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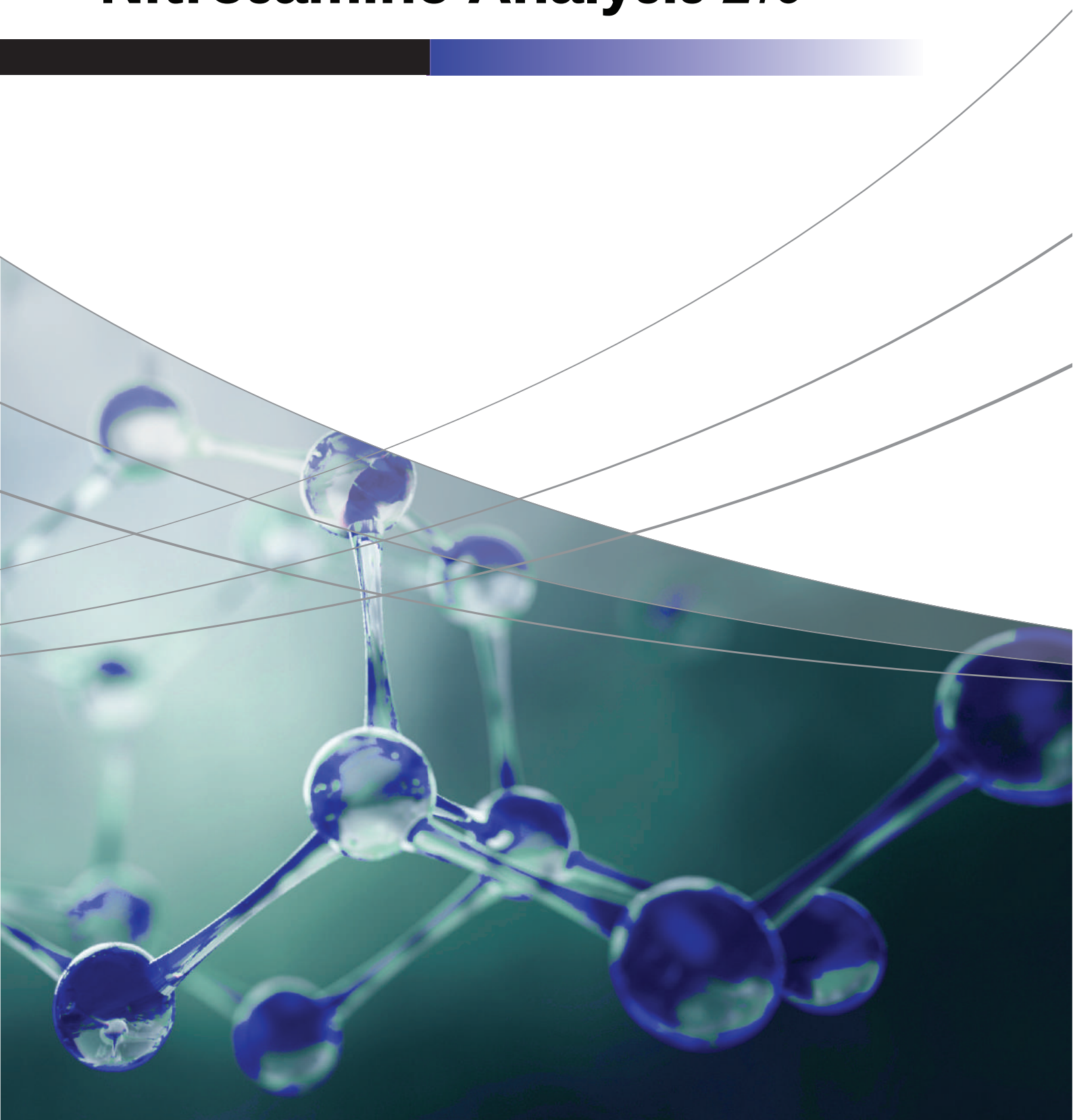
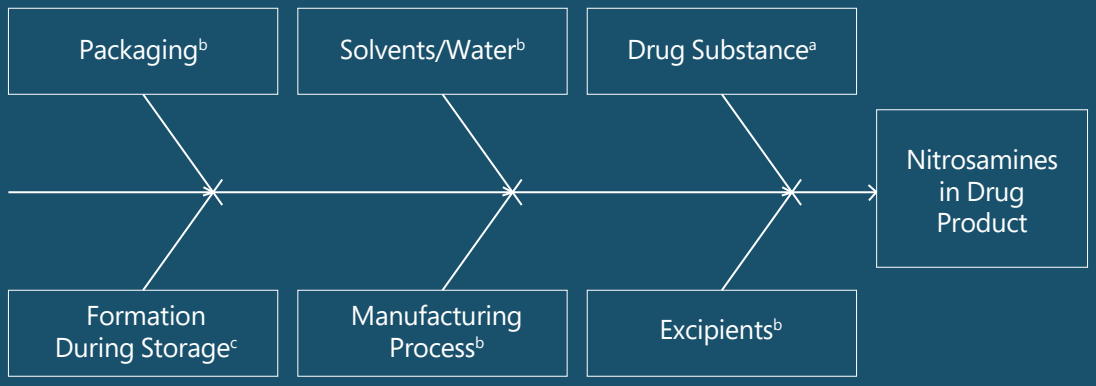
UFMS Solution for **Nitrosamine Analysis** *2.0*



Nitrosamine

Nitrosamines, or more correctly N-nitrosoamines, refer to any molecule containing the nitroso functional group. These molecules are of concern because nitrosamine impurities are probable human carcinogens. Although they are also present in some foods and drinking water supplies, their presence in medicines is nonetheless considered unacceptable. They were believed be introduced into the finished drug products as a result of the manufacturing process of the drug substance. Further investigations have proved that the source of nitrosamines can also be API's chemical structure or even the conditions in which they are stored or packaged (Figure 1)



[a]Primary/predominant source of potential nitrosamines
[b]Secondary sources of potential nitrosamines
[c]Formed by a mechanism other than degradation of the drug substance

Figure 1: Sources of Nitrosamines in drug product (Reference: From USP PF Chapter 1469)

List of Commonly Analyzed Nitrosamines

Table 1: Commonly analyzed nitrosamines

No.	Name	Abbr.	CAS No	Formula	MW
1	N-Nitrosodimethylamine	NDMA	62-75-9	$C_2H_6N_2O$	74.1
2	N-Nitroso-N-methyl-4-aminobutyric acid	NMBA	61445-55-4	$C_5H_{10}N_2O_3$	146.2
3	N-Nitrosodiethylamine	NDEA	55-18-5	$C_4H_{10}N_2O$	102.1
4	N-Nitrosoethylisopropylamine	NEIPA	16339-04-1	$C_5H_{12}N_2O$	116.2
5	N-Nitrosodiisopropylamine	NDIPA	601-77-4	$C_6H_{14}N_2O$	130.2
6	N-Nitrosodipropylamine	NDPA	621-64-7	$C_6H_{14}N_2O$	130.2
7	N-nitrosomethylphenylamine	NMPA	614-00-6	$C_7H_8N_2O$	136.2
8	N-Nitrosodibutylamine	NDBA	924-16-3	$C_8H_{18}N_2O$	158.2

In July 2018, the U.S. Food and Drug Administration (FDA) announced that the carcinogenic impurities NDMA and NDEA were detected in valsartan bulk drug substances. Further Investigations showed presence of other nitrosamines such as NDIPA, NEIPA, NMBA and NDBA in various Angiotensin II Receptor Blockers (ARBs). This resulted in many lots of ARBs being recalled.

Not long after, in September 2019, ranitidine was suspected of being contaminated with NDMA. Ranitidine is a prescription and over-the-counter drug used to treat acid reflux. This was based on findings that levels of NDMA in ranitidine may increase to unacceptable levels over time and when exposed to higher than room temperature. Eventually, FDA requested withdrawal of all remaining prescription and OTC ranitidine products from the U.S. market.

In early 2020, FDA started investigation for presence of NDMA impurity in metformin approved for sale in the U.S. Metformin is a prescription drug used to control high blood sugar in patients with type 2 diabetes. FDA testing found NDMA (above the agency's acceptable intake limit) in certain lots of extended release (ER) metformin and had recommended companies recall lots with levels of NDMA above the acceptable intake limit of 96 nanograms per day.

Additionally, FDA has also investigated presence of 1-Methyl-4-Nitrosopiperazine (MNP) in Rifampin and 1-Cyclopentyl-4- Nitrosopiperazine (CPNP) in rifapentine drug substance and drug products. These are antibacterial drugs used to treat tuberculosis.

Analysis of nitrosamine impurities at trace levels possess many challenges in terms of solubility of nitrosamines and drug substance/drug products, thermal stability of nitrosamine etc. and may require more than one analytical technique. Shimadzu's highly sensitive UFMS technologies LC-MS/MS and GC-MS/MS powered by Analytical Intelligence offer wholesome solution for quantification of trace levels of nitrosamine impurities from various drug substances, drug products, solvents etc.

ANALYTICAL INTELLIGENCE

With changes and upgradation of nitrosamine regulations- keeping up with method development, validation and regular analysis is a daunting task. Add to this new challenge of work from home and social distancing, it's an uphill battle where laboratories must possess capability of delivering reliable and robust results in time and continuously.

Power your labs with Chromatographic and Mass-Spec technologies packed with Analytical Intelligence from Shimadzu. Leverage the proven performance of UFMS along with operational functionalities of Analytical Intelligence.

- Automated support functions utilizing digital technology, such as M2M, IoT, and Artificial Intelligence (AI), that enable higher productivity and maximum reliability
- Allows a system to monitor and diagnose itself, handle any issues during data acquisition without user input, and automatically behave as if it were operated by an expert
- Supports the acquisition of high quality, reproducible data regardless of an operator's skill level for both routine and demanding applications

Nitrosamine Analysis in Sartans

This section deals with various aspects and approaches for analysis of nitrosamines in different sartan APIs

- Headspace GC-MS/MS Analysis Of Nitrosamines In Losartan API As Per USP General Chapter Prospectus <1469> (Procedure 2)
- Quantitation Of 6 Nitrosamines In 5 Sartans By LC-MS/MS As Per Proposed USP General Chapter<1469> (Procedure 3)
- High Sensitivity Analysis Of 6 Nitrosamines In Olmesartan KSM Using LCMS-8060
- High Resolution Analysis Of 7 Nitrosamines In Various Sartan Drug Substances Using LCMS-9030

Headspace GC-MS/MS Analysis Of Nitrosamines In Losartan API As Per USP General Chapter Prospectus <1469> (Procedure 2)

Proposed United States Pharmacopeia (USP) General chapter <1469> aligns with current scientific and regulatory approaches to ensure the appropriate control of nitrosamine impurities in drug substances and drug products. The objective of this standard is to provide a science-based approach for the control of nitrosamine impurities, eliminating or reducing their presence in drug products.

This application data is based on procedure 2 of General Chapter Prospectus<1469>.

Analysis details mentioned in said method were used with Shimadzu headspace autosampler and GCMS triple quadrupole system GCMS TQ-8050 NX with HS-20. In this application brief, we have analysed 3 more nitrosamines (NDPA, NDBA and NMPrZ) in addition to 4 mentioned nitrosamines (NDMA, NDEA, NEIPA and NDIPA) with eight times better sensitivity.

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Representative Data

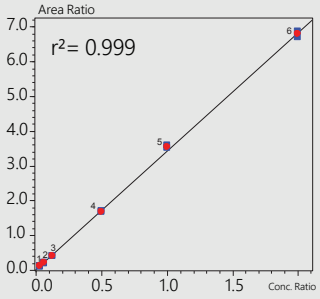

Figure 2: Calibration curve for NDMA

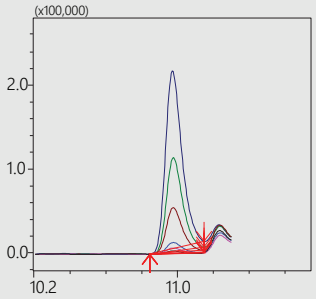

Figure 3: Overlay of linearity standards for NDMA

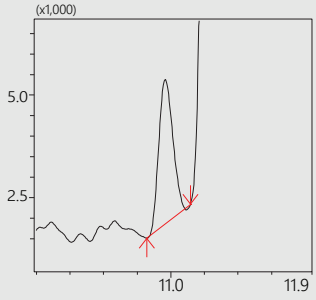

Figure 4: LOQ solution chromatogram for NDMA

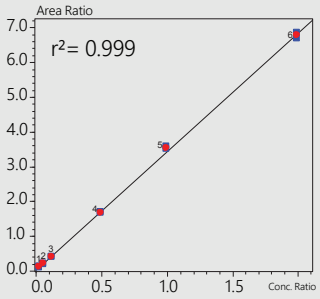

Figure 5: Calibration curve for NDEA

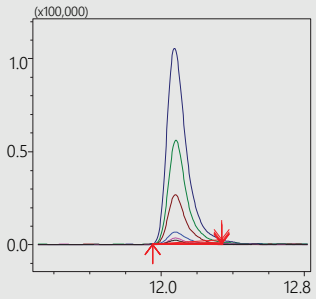

Figure 6: Overlay of linearity standards for NDEA

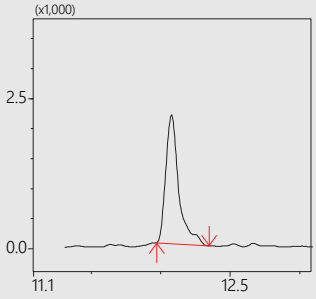

Figure 7: LOQ solution chromatogram for NDEA

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Table 2: LOQ required and achieved

Name	USP <1469>	HS-20 with GCMS-TQ8050 NX
	LOQ (ppb)	LOQ (ppb)
NDMA	20.0	2.5
NDEA		
NEIPA		
NDIPA		
NDPA	NA	10.0
NDBA		5.0
NMPrZ		25.0

Table 3: Experimental results of 7 nitrosamines in Losartan API

Comp.	Calibration Range (ppb)	LOQ (ppb)		
		Conc. (ppb)	% RSD	S/N *(Peak to Peak)*
NDMA	2.5 to 160	2.5	8.5	50
NDEA			12.6	472
NEIPA			6.6	651
NDIPA			9.5	399
NDPA	10.0 to 640	10	7.5	612
NDBA	5.0 to 320	5	9.2	58
NMPrZ	25.0 to 1600	25	14.6	28

Sample weight: 200 mg ±10 mg in 1 mL IS and 1 mL MeOH. (All above concentrations are relative to sample concentration)
Access detailed application note here.

Quantitation Of 6 Nitrosamines In 5 Sartans By LC-MS/MS As Per Proposed USP General Chapter<1469> (Procedure 3)

5 different sartans namely olmesartan, telmisartan, irbesartan, losartan and valsartan were analyzed using methodology described in USP General Chapter Prospectus <1469> using Shimadzu LCMS-8045. Analysis was done for 6 recommended nitrosamines using internal standard (stable labelled isotopes) method of quantitation. Equivalent results were obtained using Raptor ARC-18 column and Shim-pack Velox SP-C18 column.

All nitrosamines except NDEA were quantified with 0.03 ppm and NDEA was quantified with 0.013 ppm as specification limit with respect to the sample concentration of 66.6 mg/mL.

Click here >

Column used: Shim-pack Velox SP-C18 (150 mm x 3 mm; 2.7 µm) (P/N: 227-32004-04)
Raptor ARC-18 (150 mm x 3 mm; 2.7 µm)

Representative Data

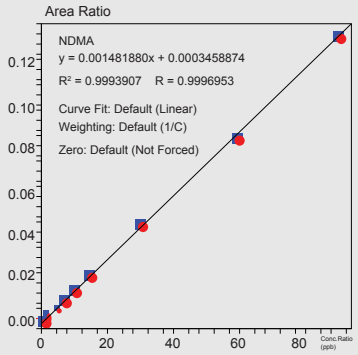

Figure 8: Calibration curve for NDMA

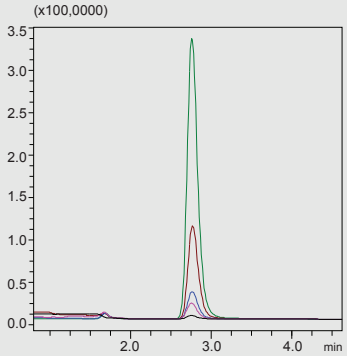

Figure 9: Overlay of linearity standards for NDMA

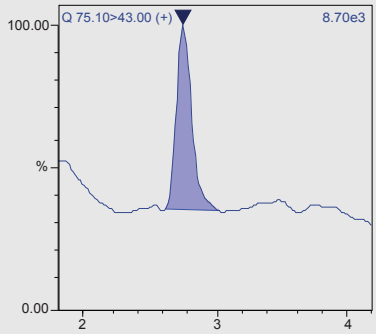

Figure 10: LOQ solution chromatogram for NDMA

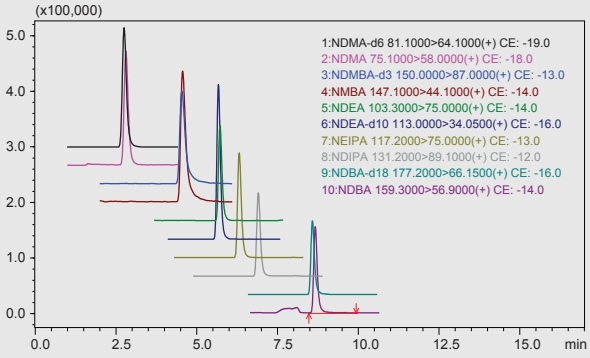

Figure 11: Representative LCMS chromatogram of 6 nitrosamines

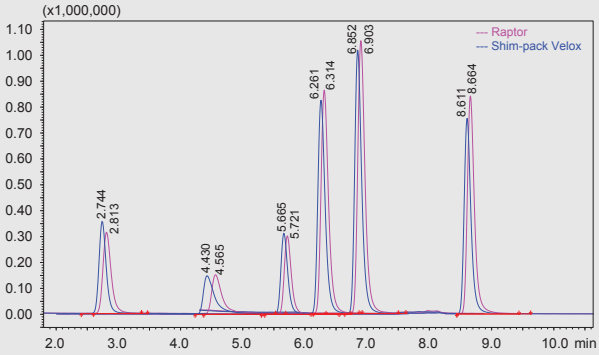

Figure 12: Overlay TIC from Raptor and Shim-pack velox column demonstrating equivalency of results

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Table 4: Summary of calibration curves

Comp.	CC range (ppb)	R2	LOQ (ppb)		
			Conc. (ppb)	%RSD (n=6)	S/N
NDMA	1.33 to 90	0.999	1.33	2.68	25.34
NMBA		0.998		15.66	15.08
NEIPA		0.999		10.3	40.19
NDIPA		0.998		1.85	90.03
NDBA		0.999		3.66	89.85
NDEA	0.66 to 59.4	0.999	0.66	5.90	29.84

Table 5: Experimental results of 7 nitrosamines in losartan API

% Recovery at 0.03ppm for 5 NSAs and 0.014ppm for NDEA					
Name	Olmesartan	Telmisartan	Irbesartan	Losartan	Valsartan
NDMA	90.7	86.9	114.2	95.7	92.1
NMBA	117.7	114.5	108	112.6	118.7
NEIPA	94.5	93.7	94.4	93.7	93.7
NDIPA	100.7	105.5	98.0	81.4	86.1
NDBA	104.5	110.5	115.2	108.7	111.8
NDEA	71.8	73.2	99.6	77.1	86.8

Sample concentration: 66.6 mg/mL (80 mg API dissolved in 1.2 mL diluent)

High Sensitivity Analysis Of 6 Nitrosamines In Olmesartan KSM With LCMS-8060

Given application highlights applicability of LCMS-8060 for nitrosamine analysis at levels lower than recommended concentration. In this data we analyzed NDMA, NMBA, NDEA, NIEPA, NDIPA and NDBA impurities at lower concentrations in olmesartan KSM.

Column used: Shim-pack Arata C18 (3 mm x 150 mm, 2.2 µm) (P/N: 227-32802-04)

Representative Data

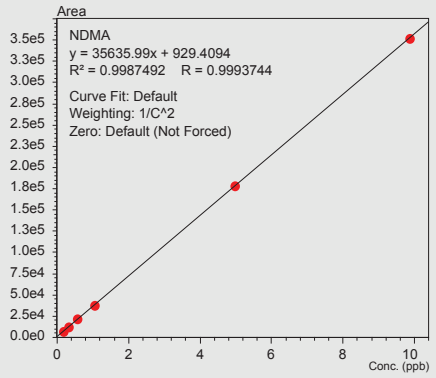

Figure 13: Calibration curve for NDMA

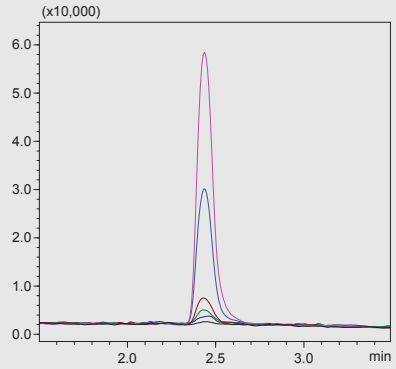

Figure 14: Overlay of linearity standards for NDMA (6 points)

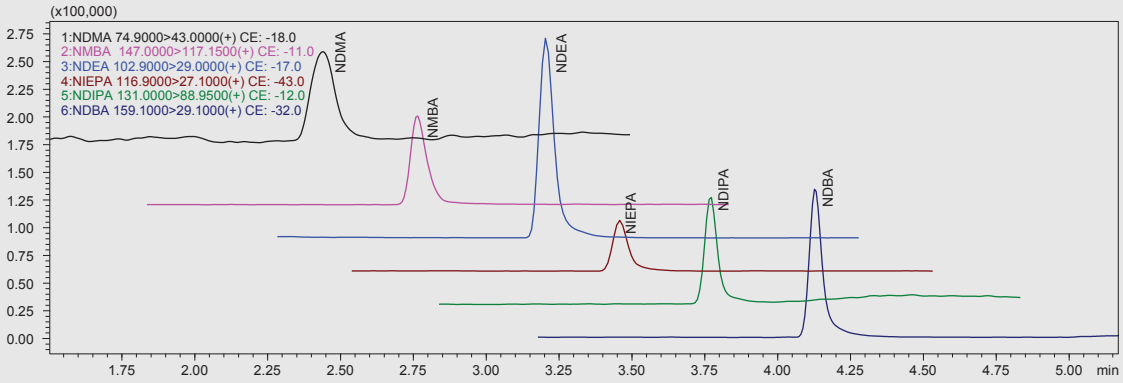

Figure 15: MRM chromatogram of 6 nitrosamines @ 5 ppb level

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Table 6: Experimental results of 6 nitrosamines in olmesartan KSM

Parameter	Value
Limit of Detection achieved	0.05 ppb (0.25 ppb in sample)
Limit of Quantitation achieved	0.1 ppb (0.5 ppb in sample)
Linearity Range	0.1 - 10 ppb (0.0005 – 0.05 ppm for sample)
Repeatability	6.55% - 9.59% (n = 3)
Recovery	30% - 95% at 1 ppb (0.005 ppm in sample, n = 3)

Sample Concentration: 200 mg/mL

High Resolution Analysis Of 7 Nitrosamines In Various Sartan Drug Substances Using LCMS-9030

Nitrosamine impurities are low molecular weight compounds and analyzed in trace concentrations. This situation directs us to sometimes consider use of high resolutions hybrid mass spectrometers like Quadrupole Time of Flight (QTOF) MS in order to confirm false positives.

In this application we share methodology for high resolution quantitation of 7 nitrosamine- NDMA, NMBA, NDEA, NIEPA, NDIPA, NDPA and NDBA in Losartan and Candesartan drug substances.

Column Used: Shim-pack Solar, C18 (4.6 mm x 250 mm, 5 µm; P/N: 227-30600-02)

Representative Data

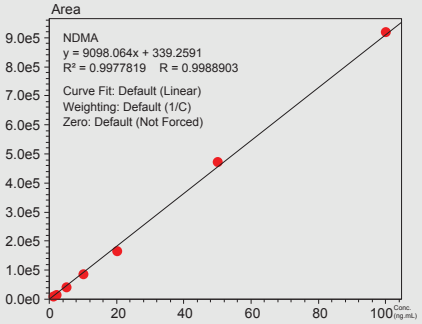

Figure 16: Calibration Curve for NDMA

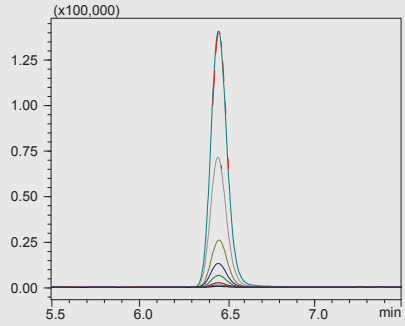

Figure 17: Overlay of linearity standards for NDMA (9 points)

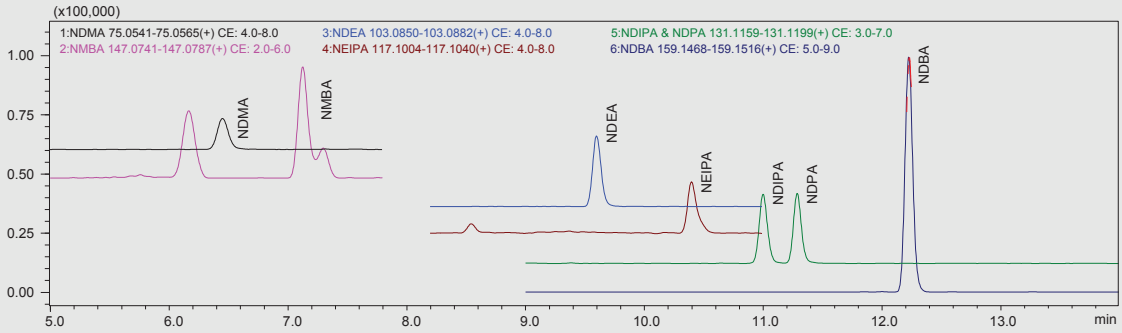

Figure 18: MRM chromatogram of 7 nitrosamines (10.0 ppb; NDBA 5.0 ppb)

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Table 7: Experimental results of 7 nitrosamine in losartan and candesartan drug substance

Parameter	Value
Limit of Detection achieved	0.1 – 0.5 ppb (0.005 – 0.025 ppm for spiked sample)
Limit of Quantitation achieved	0.25 – 1 ppb (0.013 – 0.05 ppm for spiked sample)
Linearity range	1 – 100 ppb, 0.5 -1 100 ppb, 0.5 – 20 ppb, 0.25 – 10 ppb
Recovery (Losartan)	97.5% - 131.0% at 1 ppb (NDBA 0.5 ppb) (n = 2); 99.0% -109.2% at 5 ppb (NDBA 2.5 ppb) (n = 3)
Recovery (Candesartan)	87.7% - 101.9% at 1 ppb (NDBA 0.5 ppb) (n = 2); 81.8% -104.0% at 5 ppb (NDBA 2.5 ppb) (n = 3)
Matrix effect (Losartan)	31.5% - 123.2% at 1 ppb (NDBA 0.5 ppb) (n = 2); 35.7% - 112.0% at 5 ng/mL (NDBA 2.5 ppb) (n = 3)
Matrix effect (Candesartan)	83.7% - 123.1% at 1 ppb (NDBA 0.5 ppb) (n = 2); 86.9% - 100.7% at 5 ng/mL (NDBA 2.5 ppb) (n = 3)

Sample Concentration: 20 mg/mL

Nitrosamine Analysis in Metformin

This section deals with various aspects and approaches for analysis of nitrosamines in metformin drug substance, drug product and placebo.

- Quantitation Of 8 Nitrosamines in Metformin ER (Extended Release) Tablets And Placebo Using LCMS-8045
- Quantification Of N-nitroso-dimethylamine (NDMA) In Metformin Tablets Using LCMS-8045
- LC-HRMS Method For Analysis Of 8 Nitrosamines In Metformin Drug Substance Using LCMS-9030

Quantitation Of 8 Nitrosamines In Metformin ER (Extended Release Tablet) And Placebo Using LCMS-8045

In this experiment, we analyzed 8 nitrosamines—NDMA, NMBA, NDEA, NEIPA, NDIPA, NDPA, NDBA and NMPA in metformin ER tablets and placebo using in-house developed method with liquid-liquid extraction being employed for sample preparation.

All 8 nitrosamines were quantified with the specification level of 0.01 ppm with respect to the sample concentration at 200 mg/mL. Analyzed metformin ER tablet and placebo were found to be negative for any nitrosamine impurities.

Column used: Shim-pack Scepter (250 mm x 4.6 mm; 5.0 µm) (P/N: 227-31024-06)

Representative Data

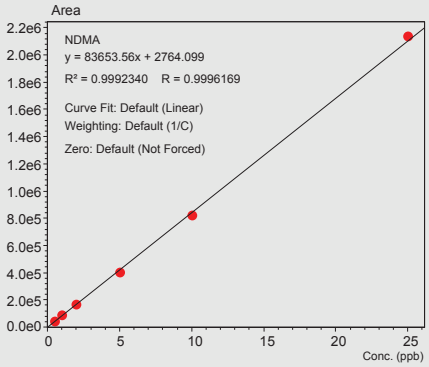

Figure 19: Calibration Curve for NDMA

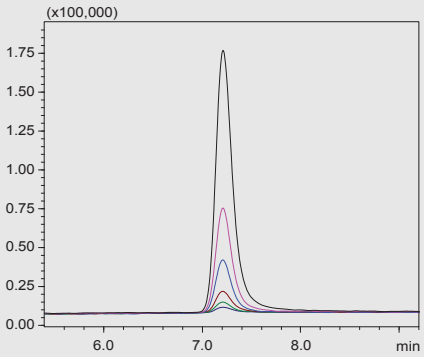

Figure 20: Overlay of linearity standards for NDMA (6 points)

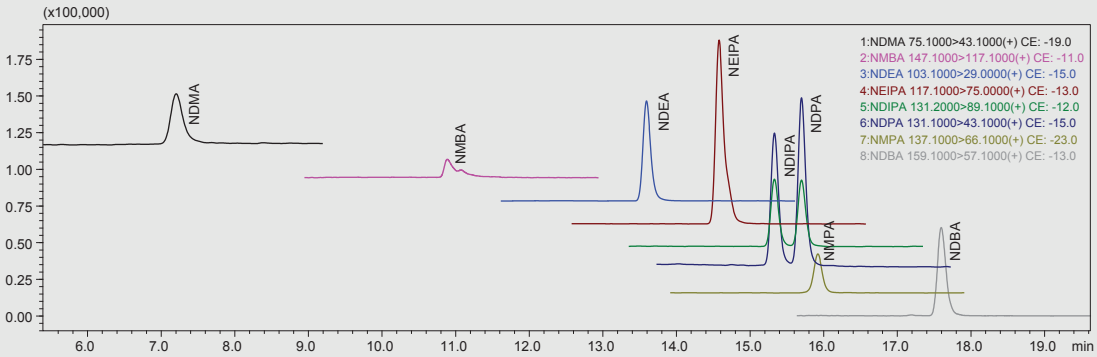

Figure 21: MRM chromatogram of 8 nitrosamines (5.0 ppb)

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Table 8: Experimental results of 8 nitrosamines in Metformin ER tablets.

Parameter	Value
Limit of Detection achieved	0.1 ppb (0.0005 ppm for sample)
Limit of Quantitation achieved	0.5 ppb (0.0025 ppm for sample)
Linearity range	0.5 - 25 ppb (0.0025 – 0.125 ppm for sample)
Repeatability	1.69% - 5.98% at 0.5 ppb (LOQ level, 0.0025 ppm in sample, n = 6), 0.60% – 2.98% at 2 ppb (spec level, 0.01 ppm in sample, n =6)
Recovery	70% - 130% at LOQ level (0.0025 ppm in sample) and spec level (0.01 ppm in sample)

Linearity was performed in the range of 0.5 ppb to 25 ppb level corresponding to the linearity range of 0.0025 ppm to 0.125 ppm with respect to the sample concentration of 200 mg/mL

Quantification Of N-nitroso-dimethylamine (NDMA) In Metformin Tablets Using LCMS-8045

Sometimes quantitation of NDMA is hampered due to close elution of DMF. In this study, we developed a method using Shimadzu Shim-pack phenyl column and gradient program to chromatographically separate DMF from NDMA.

Column used: Shim-pack Phenyl (150 mm x 4.6 mm, 5.0 µm; P/N: 227-30220-06)

Representative Data

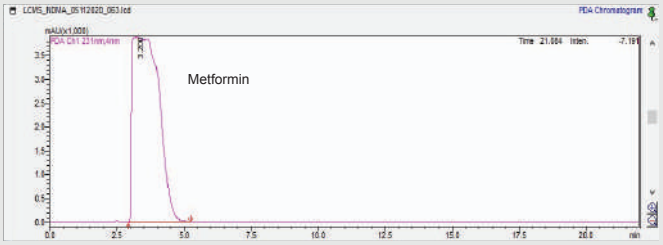

Figure 22: Metformin peak observed at about 3.2 RT at 231nm

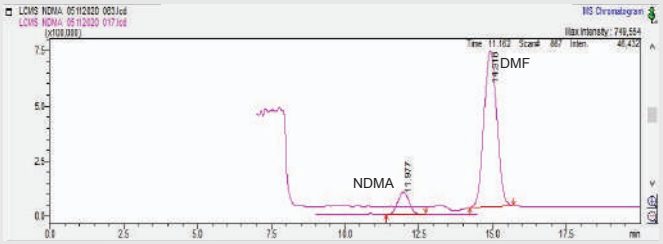

Figure 23: DMF has been well separated from NDMA peak, hence no interference is observed

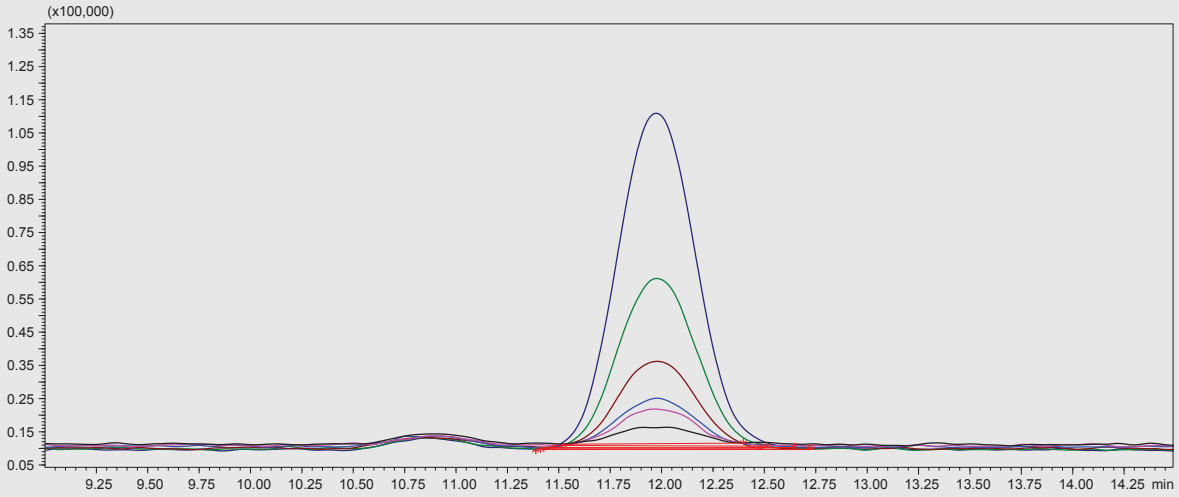

Figure 24: Overlay of NDMA linearity levels

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Table 9: Experimental results for analysis of NDMA in metformin tablet

Parameter	Value
Limit of Detection achieved	0.3 ppb (0.003 ppm for sample)
Limit of Quantitation achieved	0.9 ppb (0.009 ppm for sample)
Linearity range	0.9 - 24 ppb (0.009 – 0.24 ppm for sample)
Repeatability	2.67% at 0.9 ppb (LOQ level, 0.009 ppm in sample, n = 6), 1.42% at 3 ppb (spec level, 0.03 ppm in sample, n =6)
Recovery	83.7% - 84.4% (two batches of 500 mg tablet and one batch of 1000 mg tablet) at spec level (0.03 ppm in sample)

Sample Concentration: 100 mg/mL

LC-HRMS Method For Analysis Of 8 Nitrosamines In Metformin Drug Substance Using LCMS-9030

In this application, we showcase high resolution quantitative analysis of 8 nitrosamines—NDMA, NMBA, NDEA, NEIPA, NDIPA, NDPA, NDBA and NMPA in metformin hydrochloride. Analysed sample was found to be negative for 8 tested nitrosamines.

Column used: Shim-pack Solar, C18 (4.6 mm x 250 mm, 5 µm; P/N: 227-30600-02)

Representative Data

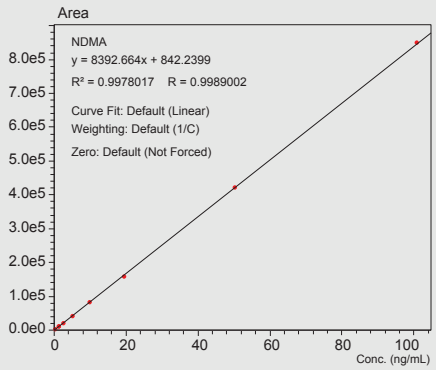

Figure 25: Calibration Curve for NDMA

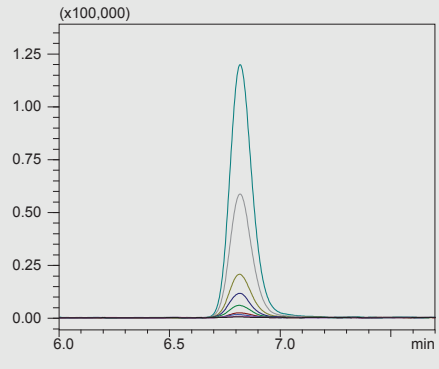

Figure 26: Overlay of Linearity Standards for NDMA (6 points)

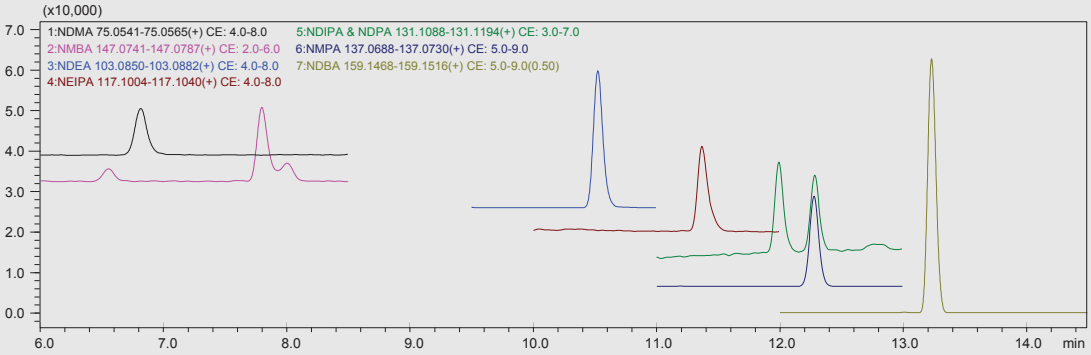

Figure 27: MRM chromatogram of 8 nitrosamines (5.0 ppb)

Performance Report

Table 10: Experimental results of 7 nitrosamines in metformin tablet using LCMS-9030

Parameter	Value
Limit of Detection achieved	0.1 - 0.5 ppb (0.001-0.005 ppm for spiked sample)
Limit of Quantitation achieved	0.2 - 1 ppb (0.002-0.01 ppm for spiked sample)
Linearity range	1-100 ppb, 0.5-100 ppb, 0.2-100 ppb, 0.25-50 ppb (for NDBA, not linear but quadratic)
Repeatability	1.85% - 18.2% at 1ppb (NDBA 0.5 ppb) (0.01 & 0.005 ppm in sample, n = 6); 0.46% - 3.38% at 5 ppb (NDBA 2.5 ppb) (0.05 & 0.0025 ppm in sample, n = 6)
Recovery	80.7% - 96.6% at 1 ppb (NDIPA & NDPA were not detected, recovery 0%) (n = 2); 83.1% -124.8% at 5 ppb (n = 2)
Matrix effect	ME 0%) (n = 2); 26.2% - 136.1% at 1 ppb (NDIPA & NDPA were not detected, 60.8% - 129.1% at 5 ppb (n = 2)

Sample Concentration: 100 mg/mL

Nitrosamine Analysis in Other API

This section deals with analysis of nitrosamine impurities in different API

- Quantitative Analysis Of NDMA In Ranitidine Drug Substance
- Quantitative Analysis NMBA In Tenofovir Disoproxil Fumarate Using LCMS-8060

For analysis of nitrosamines in any other API, please contact us here

Quantitative Analysis Of NDMA In Ranitidine Drug Substance Using LCMS-8045

Levels of NDMA in ranitidine may increase to unacceptable levels over time and when exposed to higher than room temperatures. Based on these findings, ranitidine is withdrawn from US markets.

In this application we analyze trace levels of NDMA in ranitidine drug substance using LCMS-8045 using methodology described by US FDA.

Representative Data

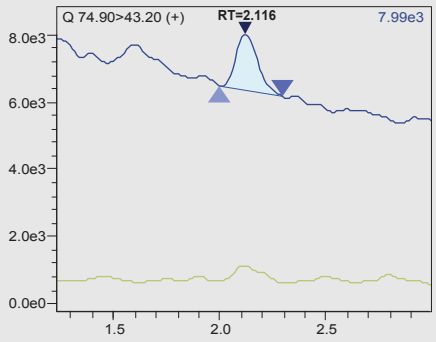

Figure 28: MRM chromatogram NDMA at LOQ level

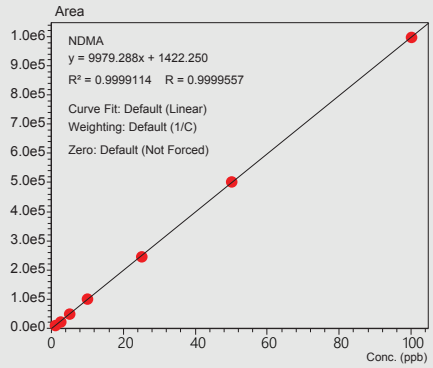

Figure 29:Calibration curve for NDMA

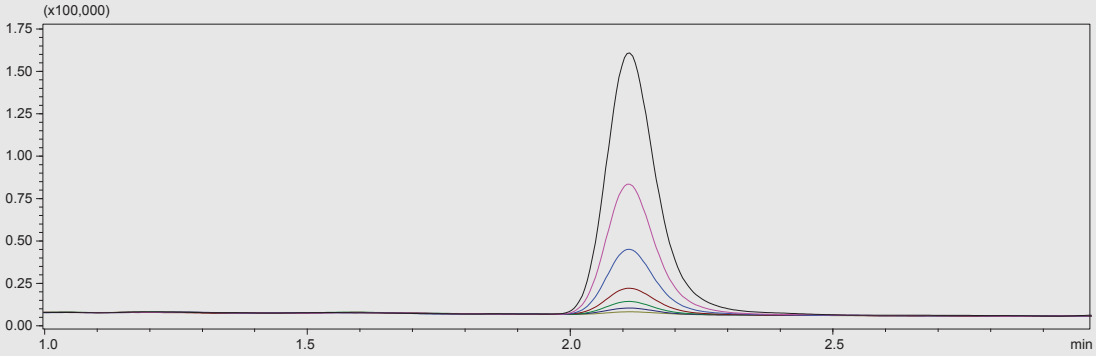

Figure 30: Overlay of linearity standards for NDMA (7 points)

Performance Report

Table 11: Experimental results for analysis NDMA in ranitidine drug substance

Parameter	Value
Limit of Detection achieved	0.3 ppb (0.01 ppm for sample)
Limit of Quantitation achieved	1 ppb (0.033 ppm for sample)
Linearity range	1.0 - 100 ppb (0.033 – 3.33 ppm for sample)
Repeatability	7.8% at 1 ppb (LOQ level, 0.033 ppm in sample, n = 6), 2.54% at 10 ppb (spec level, 0.33 ppm in sample, n =6))
Recovery	93.6% at spec level (0.33 ppm in sample, n = 3)

Sample Concentration: 30 mg/mL

Quantitative Analysis NMBA In Tenofovir Disoproxil Fumarate Using LCMS-8060

This application deals with high sensitivity analysis of NMBA in tenofovir drug substance.

Column used: Shim-pack GISS C18 (4.6 mm x 250 mm, 5 µm; P/N: 227-30061-07)

Representative Data

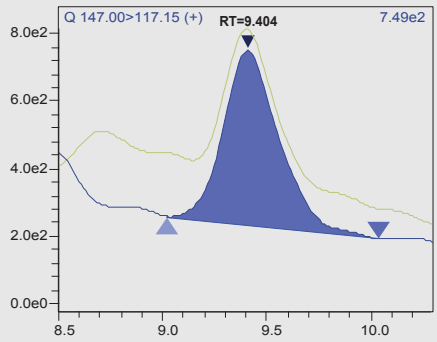

Figure 31: MRM chromatogram NMBA at LOQ level

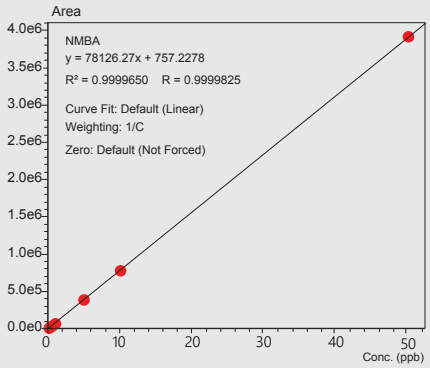

Figure 32: Calibration curve for NMBA

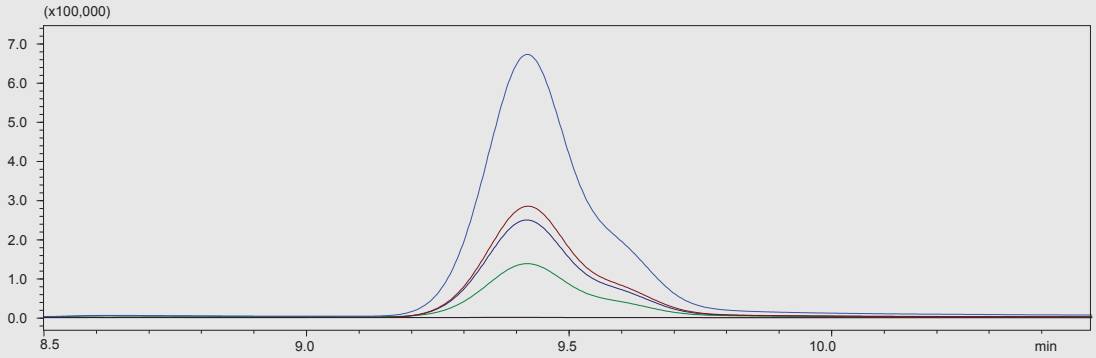

Figure 33: Overlay of linearity standards for NMBA (7 points)

Performance Report

Table 12: Experimental results for analysis NMBA in Tenofovir disoproxil drug substance

Parameter	Value
Limit of Detection achieved	0.02 ppb (0.0004 ppm for sample)
Limit of Quantitation achieved	0.1 ppb (0.002 ppm for sample)
Linearity range	0.05 - 50 ppb (0.001 – 1 ppm for sample)
Repeatability	5.7% at 0.1 ppb (n = 3)
Recovery	83% at 0.1 ppb (0.002 ppm in sample, n = 3)

Sample Concentration: 50 mg/mL

Nitrosamine Analysis in Residual Solvents

This section deals with different approaches for assessment of nitrosamines in various solvent systems

- Quantitative Analysis Of Nitrosamines In 5 Different Solvents Using GCMS-TQ8040 NX
- Quantitative Analysis Of 8 Nitrosamine Impurities In 12 Different Solvents Using LCMS-8045

Quantitative Analysis Of Nitrosamines In 5 Different Solvents Using GCMS-TQ8040 NX

Recovered materials such as solvents, reagents, and catalysts pose a risk of nitrosamine impurities due to the presence of residual amines (such as trimethylamine or diisopropylethylamine). Quenching step (i.e., nitrous acid used to decompose residual azide) can be a potential source for introduction of nitrosamines during solvent recovery process.

In this application we analysed NDMA, NDEA, NEIPA, NDIPA and NDBA in DMF (HS grade), IPA, DMF, DMF-IPA and DMF-Water. Solvent samples were either injected as such or diluted to 10,000 times in DCM. These samples were analysed using Shimadzu GCMS-TQ8040 NX with AOC-20i Plus autosampler.

Representative Data

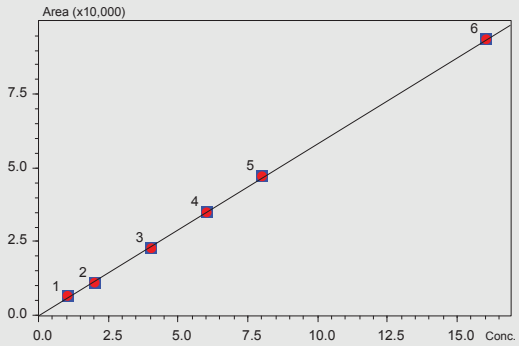

Figure 34: Calibration curve for NDMA

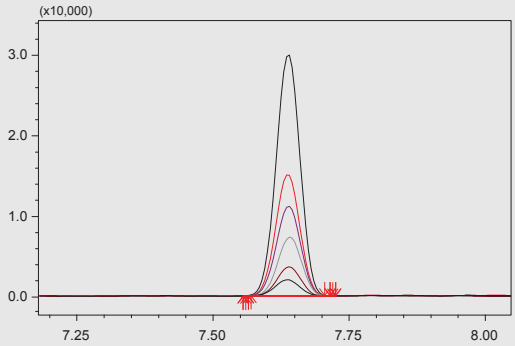

Figure 35: Chromatographic overlay of linearity levels of NDMA

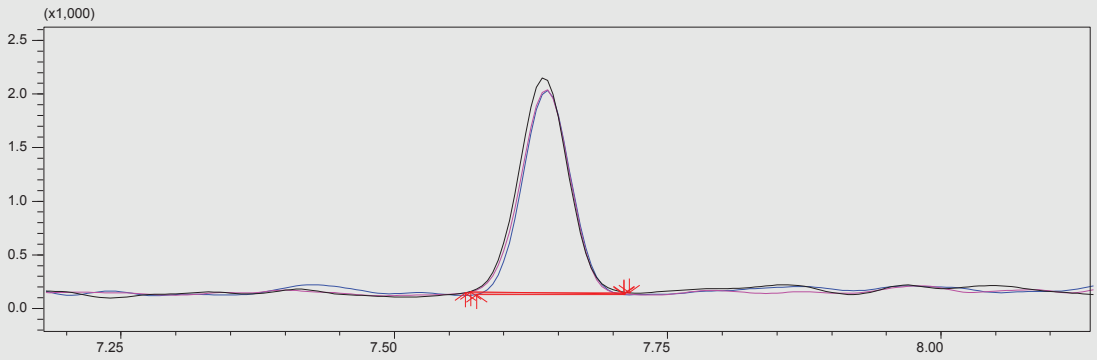

Figure 36: Top chromatographic overlay of LOQ (n=3, NDMA)

Performance Report

Table 13: Experimental results for analysis of 5 nitrosamines in recovered solvents

Parameter	Value
Limit of Detection achieved	0.3 ppb (NDMA, NDEA, NEIPA & NDIPA) 0.6 ppb (NDBA)
Limit of Quantitation achieved	1.0 ppb (NDMA, NDEA, NEIPA & NDIPA) 2.0 ppb (NDBA)
Linearity range	1.0 to 16.0 ppb (NDMA, NDEA, NEIPA, NDIPA & NDBA) 2.0 to 32.0 ppb (NDBA)
Repeatability	0.3% – 4.1% at 1.0 ppb & 2.0 ppb (LOQ level) (n = 3)

Quantitative Analysis Of 8 Nitrosamine Impurities In 12 Different Solvents Using LCMS-8045

8 nitrosamines, namely NDMA, NMBA, NDEA, NEIPA, NDPA, NDIPA, NMPA and NDBA were analysed in different solvent systems using internal standard (stable labelled isotopes) method of quantitation.

Samples were prepared based on the solvent properties and three different sample pretreatment methods were employed-direct method, evaporator method and dilution method.

Click here

Column used: Shim-pack GIST C18-AQ (4.6 mm x 100 mm, 3.0 um)

Table 14: Tabulation of boiling points and method of sample preparation

No.	Solvents	Boiling Points (ºC)
1	Dichloromethane(DCM)	40
2	Acetone	56
3	Chloroform	61
4	Methanol	65
5	Ethyl Acetate	77
6	Ethanol	78
7	Acetonitrile	82
8	Isopropanol	82
9	Water	100
10	Toluene	111
11	Dimethyl Formamide (DMF)	153
12	Dimethyl Sulfoxide (DMSO)	189

Evaporation Direct injection Dilution

Representative Data

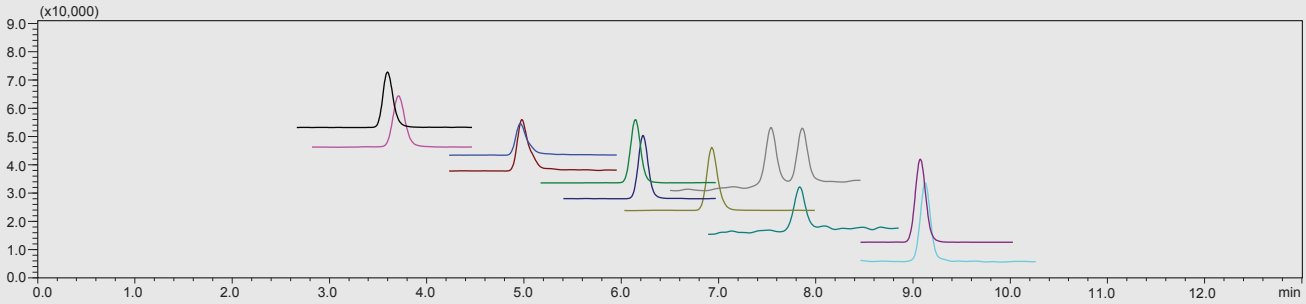

Figure 37: Representative MRM chromatogram

Performance Report

Table 15: Tabulation of LOQ values in ppm

No.	Solvents\NSA	NDMA	NMBA	NDEA	NIEPA	NDPA	NDIPA	NMPA	NDBA
1	Water	0.001	0.001	0.001	0.001	0.002	0.003	0.010	0.002
2	Methanol	0.005	0.005	0.005	0.005	0.005	0.005	0.010	0.005
3	Acetonitrile	0.005	0.005	0.005	0.005	0.005	0.005	0.010	0.005
4	IPA	0.005	0.010	0.005	0.005	0.005	0.005	0.010	0.005
5	Ethanol	0.005	0.005	0.005	0.005	0.005	0.005	0.010	0.005
6	DMSO	0.005	0.005	0.005	0.005	0.005	0.005	0.010	0.005
7	DCM	0.005	0.005	0.005	0.005	0.005	0.005	0.010	0.005
8	Acetone	0.005	0.005	0.005	0.005	0.010	NA #	0.010	0.005
9	Chloroform	0.005	0.005	0.005	0.005	0.005	0.010	0.010	0.005
10	Ethyl Acetate	0.005	0.005	0.005	0.005	0.005	0.005	0.010	0.005
11	Toluene	0.010	0.010	0.010	0.010	0.010	0.010	0.010	0.010
12	DMF	NA	0.010	0.010	0.010	0.010	0.010	0.010	0.010

 # NSA was found to be present, but cannot be calculated

Table 16: Tabulation of % Recovery of nitrosamines from different solvent

No.	Solvents\NSA	NDMA	NMBA	NDEA	NIEPA	NDPA	NDIPA	NMPA	NDBA
1	Water	101.0	102.0	101.4	101.0	99.5	100.4	100.7	100.7
2	Methanol	101.5	98.6	100.4	98.4	103.8	110.0	106.6	94.2
3	Acetonitrile	93.0	110.8	110.5	111.6	112.1	105.6	57.4	93.4
4	IPA	115.8	92.7	116.2	107.3	98.0	80.8	99.4	95.8
5	Ethanol	118.3	108.2	112.0	106.7	97.8	91.9	101.8	101.3
6	DMSO	99.7	96.0	108.8	90.5	94.9	99.7	66.0	93.5
7	DCM	88.3	96.9	100.0	108.4	105.6	94.1	46.2	95.5
8	Acetone	88.4	91.4	95.8	99.9	94.4	NA	50.9	95.4
9	Chloroform	67.8	87.4	93.3	95.8	93.5	118.3	35.1	107.4
10	Ethyl Acetate	76.3	91.3	96.4	106.8	64.5	65.1	40.1	95.5
11	Toluene	106.4	112.4	101.3	112.9	98.8	162.5	233.9	103.0
12	DMF	NA	104.7	111.0	101.4	80.0	205.9	285.3	103.1

Evaporation Direct injection Dilution

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- GCMS-TQ8050 NX
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GCMS-TQ8050 NX with HS-20

Shimadzu's Ultra High Sensitivity Triple Quadrupole GC-MS with Headspace autosampler for Pharma Impurity Analysis

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GCMS-TQ8050 NX with HS-20

Equipped with a new, highly efficient detector and three forms of noise reduction technologies, the GCMS-TQ8050 NX is capable of performing unprecedented quantitative analyses of ultra-trace amounts, down to femtogram level.

Moreover, with its ultra-high sensitivity and high mass resolution, a whole new realm of quantitative analysis is offered, with reduced long –term operational costs and greater uptimes along with HS-20 headspace autosampler.

UFMS™ Throughput

UFMS ensures no compromise in sensitivity even when you run applications at maximum speed. This allows you to perform both Targeted screening and Quantitation with the same confidence. The combination of multiple injection modes (liquid or headspace) and acquisition modes (MRM, SIM or Scan) are designed to cater to all your impurity analysis needs. This can be performed with maximum ease and flexibility.

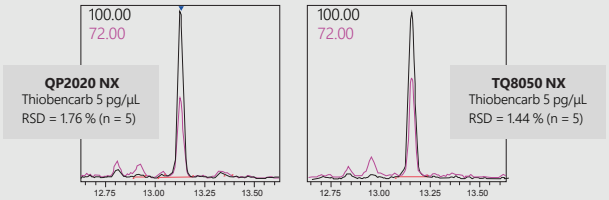


Figure 38: MSMS – two instruments in one. Use GC-MS and GC-MS/MS functions interchangeably with no compromise in sensitivity and selectivity

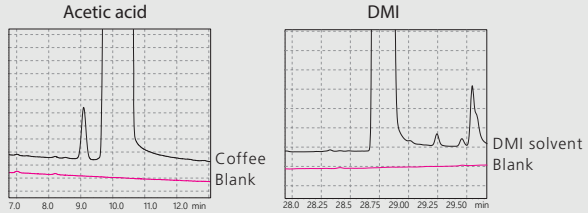


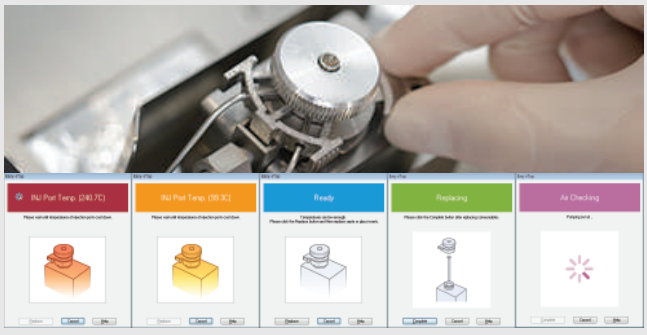
Figure 39: Pink chromatograms indicate a blank run (pure water) right after an analysis of coffee aroma – carryover is negligible!

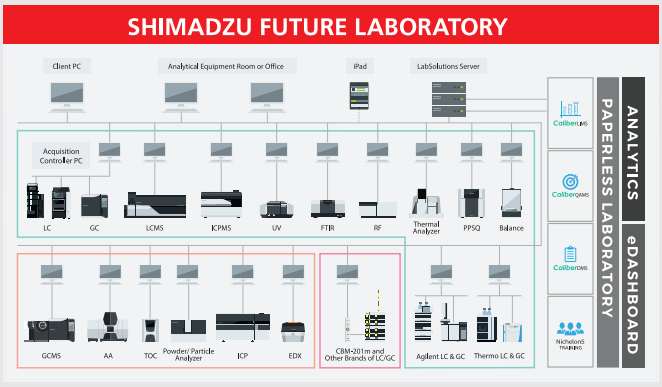
Minimal carryover

In high throughput labs, where time is money, you don't want to spend time doing trouble-shooting and re-analysis. One of the key contributors to this trouble is the transfer line between headspace and GCMS. Shimadzu HS-20 is equipped with not only the shortest but also most inert transfer line. This means near zero carryover even for very polar compounds like triethylamine.

Minimal Maintenance

In rush of work, we need our instruments to make life easy for us. Regular tasks like maintaining the injection port or installing column are made super easy and hassle free using ClickTek™ and Easy sTop function. Active Time Management™ helps plan work schedules by giving clear estimates of autotuning, batch completion, time management during maintenance etc.





Regulatory Compliance

Rest assured that data integrity and authenticity is maintained in accordance with industry regulation norms such as FDA 21 CFR Part 11. Your data is always backed up and protected from unauthorised access. We continuously provide enhanced solutions and upgrades to keep up with regulators direction.

LCMS-8045/
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What's more - You can always upgrade LCMS-8045 to LCMS-8060NX!

UFscanning™ & UF-MRM™ with High Sensitivity

Equipped with a heated ESI probe, the LCMS-8045 has the highest sensitivity in its class. It is capable of providing accurate and stable data over long periods of time. The inclusion of Shimadzu's ultra-high-speed high-voltage power supply enables the world's fastest scan speed (30,000 u/s) and polarity switching time (5 ms). High-speed acquisition benefits the laboratory by reducing run times for increased throughput, and also shortens method development time.

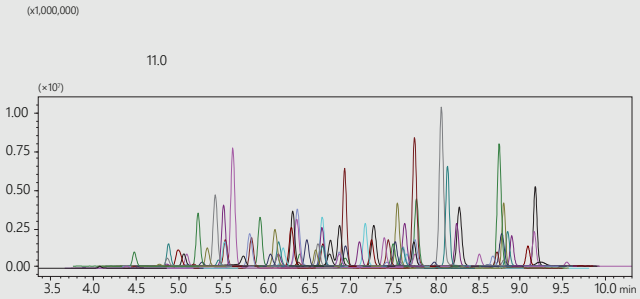


Figure 40: MRM chromatogram of 100 pesticides (0.02ppm) in crops

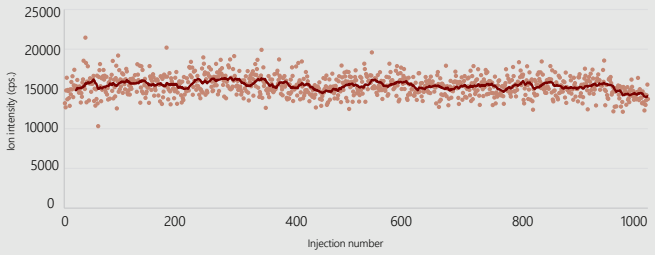


Figure 41: Analytical results of repeated injections of metabolites in urine

Superior Robustness

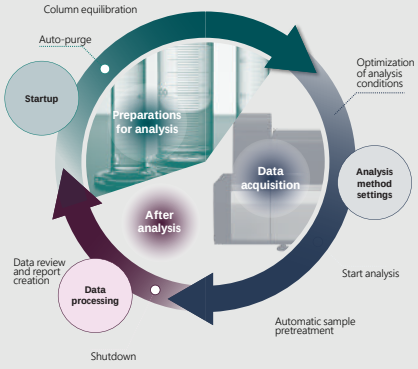
The LCMS-8045 is designed to be robust. The heated ESI probe, high-temperature heating block, heated desolvation line, drying gas, and focusing optics all act to maximize sensitivity and minimize contamination. This means long periods of continuous operation in the laboratory with reliable data collection.

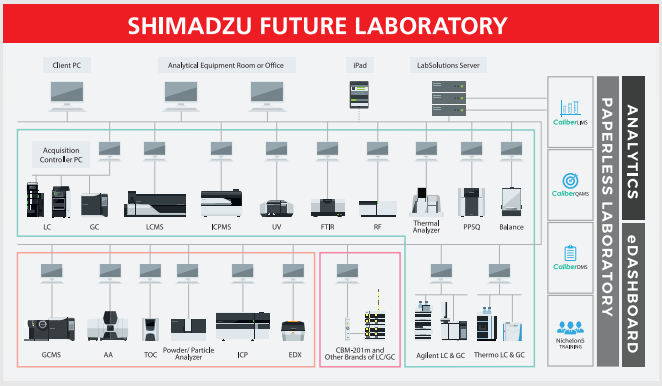
Building up on these features, LCMS-8060NX boasts of 6 times more sensitivity and unsurpassed robustness owing to newly designed IonFocus™ unit and re-engineered ion guide system.

Easy Workflow

LabSolutions LCMS features an intuitive user interface. It offers the latest features designed to enhance laboratory productivity and streamline workflows with complete compliance

Analytical Intelligence of LCMS-8060NX with the Nexera UHPLC improves the efficiency of your entire workflow and maximizes laboratory throughput.





Regulatory Compliance

Simple and easy to use workflows are inherently designed to deliver compliance. Your data is always backed up and protected from unauthorized access. We continuously provide enhanced solutions and upgrades and keep up with regulators direction.

LCMS-9030

The LCMS-9030 quadrupole time-of-flight (Q-TOF) mass spectrometer integrates the world's fastest and most sensitive quadrupole technology with TOF architecture- making it a perfect solution for both qualitative assessment and quantitative determination of pharmaceutical impurity

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LCMS-9030

A product of Shimadzu's engineering DNA, speed and effortless performance enable the LCMS-9030 to address qualitative and quantitative challenges with genuine confidence and ease. The LCMS-9030 uses newly patented technologies to deliver both high resolution and accurate mass-attributes essential for confident formula assignment and unknown identification.

Excellence in Mass Measurement Accuracy (MMA)

Mass measurement accuracy (MMA) is the key performance attribute underlying all application fields using high- resolution accurate-mass (HRAM) spectrometers. The LCMS-9030 delivers the MMA needed for high-confidence identification of unknown compounds with an unprecedented level of stability. New technologies implemented in the Intelligent Temperature Control System and the UF-FlightTube makes it possible to accurately offset the changes occurring to both internal and external environments.

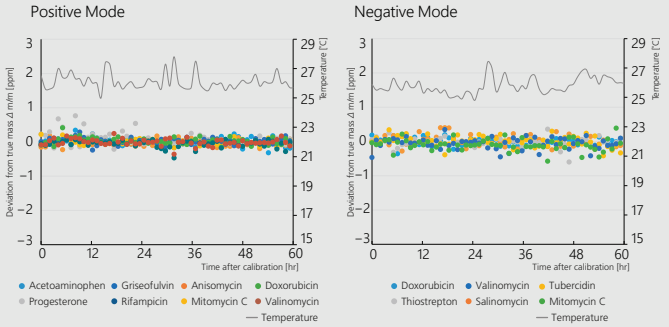

Figure 42: Graphical representation of measured accurate masses of all compounds

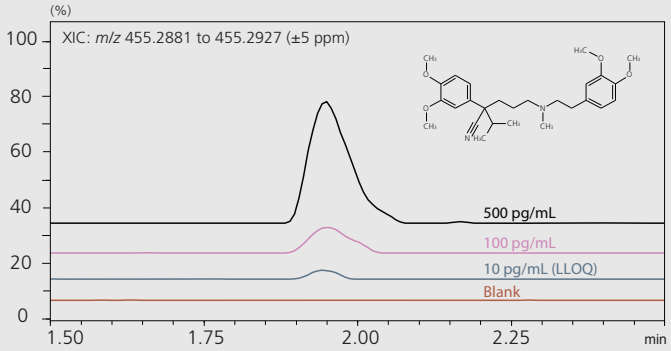

Figure 43: XIC of Verapamil [M + H]+ (exact mass 455.29042)

High MMA Over Wide Concentrations

The LCMS-9030 breaks new ground for quantitative analysis not only by its high sensitivity but also by the selectivity afforded by high MMA over a wide range of concentrations. Genuine ion statistics ensure that all measurements throughout the peak elution result within a narrow m/z window of the extracted ion chromatogram (XIC). Moreover, stability of MMA allows the same XIC setting to be comfortably used for series of analyses.

Same MMA Across Acquisition Modes

MS/MS spectra are a key tool for structural elucidation of unknown compounds, and ease of data interpretation is directly dictated by the MMA of MS/MS acquisition. This makes the LCMS-9030 an ideal instrument for structural analysis as its MS/MS mode achieves equally high MMA as the MS mode, thanks to the collision cell technologies that generate high-abundance fragment ions.

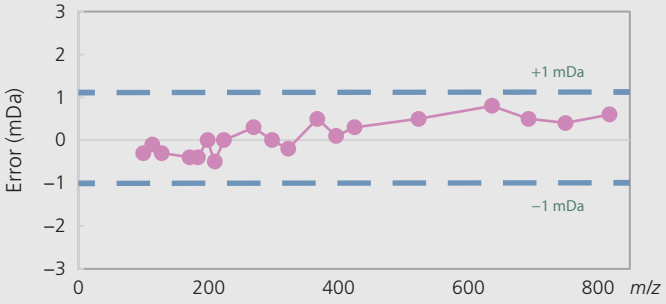

Figure 44: Mass Error of Product Ions

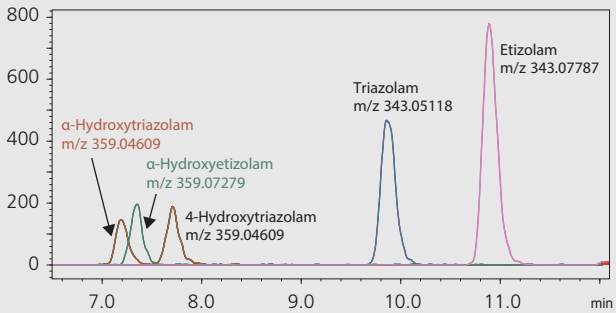

Figure 45: LCMS-9030 Mass Chromatogram of Etizolam, Triazolam, and Metabolites Spiked at 10 ng/mL in Whole Blood.

HRAM for Selective Detection of Isobaric Compounds

The LCMS-9030 produces the high-resolution accurate mass data needed to distinguish between compounds having the same nominal mass. Even with incomplete chromatographic separation isobaric compounds can be detected as an isolated ion without cross talk.

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