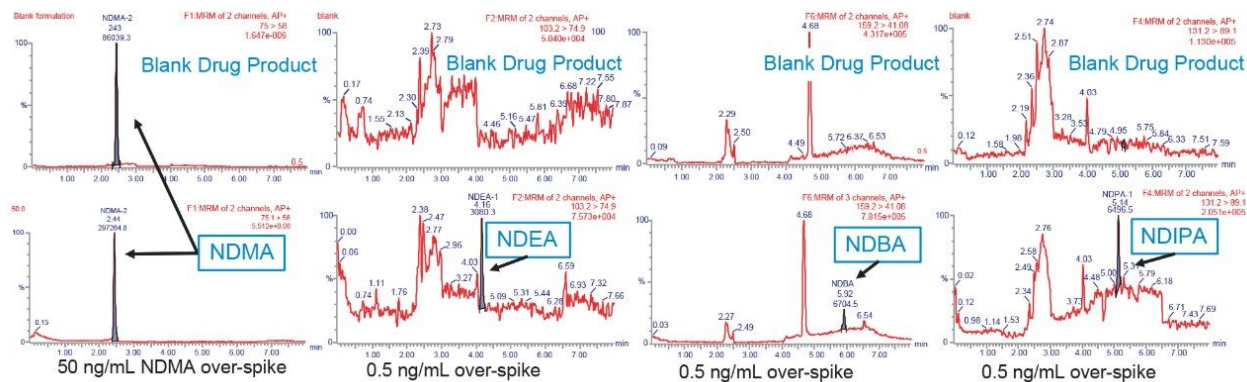


Figure 7. Representative chromatographic performance of prepared ranitidine drug product samples, comparing blank to a 0.5 ng/mL nitrosamine impurity over-spike sample for NDMA, NDEA, NDBA, and NDIPA.

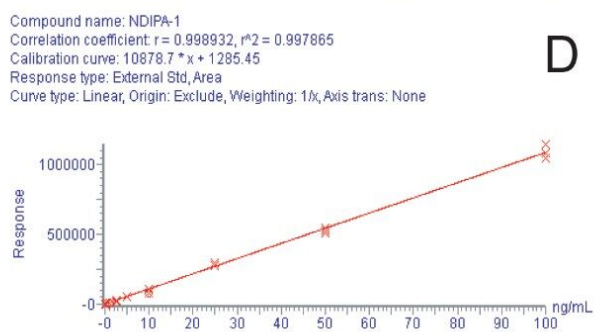
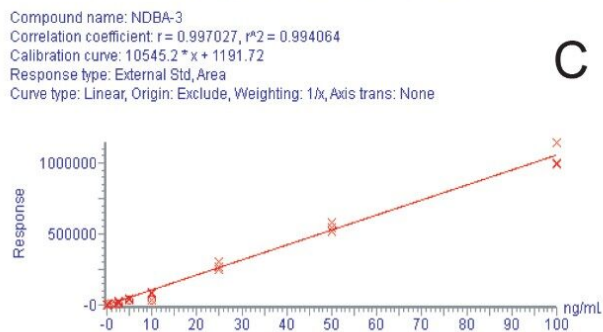
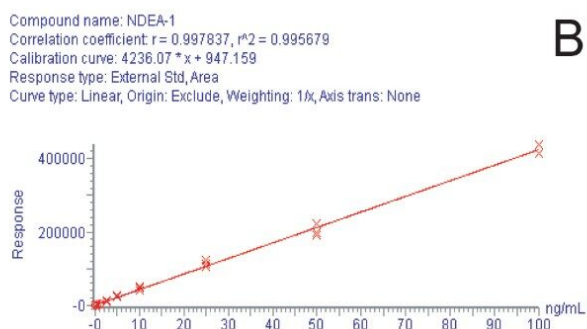
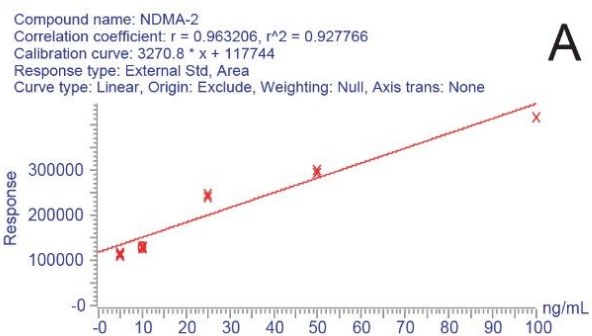
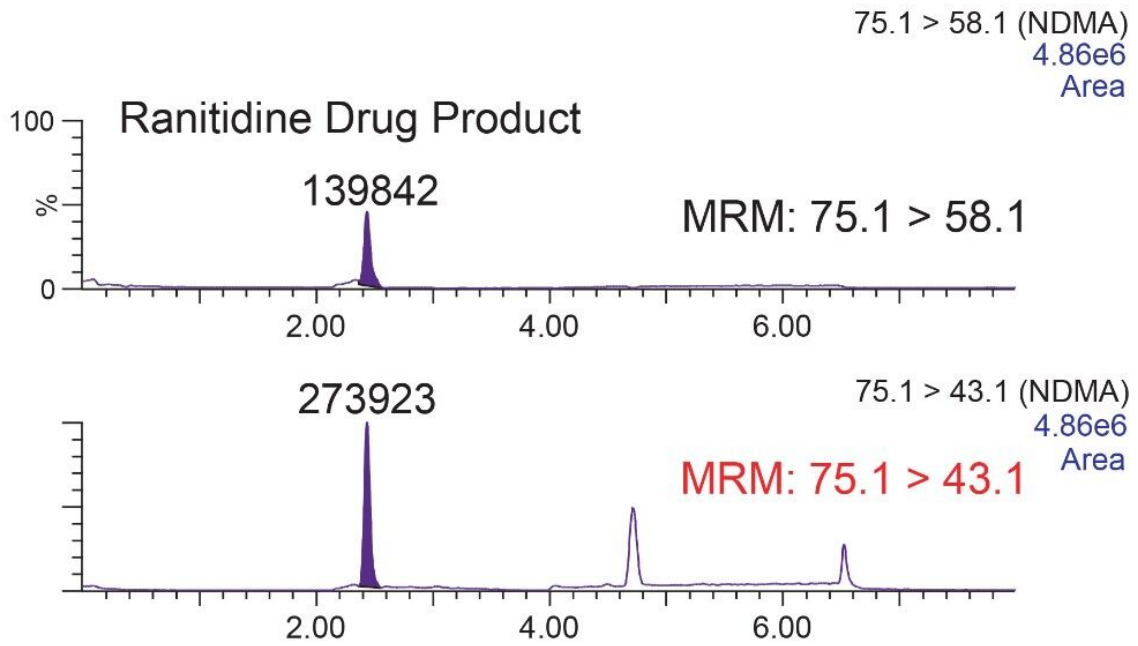


Figure 8. Representative ranitidine drug product calibration curves (0.1–100 ng/mL) with linearity ≥ 0.99 for the NDMA (A), NDEA (B), NDMA (C), and NDIPA (D) nitrosamine impurities. Note: Due to endogenous NDMA levels found in drug product, the NDMA intercept does not pass through zero.

NDMA

A



B

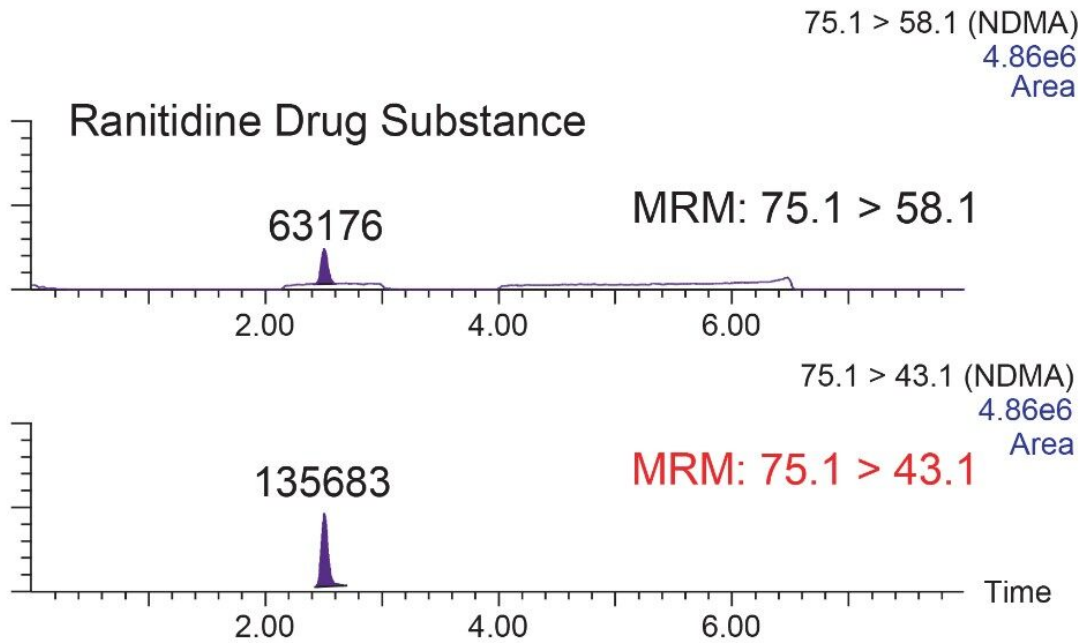


Figure 9. Chromatography illustration highlighting better MS sensitivity of the NDMA nitrosamine in ranitidine drug product (A) and drug substance (B) using the 75.1 > 43.1 MRM transition, shown by increased peak area.

Due to the detection of a large NDMA impurity peak for the prepared ranitidine drug product with unknown age, expiry, and storage conditions, highlighted in Figure 7, the analysis was repeated with re-prepared DP samples. For the repeated assay, the gradient was slowed to 0.3 mL/min and the divert valve was not employed. Figure 10 shows confirmation of a large NDMA peak in DP, using both MRM transitions, which is well separated from ranitidine (Panel A). Peak area of both MRM transitions increases with NDMA over-spike of 10 ng/mL (Panel B). Green dashed lines indicate where the divert valve would be used to switch to waste during normal analysis, shuttling ranitidine API to waste.

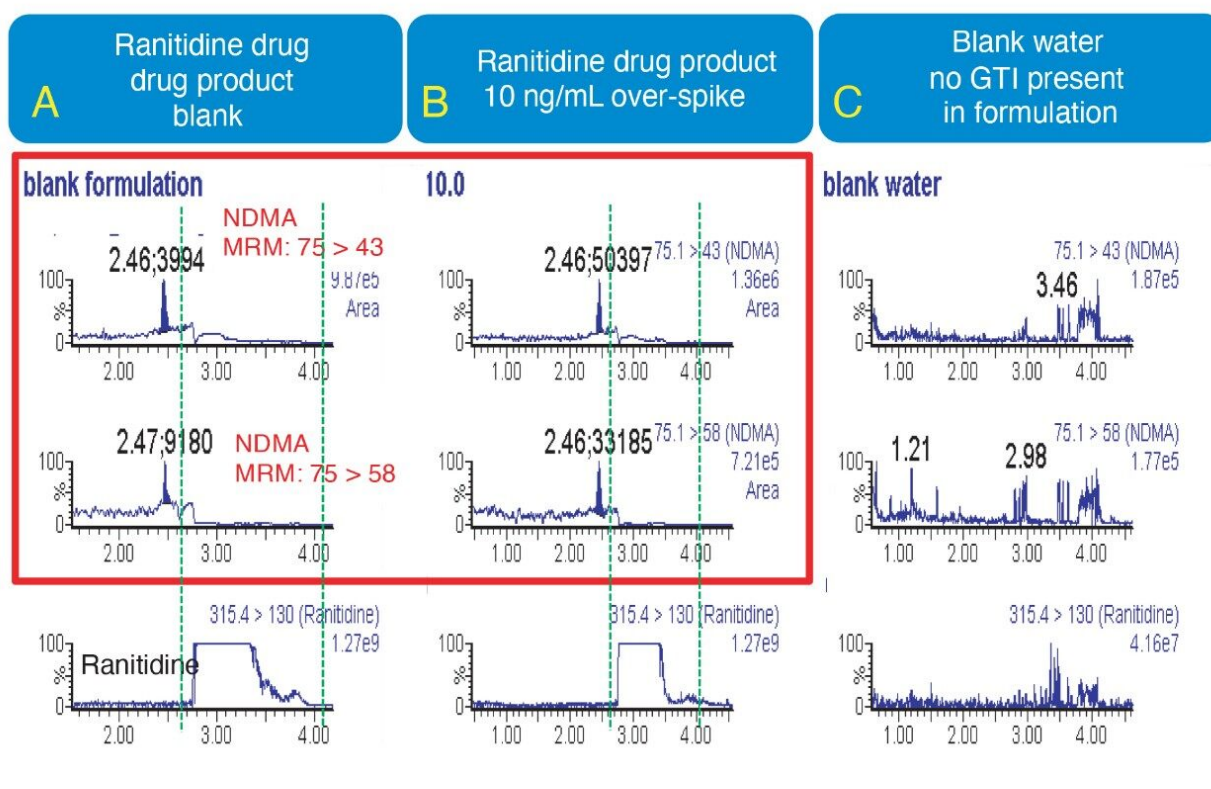


Figure 10. Confirmation of endogenous NDMA nitrosamine impurity (2 MRM transitions) in ranitidine DP (A), increase in NDMA peak response with 10 ng/mL NDMA over-spike in DP (B), and absence of the NDMA peak in blank neat solutions before and after injection of DP samples (C). Green dashed line indicates time divert valve switched to shuttle ranitidine API to waste during analysis.

Finally, there was no detection of the NDMA GTI in blank water, which was injected before and after the blank, un-spiked, and DP samples (Panel C). This confirmed that the NDMA was real and not a result of contamination from other samples or carry over due to the LC-MS method.

Due to the presence of endogenous NDMA in the DP sample, the standard addition method was used to

determine NDMA concentration. Using linear least squares analysis, the slope (3270.8), and intercept (117744) of the calibration line were used to estimate NDMA levels. Performing this regression analysis, NDMA levels in DP sample were estimated to be 36 ng/mL (>1 ppm) and was confirmed with both MRM transitions. Following NDMA level estimation, all calibration points were corrected, by adding the estimated 36 ng/mL to each spiked NDMA impurity concentration and a corrected calibration curve was regenerated. The dynamic range of the corrected calibration curve was 1–100 ng/mL ($R^2 \geq 0.99$ using 1/x weighting) with recoveries between 85–115%. This performance is highlighted in Table 3. Mean calculated NDMA concentration in the DP samples (N=4) was determined to be 28.18 ng/mL (~1 ppm), as shown in Table 4.

Corrected standard curve performance of NDMA in DP with recoveries between 85–115%

Name	Sample Text	Vial	Type	Std. C...	Area	Response	S/N	ng/mL	%Rec
18	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1015	0.25	1:F,9		3.17e4	31700	168.607	11.01	
19	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1016	0.5	1:F,8		1.08e5	108000	225.363	20.36	
20	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1017	0.5	1:F,8		7.61e4	76100	326.839	16.47	
21	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1018	1.0	1:F,7	Analyte	36.000	1.07e5	107000	345.026	20.31
22	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1019	1.0	1:F,7	Standard	36.000	2.34e5	234000	663.546	35.89
23	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1020	1.0	1:F,7	Standard	36.000	2.24e5	224000	381.029	34.72
24	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1021	2.5	1:F,6	Standard	37.500	2.49e5	249000	500.458	37.69
25	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1022	2.5	1:F,6	Standard	37.500	2.46e5	246000	616.546	37.33
26	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1023	5.0	1:F,5	Standard	41.000	2.66e5	266000	764.654	39.79
27	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1024	5.0	1:F,5	Standard	41.000	2.68e5	268000	698.564	40.06
28	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1025	5.0	1:F,5	Standard	41.000	2.73e5	273000	342.203	40.63
29	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1026	10.0	1:F,4	Standard	46.000	3.04e5	304000	1031.6...	44.50
30	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1027	10.0	1:F,4	Standard	46.000	3.05e5	305000	917.715	44.65
31	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1028	10.0	1:F,4	Standard	46.000	3.08e5	308000	999.476	44.93
32	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1029	25.0	1:E,3	Standard	61.000	4.93e5	493000	2650.8...	67.76
33	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1030	25.0	1:E,3	Standard	61.000	4.85e5	485000	1976.1...	66.81
34	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1031	50.0	1:E,2	Standard	86.000	6.57e5	657000	2071.5...	87.87
35	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1032	50.0	1:E,2	Standard	86.000	6.51e5	651000	2624.0...	87.15
36	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1033	100.0	1:E,1	Standard	136.000	9.84e5	984000	3843.5...	128.16
37	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1034	blank water	1:H,3	Blank					
38	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1035	blank water	1:H,2	Blank		1.35e3	1350	2.160	7.27

Table 3. Corrected NDMA standard curve performance in prepared ranitidine DP samples (1.0–100 ng/mL) with NDMA recoveries between 94.2–111.1%.

Mean (N=4) Calculated NDMA concentrations in DP = 28.18 ng/mL (~1 ppm)

	Name	Sample Text	Vial	Type	Std. C...	Area	Response	S/N	ng/mL	%Rec
1	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1001	blank water	1:H,3	Blank						
2	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1002a	blank water	1:H,2	Blank						
3	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1002b	blank water	1:H,2	Blank						
4	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1002	blank water	1:H,2	Blank						
5	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1003	blank formul...	1:H,7	Analyte		1.20e5	120000	189.655	21.915	
6	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1004	blank formul...	1:H,8	Analyte		1.79e5	179000	421.920	29.133	
7	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1004_2	blank formul...	1:H,8	Analyte		1.88e5	188000	376.751	30.193	
8	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1005	blank formul...	1:H,9	Analyte		1.98e5	198000	694.523	31.487	
9	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1006	blank water	1:H,1	Blank						
10	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1007	blank water	1:H,2	Blank						
11	24Mar2020_Zantac Drug Formulation30mgmL_6mixGTI_1008	blank water	1:H,3	Blank						

Table 4. Mean (N=4) calculated NDMA concentration (29.0 ng/mL) in prepared ranitidine DP samples.

Conclusion

Use of the reversed-phase HSS T3 Column provided excellent retentivity for nitrosamine impurities, particularly the most polar nitrosamine, NDMA, while also providing separation from ranitidine API. Detection using a tandem quadrupole MS system with MRM analysis using atmospheric pressure chemical ionization (APCI), provided a 10X fold sensitivity improvement compared to electrospray ionization (ESI) for the nitrosamines. With this developed assay, LLOQs 0.025–0.1 ng/mL (<3 pg/mL on-column), for the various nitrosamine impurities were achieved for neat standard solutions, DS, and DP, with recoveries between 85–115% for the calibration points. The specificity, sensitivity, and broad linear dynamic range of this developed assay easily detected 0.1 ng/mL (0.0033 ppm, relative to 30 mg/mL DP or DS) of the nitrosamines in ranitidine drug product. Using this method, endogenous levels of NDMA from a prepared ranitidine drug tablet were detected and calculated to be 28 ng/mL (~1 ppm). The performance of this developed assay demonstrates a highly sensitive, accurate, and robust method for simultaneous nitrosamine impurity detection and quantitation, easily achieving regulatory guidance threshold values for these nitrosamine impurities in drug substance and drug product.

References

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