APPLICATION NOTE 74059

Highly sensitive and robust LC-MS/MS solution for quantitation of nitrosamine impurities in metformin drug products

Authors: Hao Yang[1], Edmund Moy[1], Michael Volny[1], Claudia Martins[1], Min Du[2], Wael Elmasri[3], Tanya Tadey[4]

[1]Thermo Fisher Scientific, San Jose, CA;
[2]Thermo Fisher Scientific, Boston, MA;
[3]Thermo Fisher Scientific, Greenville, NC;
[4]Thermo Fisher Scientific, Princeton, NJ

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Application benefits

- Detection and quantitation of 10 nitrosamines with a single liquid chromatography triple quadrupole selected reaction monitoring mass spectrometry (LC-SRM-MS) method using both heated electrospray ionization (HESI) and atmospheric pressure chemical ionization (APCI)
- Quantitation of nitrosamine impurities in metformin drug product below the daily acceptable intake level, meeting both European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) regulatory guidelines
- Reproducible and accurate quantitative method suitable for routine screening of nitrosamine impurities in drug products
- Use of the Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) for both data collection and processing in compliant environments with full data integrity and security capabilities for cGMP facilities, including 21 CFR part 11

Goal

To demonstrate robust and sensitive quantitation of 10 nitrosamines with a Thermo Scientific™ TSQ Quantis™ mass spectrometer, and the use of the LC-SRM-MS method to quantify nitrosamine impurities in metformin drug products.

Introduction

Nitrosamine contaminations in drug products

After the discovery of unacceptable levels of nitrosamine contaminations in certain drug products over the last two years, regulatory agencies around the world have mandated stringent guidelines and analytical testing of all pharmaceuticals, especially for chemically synthesized ones, to control and limit the level of these genotoxic impurities in drugs.[1-3] To ensure patient health and safety, and quality of these drugs, international regulators have set acceptable daily intake (AI) limits, and a total nitrosamine content of less than 30 ppb, based on the daily dose of the drug substance considering different strength availability of drug products.[2,3] Given these low AI limits, pharmaceutical manufacturers have to develop highly selective and sensitive methods for both the active pharmaceutical ingredients and finished drug products to meet the requirement, and to enable control of nitrosamine impurities within their supply chains.

To assist analytical testing, the US FDA has published several validated liquid chromatography-mass spectrometry methods for the determination and quantitation of nitrosamines in drug products. Although primary screening was performed using liquid chromatography-electrospray ionization-high resolution mass spectrometry (LC-ESI-HRMS) methods,[4-6] given the robust performance and wide availability of triple quadrupole systems, the US FDA later published a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method as an alternative for quantifying nitrosamines in drug products.[7] However, that method was only validated for determining N-nitrosodimethylamine (NDMA) in ranitidine drug substance and products. It is imperative to develop an LC-MS/MS method that is capable of detecting multiple nitrosamines simultaneously as shown in the previously published application note 65911 “Determination of six nitrosamine impurities in angiotensin II receptor blocker drugs by LC-MS/MS”.[8]

Here, we describe a highly sensitive and robust LC-SRM-MS method using the Thermo Scientific™ Vanquish™ Horizon UHPLC system coupled to a TSQ Quantis triple quadrupole mass spectrometer to detect and quantify 10 nitrosamines in metformin drug products. The method was run in both HESI and APCI mode, with the quantitation limit for all nitrosamines below 10 ppb using HESI, or 5 ppb using APCI in both neat solution and metformin drug products. We also conducted a 1,000 sample injection test to demonstrate method reproducibility and robustness that are essential for routine screening of nitrosamines in drug products. All data acquisition and processing were carried out in the compliance-ready Chromeleon CDS, to meet the regulatory requirements for user access, audit trails, data integrity, and data security.

Experimental

Reagents and consumables

- Thermo Scientific™ Water, UHPLC-MS grade, (P/N W81)
- Thermo Scientific™ Methanol (MeOH), UHPLC-MS grade (P/N A4581)
- Fisher Chemical™ Isopropanol (IPA), Optima™ LC-MS grade, (P/N A461-1)
- Thermo Scientific™ Pierce™ Formic acid, LC-MS grade, 10 x 1 mL ampules, (P/N PI28905)
- Metformin hydrochloride extended-release tablets USP 500 mg (Provided by a CDMO pharmaceutical company, LOT A40016)
- Nitrosamine reference standards (See Table 1)
- Thermo Scientific™ Pierce™ Protein Concentrator PES, 100K MWCO filter (P/N 88524)
- Falcon™ 15 mL conical centrifuge tubes, Falcon (P/N 14-959-53A)
- N,N-dimethyl formamide (DMF), HPLC grade (Sigma-Aldrich, P/N 270547-100ML)

Sample preparation

Reference standard preparation: Working solutions of pooled standards ranging from 10 to 2,000 ng/mL were prepared by diluting the 1 mg/mL stock solutions with methanol. A working solution of pooled internal standards at 2,000 ng/mL was prepared by diluting the 1 mg/mL stock solutions with methanol. Reference standards ranging from 0.1 to 20 ng/mL were prepared by mixing 10 µL of working standards with 10 µL of working internal standards, followed by adding 980 µL of methanol.

Metformin drug product preparation: Metformin drug samples were prepared by crushing two metformin hydrochloride extended-release tablets and grinding them into fine powders before transferring the contents into 15 mL Falcon tubes. 10 mL of methanol containing 20 ng/mL of internal standards were then added, and the mixture was shaken for 30 minutes on a mechanical shaker followed by cold centrifugation at 4,200 rpm for 30 minutes. After centrifugation, 6 mL of supernatant were transferred to two protein concentrator tubes (3 mL each), and then cold centrifuged at 4 °C for an additional 60 minutes at 4,200 rpm. The filtered extracts were

collected and transferred to 1.5 mL amber autosampler vials and stored at -20 °C prior to analysis. For spiked metformin drug product samples, the appropriate amounts of working standards were added to the 15 mL tube prior to cold centrifugation such that the spiked amount ranged from 0.1 to 20 ng/mL, or 1 to 200 ppb relative to metformin concentration, and the internal standard concentration was 20 ng/mL or 200 ppb.

For all samples, the filtered extract was diluted with UHPLC grade water at 4:1 ratio (e.g., take 200 µL of extract and add 800 µL of water) then transferred to a clean autosampler vial for LC-SRM-MS analysis. Hence, the final nitrosamine concentration in solution is diluted by 5 fold from the spiked concentration (e.g., 20 mg/mL metformin).

LC-SRM-MS method

A single targeted LC-SRM-MS method was developed using a Vanquish Horizon UHPLC system coupled to an TSQ Quantis triple quadrupole mass spectrometer. The Vanquish Horizon UHPLC system is equipped with a 100 µL sample loop (P/N 6850.1913), and for every sample analysis, 50 µL aliquot of diluted samples were injected onto a Thermo Scientific™ Hypersil GOLD™ Phenyl LC column (P/N 25903-104630) using the LC gradient and conditions outlined in Table 2. All nitrosamines were analyzed using both the HESI (OPTON-32103) and APCI (OPTON-32101) probes with optimized source and quadrupole scan settings as outlined in Tables 3 and 4, respectively. Optimized SRM transitions were used as in Table 5. A 2-position diverter valve (P/N 00109-99-00046) was used to divert the eluent stream to waste, and to MS between 3.2 and 13.5 minutes.

Chromeleon CDS version 7.2.10 was used for both data acquisition and analysis, to meet current regulatory requirements including US FDA 21 CFR Part 11 and European Commission (EU) Annex 11.

1,000 sample injection test

The test consisted of 10 injection sequences, each sequence was composed of 5 spiked samples (5/10/20/50/200 ppb), and 20 replicate injections per spiked concentration were collected. Each sequence also contained 5 check standards, with 3 replicate injections per concentration, bracketing the spiked samples. These check standards are reference standards in neat solution and were used to check the MS sensitivity after each sequence. For each sequence, all samples were freshly prepared as long-term stability of the extracted drug samples has not been evaluated. Only APCI data were collected. For consistency, no hardware and method changes were made, except for replenishing solvents (e.g., mobile phase, needle wash, seal rinse) and samples during the entire test. After completing 10 sequences, the injections were combined into a single sequence, and data were analyzed using a single processing method in Chromeleon CDS.

Table 1. Nitrosamine reference standards

Standards	CAS	Vendor	P/N
N-Nitrosodiethylamine (NDEA)	55-18-5	Restek	31898
N-Nitrosodimethylamine (NDMA)	62-75-9		
N-Nitrosodi-n-butylamine (NDBA)	924-16-3		
N-Nitroso-di-n-propylamine (NDPA)	621-64-7		
N-Nitrosomethylethylamine (NMEA)	10595-95-6		
N-Nitrosopyrrolidine (NPYR)	930-55-2		
N-Nitroso-n-methyl-4-aminobutyric acid (NMBA)	61445-55-4	Cambridge Isotopes	ULM-10857-1.2
N-Ethyl-N-nitroso-2-propanamine (NEIPA)	16339-04-1	Enamine	EN300-1296534
N-Nitroso-di-isopropylamine (NDIPA)	601-77-4	Enamine	EN300-7456222
N-Nitroso-N-methylaniline (NMPA)	614-00-6	Toronto Research Chemicals	N529925
NDEA-D10	55-18-5	Cambridge Isotopes	DLM-7982-S
NDMA-D6	62-75-9	Restek	33910
NDBA-D18	924-16-3	CDN Isotopes	D-6711-0.05g
NDPA-D14	621-64-7	Cambridge Isotopes	DLM-2131-S
NMEA-D3	10595-95-6	CDN Isotopes	D-6874-0.01g
NPYR-D8	930-55-2	Cambridge Isotopes	DLM-8252-1.2
NMBA-13C4	61445-55-4	Cambridge Isotopes	CLM-10856-1.2
NEIPA-D5	16339-04-1	Toronto Research Chemicals	E932796
NDIPA-D14	601-77-4	Toronto Research Chemicals	N525602

Table 2. LC conditions

HPLC column	Hypersil GOLD Phenyl, 100 x 4.6 mm, 3 µm		
Column temperature	30° C		
Flow rate	0.5 mL/min		
Mobile phase A	Water + 0.1% formic acid		
Mobile phase B	Methanol + 0.1% formic acid		
Gradient	Time (min)	% Mobile phase A	% Mobile phase B
	0.0	95	5
	2	95	5
	9	5	95
	15	5	95
	15.5	95	5
	20	95	5
Injection volume	50 µL		
Needle wash solution	80% Methanol with 0.1% formic acid		
Rear seal wash solution	75% IPA in water with 0.1% formic acid		
Autosampler temperature	4 °C		
Needle wash option	Before and after injection		
Wash speed and time	30 µL/s for 10 s		
Divert to source	3.2–13.5 min		

Table 3. MS ion source parameters

Ionization	HESI	APCI
Polarity	Positive	Positive
Spray current/voltage	3,500 V	4 µA
Sheath gas	45	45
Auxiliary gas	10	10
Sweep gas	0.5	0.5
Ion transfer tube temperature	200 °C	200 °C
Vaporizer temperature	300 °C	300 °C

Results and discussion

Specific determination of nitrosamine impurities

The method was operated in SRM mode with optimized transitions and ion optic settings for specific target nitrosamine as listed in Table 5. The quantifiers were selected with a better signal-to-noise ratio (S/N) and interference free from the metformin drug product matrices. Figure 1 shows a comparison of the extracted ion chromatogram (XIC) of the quantifiers between metformin drug sample and a 20 ppb spiked sample. Except for NDBA, no other endogenous interferences in metformin drug sample were observed. In fact, when we ran pure methanol extract without any standards present, we still observed a similar amount of interference, suggesting that this could come from the mobile phase solvent. Nonetheless, the amount of interfering substance was ≤20% at the 20 ppb spiked sample. In addition to nitrosamines, we also screened for DMF, and the tested drug product did not contain any significant amount of DMF (data not shown) that could invalidate the quantitation of NDMA.

With this method, baseline separation of metformin from the nitrosamines was achieved as the retention time (RT) of metformin is around 2.7 minutes with a peak width around 0.5 minutes. Hence, a diverter valve was used to direct the effluent to source after 3.2 minutes to avoid spraying the active pharmaceutical ingredient (API) into the source.

Table 4. Quadrupole scan settings

Scan type	SRM
Q1 FWHM (Da)	1.2
Q3 FWHM (Da)	1.2
Cycle time (s)	0.8
CID gas (mTorr)	1.5

Table 5. SRM transitions for target nitrosamines, only standards are shown. RT windows for all targets are 2 minutes.

Standards	Precursor ion	Quantifier ion	Qualifier ion	CE (V) Quan, Qual	RF lens (V)	Source fragmentation (V)
NDMA	75.055	58.054	43.03	15.57, 12.75	79	20
NMEA	89.071	61.071	29.167	11.91, 18.73	61	19
NPYR	101.071	55.071	39.125	16.12, 34.28	70	20
NMBA	147.076	117.125	44.018	7.32, 14.22	45	2
NDEA	103.087	75.113	29.208	11.19, 14.65	61	12.2
NEIPA	117.102	75.054	47	10.48, 16.67	55	18.4
NDIPA	131.118	89.125	47	9.34, 14.56	70	10.2
NDPA	131.118	89.125	41.054	10.48, 18.82	70	10.2
NMPA	137.1	66.1	107.1	19, 12	70	10.2
NDBA	159.149	103.054	41.054	11.36, 17.72	74	14.3

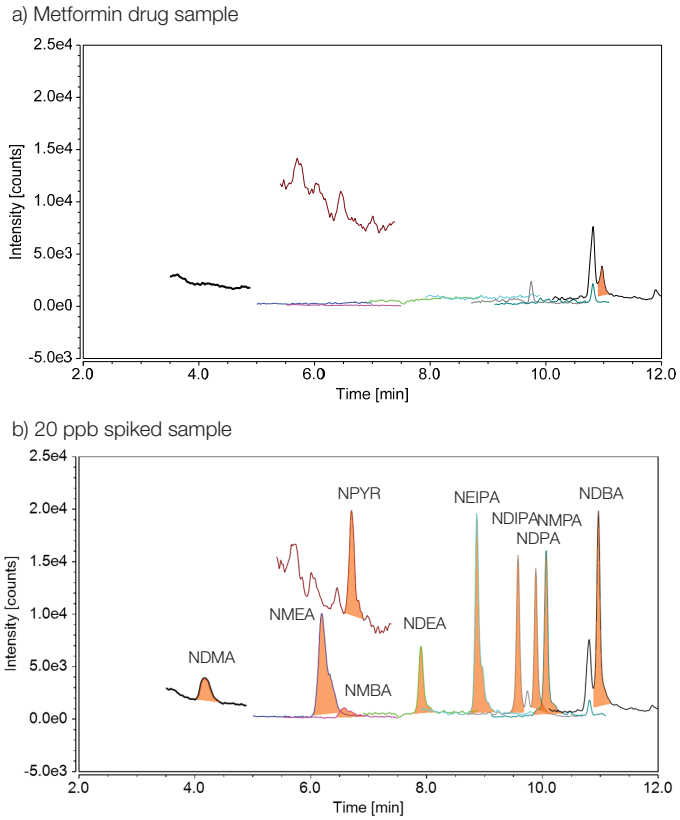

Figure 1. XIC of nitrosamine quantifier ions in a) metformin drug sample, and b) 20 ppb spiked sample. APCI data are shown here.

Quantifying nitrosamines impurities in drugs below the regulatory performance limits

The analysis of these extended-release formulations is challenging due to the presence of high molecular weight (MW) polymers, which are typically used to control the release rate of oral solid forms,[9] and can swell and gelatinize in aqueous solutions. Therefore, in addition to methanol extraction, a MW cutoff filter was used along with cold centrifugation to minimize the extraction of these polymers into the sample solution. The LC condition was 20 ppb spiked sample also optimized such that nitrosamines were well retained on the Hypersil GOLD phenyl column, resulting in comparable detection and quantitation limits for standards spiked in the finished drug products as well as in neat solution. Diluting the methanol extract with water in a 4:1 ratio (i.e., 80% water) prior to injection reduces the sample solvent strength and facilitates injection of large sample volume (e.g., 50 µL) without compromising the chromatographic peak shape, which would otherwise complicate the data analysis. Figure 2 shows a typical XIC of NDMA, for both quantifier and qualifier ion in metformin drug product, spiked with 2 ppb and 5 ppb standards. Since we did not observe any detectable NDMA or any other nitrosamines in this drug product, this candidate provides an ideal sample matrix for method validation and robustness test.

With this method, we can quantify all nitrosamines in both neat solution (data not shown) and finished metformin drug products with a lower limit of quantitation (LLOQ) of less than 10 ppb using HESI as shown in Table 6, and with a LLOQ of lower than 5 ppb using APCI as shown in Table 7. Limit of detection (LOD) and limit of quantitation (LOQ) were determined based on accuracy and precision of tested spiked concentration. We can also achieve excellent accuracy and precision for all nitrosamines at 5 ppb, all within 15% as shown in Table 8. While the majority of the nitrosamines have identical quantitation limits in both ionization modes, APCI is preferred for the analysis of NDIPA, NDPA, and NMPA because it selectively improves the ionization for these less polar, more volatile molecules; however, it does cause more fragmentation to NMBA, a relatively fragile molecule that tends to favor a softer ionization mechanism like HESI. Figure 3 shows typical calibration curves generated for nitrosamines in drug product. Calibration curves were constructed by plotting the peak area ratios of each standard over the

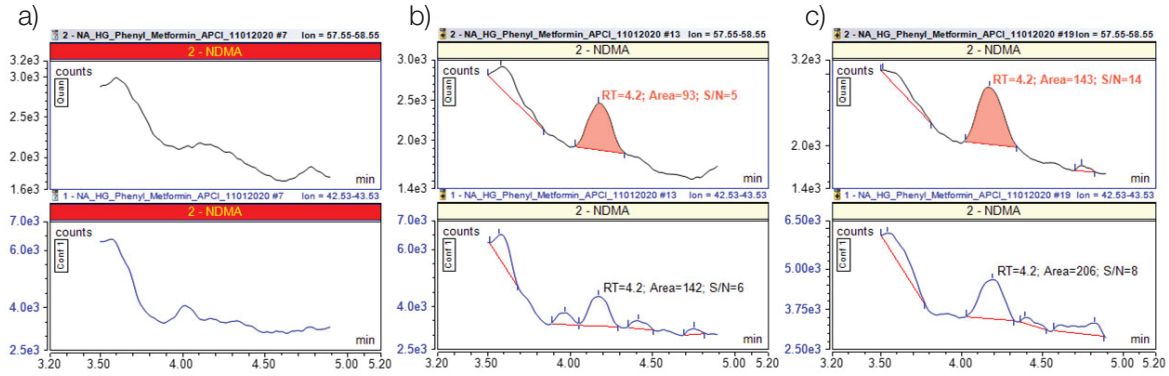

Figure 2. Example XIC of NDMA quantifier ion (top) and qualifier ion (bottom) in a) metformin drug product, b) spiked with 2 ppb, and c) spiked with 5 ppb standards. 2 ppb and 5 ppb are the LOD and LOQ for NDMA, respectively. APCI data are shown here.

Table 6. Nitrosamine detection and quantitation limits in metformin extended-release tablets, HESI

Standards	LOD (ng/mL)	LOD (ppb)	LOQ (ng/mL)	LOQ (ppb)	Linearity
NDMA	0.1	5	0.1	5	LOQ – 4 ng/mL
NMEA	0.02	1	0.04	2	
NPYR	0.04	2	0.04	2	
NMBA	0.02	1	0.04	2	
NDEA	0.04	2	0.1	5	
NEIPA	0.02	1	0.04	2	
NDIPA	0.1	5	0.2	10	
NDPA	0.1	5	0.2	10	
NMPA	0.04	2	0.1	5	
NDBA	0.02	1	0.1	5	

*ppb is calculated based on 20 mg/mL metformin concentration.

Table 7. Nitrosamine detection and quantitation limits in metformin extended-release tablets, APCI

Standards	LOD (ng/mL)	LOD (ppb)	LOQ (ng/mL)	LOQ (ppb)	Linearity
NDMA	0.04	2	0.1	5	LOQ – 4 ng/mL
NMEA	0.02	1	0.04	2	
NPYR	0.1	5	0.1	5	
NMBA	0.1	5	0.1	5	
NDEA	0.04	2	0.1	5	
NEIPA	0.02	1	0.04	2	
NDIPA	0.02	1	0.04	2	
NDPA	0.02	1	0.04	2	
NMPA	0.02	1	0.04	2	
NDBA	0.02	1	0.1	5	

*ppb is calculated based on 20 mg/mL metformin concentration.

Table 8. Example accuracy and precision at 5 ppb (N = 5), APCI

Standards	Accuracy	Precision (% RSD)
NDMA	86%	12.0
NMEA	92%	3.7
NPYR	112%	8.2
NMBA	102%	13.4
NDEA	94%	4.4
NEIPA	94%	6.0
NDIPA	99%	7.6
NDPA	103%	3.2
NMPA	101%	5.7
NDBA	93%	4.2

corresponding internal standard against the concentrations of the whole standard range from 1 to 200 ppb or 0.1 to 4 ng/mL spiked in 20 mg/mL metformin drug samples, with a linear fit, and a 1/x weighting. Although only APCI data are shown here, this method can deliver excellent accuracy and precision, and linear regression coefficients above 0.995 for all nitrosamines using either HESI or APCI. In either case, we can easily achieve a sensitivity limit that is required under new regulatory guidelines.

Demonstrating method reproducibility and robustness for nitrosamine impurity analysis in drug product

Due to recent changes in the regulatory guidelines for controlling the level of nitrosamine impurities in finished drug products and APIs, a large number of on-market drugs and pending new drug applications are affected, and routine screening and quality control of these impacted products are inevitable. Therefore, analytical methods must not only demonstrate high sensitivity to meet the AI limit, but methods should exhibit adequate reproducibility and robustness against variations that could result from sample preparation, system performance deviations, or replacement of failing hardware (e.g., column, source components).

To address the above analytical challenge, this method was tested against 1,000 continuous injections of spiked samples without any changes to the hardware and method settings. %RSD of the peak area ratios, standards over internal standards, were used to evaluate the reproducibility of the method. Although pooled samples are desirable for this type of test to reduce variations derived from sample preparations, the long-term stability of extracted samples is unknown and thus fresh samples are prepared for each injection sequence. Despite this practice, this method demonstrated superb reproducibility over the course of 1,000 injections. As illustrated in Table 9, we can achieve less than 20% RSD (peak area ratios) for seven key nitrosamines as outlined in the US FDA guideline for concentrations as low as 5 ppb, and with less than 10% RSD for 20 ppb spiked samples.

There were no noticeable changes in the chromatographic separation of the nitrosamines as both the RT and peak capacity remain the same after the 1,000 injection test. Using NDMA as an example, as shown in Figure 4, the RT and peak width at 50% height (FWHM) are almost identical between the first and last injection of the 200 ppb spiked sample. Using the RT and FWHM obtained from NDMA, the change in calculated theoretical plates was

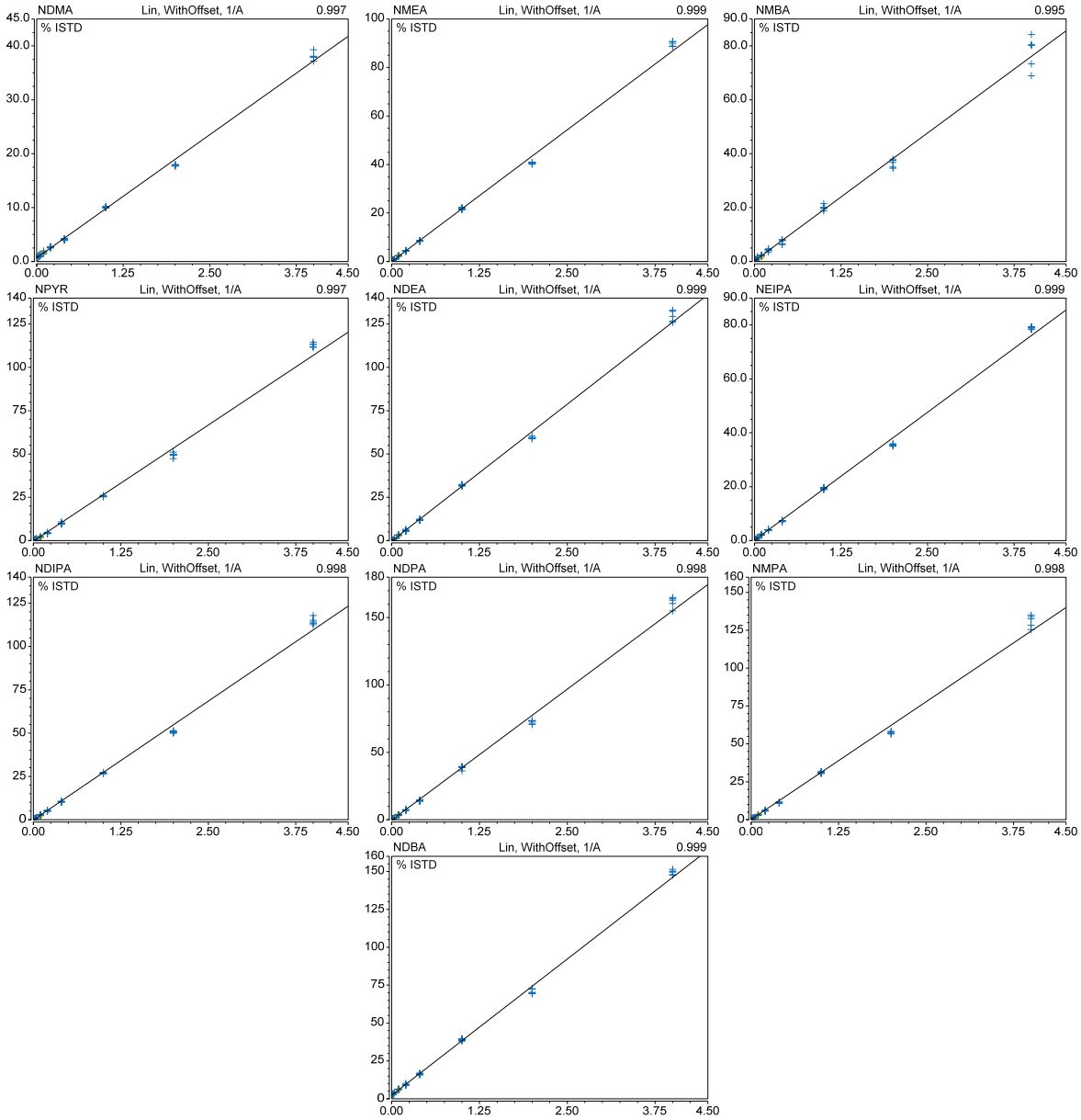

Figure 3. Calibration curves of target nitrosamines using spiked metformin drug samples. Five replicates were collected per concentration. APCI data are shown here.

less than 5% after 1,000 injections. Although there was a slight decrease in the peak area, the internal standard also had a similar effect possibly due to variation in the sample preparation. A closer examination of the NDMA calibration plots generated from the first injection sequence and the last sequence (Figure 5) yielded negligible change in concentration-response, via standard curve fitting, for the quantitation of NDMA. Moreover, the concentration-response obtained from check standards in the last injection sequence was also comparable with the one obtained from the first injection sequence (data not shown), suggesting that there was minimal loss in MS sensitivity after 1,000 injections.

Table 9. %RSD of peak area ratio (analyte to internal standard) for each spiked concentration (N=200 of each level)

Standards	5 ppb	10 ppb	20 ppb	50 ppb	200 ppb
NDMA	13.0	10.6	7.3	8.2	4.1
NMBA	11.9	9.8	9.0	7.2	6.1
NDEA	16.1	8.3	6.6	3.7	3.4
NEIPA	6.1	6.7	4.6	2.8	3.0
NDIPA	5.5	5.6	5.5	3.0	3.6
NMPA	8.1	6.1	5.3	5.0	5.2
NDBA	9.5	5.7	5.5	2.9	2.9

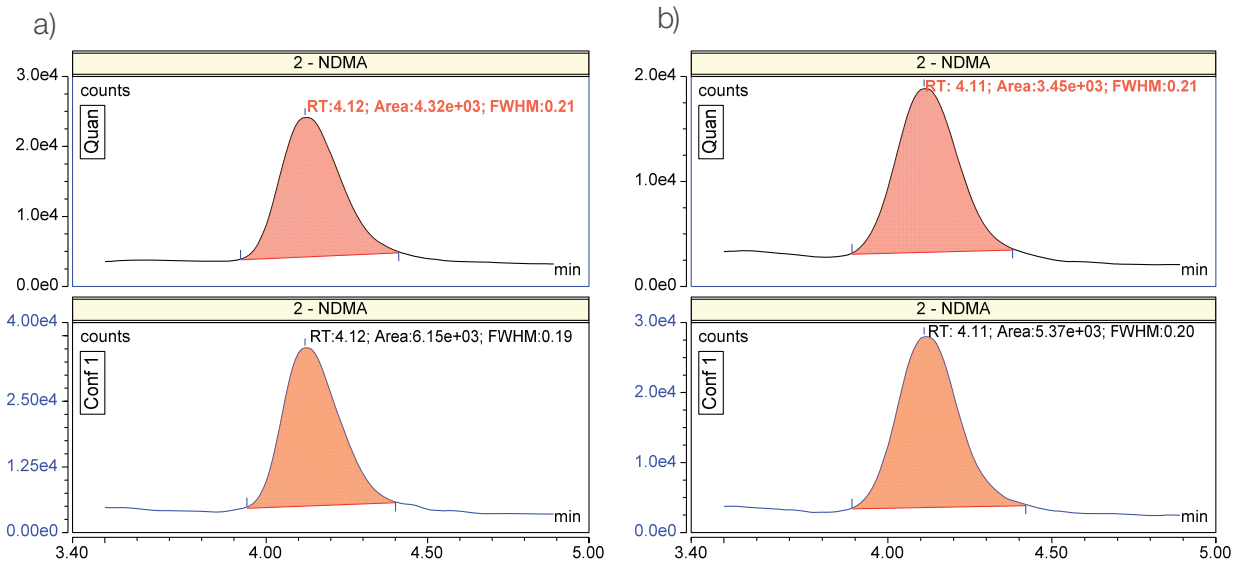

Figure 4. XIC of NDMA comparison between the a) first and b) last injection of the 200 ppb spiked sample

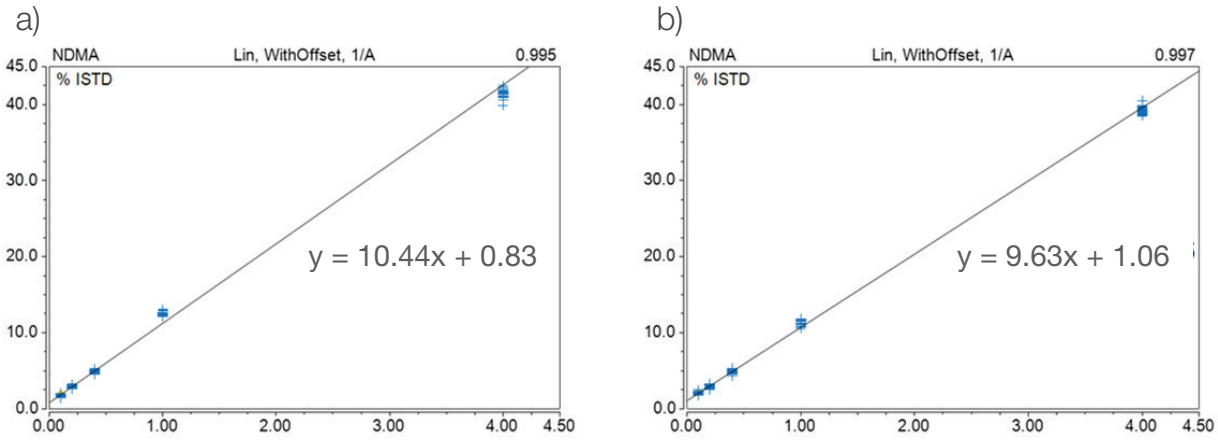

Figure 5. Calibration plot comparison between a) first 100 injections and b) last 100 injections.
Only NDMA data from spiked samples are shown.

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Conclusion

A highly sensitive and robust LC-SRM-MS method was developed using the Vanquish Horizon UHPLC system equipped with a Hypersil GOLD phenyl column coupled to a TSQ Quantis triple quadrupole mass spectrometer, and utilizing the Chromeleon CDS for the detection and automated quantitation of 10 nitrosamines in metformin drug products. Not only can this method quantify target nitrosamines as low as 5 ppb using APCI and 10 ppb using HESI, it also provides excellent reproducibility for nitrosamine quantitation over 1,000 sample injections with minimal change in column performance as well as MS sensitivity. This complete solution has been shown to adequately address any currently highlighted and potential future analytical challenges, as being future-proof and flexible to extend to further nitrosamines.

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