Overcome N-Nitrosamine Analysis Challenges with Chromatography and Mass Spectrometry Techniques

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Agenda

- Why is nitrosamine assessment necessary?
- Origin of nitrosamines
- Evaluation of nitrosamines
  - FDA evaluation
    - High-resolution mass spectrometry
    - Nominal mass spectrometry: QTRAP system
  - SCIEX solution

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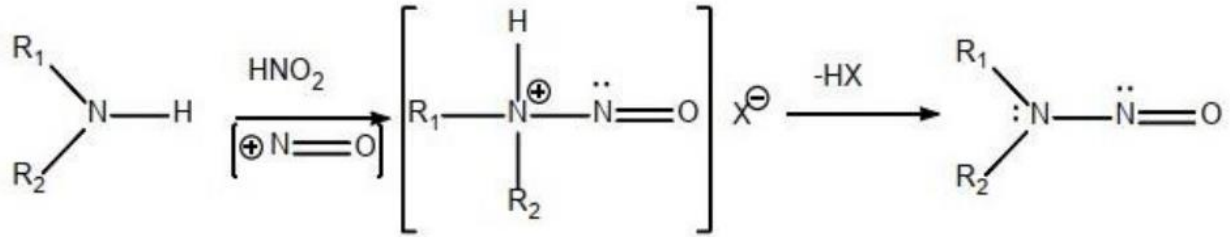
What are N-nitrosamines?

- They are molecules containing a nitroso functional group
- They are of concern because their impurities could be carcinogenic to humans
- Their presence in medicines is considered unacceptable



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Why is nitrosamine assessment necessary?

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Why is nitrosamine assessment necessary?

- Nitrosamines are chemical compounds that have been determined in animal studies to cause cancer in humans
- US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines require screening limits of 26.5 ng/day or 96 ng/day, depending on the nitrosamine
- In February 2021, European Pharmacopoeia Comission published a new chapter (chapter 2.5.42) that proposes new procedures for the analysis of N-nitrosamines in active substances
- The new chapter focuses on 5 monographs: valsartan, losartan potassium, candesartan cilexetil, irbersartan and olmesartan medoxomil
  - The proposed procedures cover N-nitrosamines: NDMA, NDEA, NDBA, NMBA, NDiPA, NEiPA and NDPA

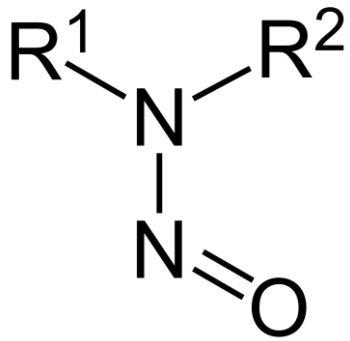

Figure 1. Structure of a nitrosamine

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- In 2018, the presence of nitrosamines (including NDMA) was detected in several blood pressure control drugs known as sartans
- Subsequently, nitrosamines were detected in lots of ranitidine (a drug for the treatment of gastritis and stomach ulcers), and as a result, it was withdrawn from the Mexican market by COFEPRIS, the Mexican ministry of health
- In 2020, the presence of nitrosamines was found in metformin, causing COFEPRIS to add it to the list of drugs that must be tested to rule out the presence of nitrosamines
- New monographs for pharmaceutical requirements were mandate by FEUM, the pharmaceutical standard issues by COFEPRIS

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Nitrosamines - limits

FDA – CONTROL OF NITROSAMINE IMPURITIES IN HUMAN DRUGS

Table 1. AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

[1] The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA,NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure. Appendix B includes a description of the AI derivation for NDMA, which is an example of how FDA applied ICH M7(R1) to set a limit.

[2] The conversion of AI limit into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

These limits are applicable only if a drug product contains a single nitrosamine. If more than one of the nitrosamine impurities identified in Table 1 is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day (the AI for the most potent nitrosamines) based on the maximum daily dose (MDD), the manufacturer should contact the Agency for evaluation. For drug products with an MDD of less than 880 mg/day, a recommended limit for total nitrosamines of 0.03 ppm is not more than 26.5 ng/day and is considered acceptable. For drug products with an MDD above 880 mg/day, the limit for total nitrosamines should be adjusted so as not to exceed the recommended limit of 26.5 ng/day

https://www.fda.gov/media/141720/download

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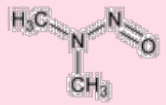
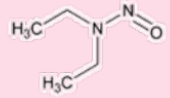
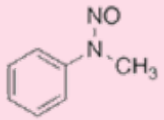
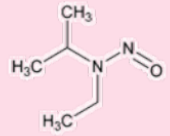
Common Name and Chemical Name	Acronym	CAS #	Structure	Chemical Formula	Acceptable Intake Limits (ng/day)
Nitrosodimethylamine; *N*-Methyl-*N*-nitrosomethanamine	NDMA	62-75-9		$C_2H_6N_2O$	96
Nitrosodiethylamine; *N*-Ethyl-*N*-nitrosoethanamine	NDEA	55-18-5		$C_4H_{10}N_2O$	26.5
N-nitrosomethylphenylamine	NMPA	614-00-6		$C_7H_8N_2O$	26.5 (USFDA) / 34.5 (EMA)*
Nitrosoisopropyethylamine; *N*-Ethyl-*N*-nitroso-2-propanamine	NIPEA	16339-04-1		$C_5H_{12}N_2O$	26.5

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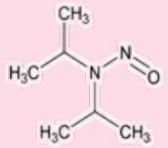
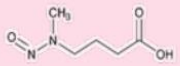
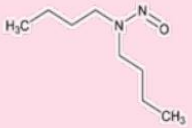
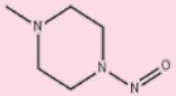
Common Name and Chemical Name	Acronym	CAS #	Structure	Chemical Formula	Acceptable Intake Limits (ng/day)
Nitrosodiisopropylamine; *N*-Isopropyl-*N*-nitrosoisopropyl-amine	NDIPA	601-77-4		$C_6H_{14}N_2O$	26.5
N-Nitroso-N-methyl-4-aminobu-tyric Acid; 4-[Methyl(nitroso)amino] butanoic acid	NMBA	61445-55-4		$C_5H_{10}N_2O_3$	96
Nitrosodibutylamine; *N*-Butyl-*N*-nitroso-1-butanamine	NDBA	924-16-3		$C_8H_{18}N_2O$	26.5
1-methyl-4-nitrosopiperazine	MeNP	16339-07-4		$C_5H_{11}N_3O$	26.5

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Root cause of Nitrosamine contaminated

- Sodium nitrite ($NaNO_2$)
- Contaminated Solvent or reagents
- Recycled solvents
- Contaminated intermediate
- Manufacturing process
- Storage process

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Evaluation of nitrosamines

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System Components

1. Dilution

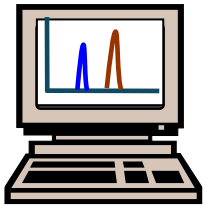
2. The liquid sample is introduced into the ionization source

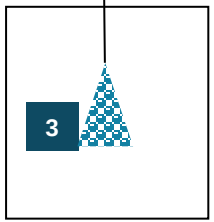
3. The molecules of interest are converted into ions in the source, in the gas phase

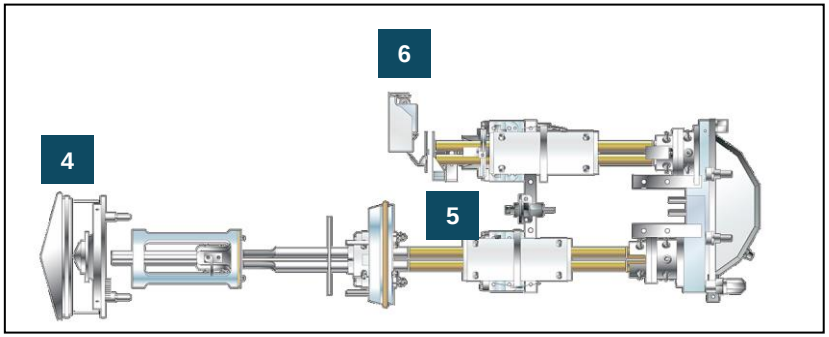
4. Under the action of an electric field and a pressure gradient, the ions pass through the interface

5. Ions can be transmitted, selected, or fragmented in quadrupoles

6. The ions are detected, then the signal is transmitted to the workstation which displays the data in the form of a mass spectrum







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Components of MS

- ✓ API: ESI
  APCI

- ✓ Quadrupole
- ✓ Time of flight (TOF)
- ✓ Ion trap (IT)

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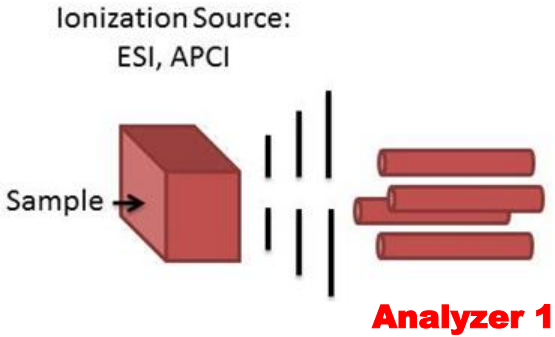
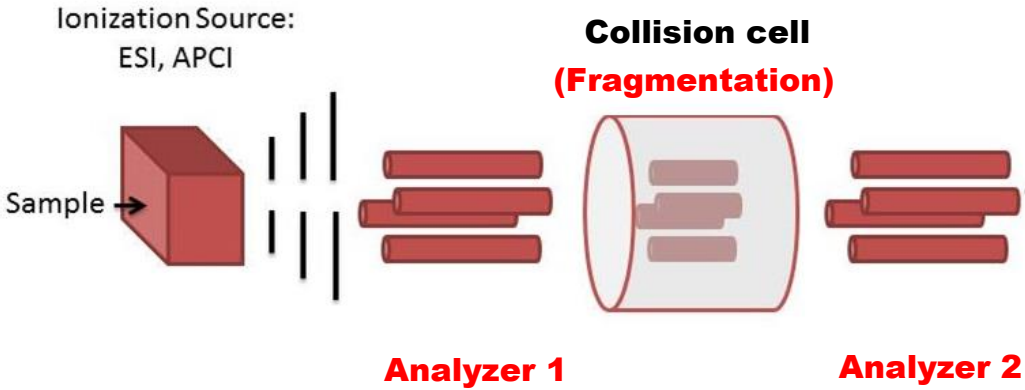
LC-MS VS LC-MS/MS

LC-MS



LC-MS/MS



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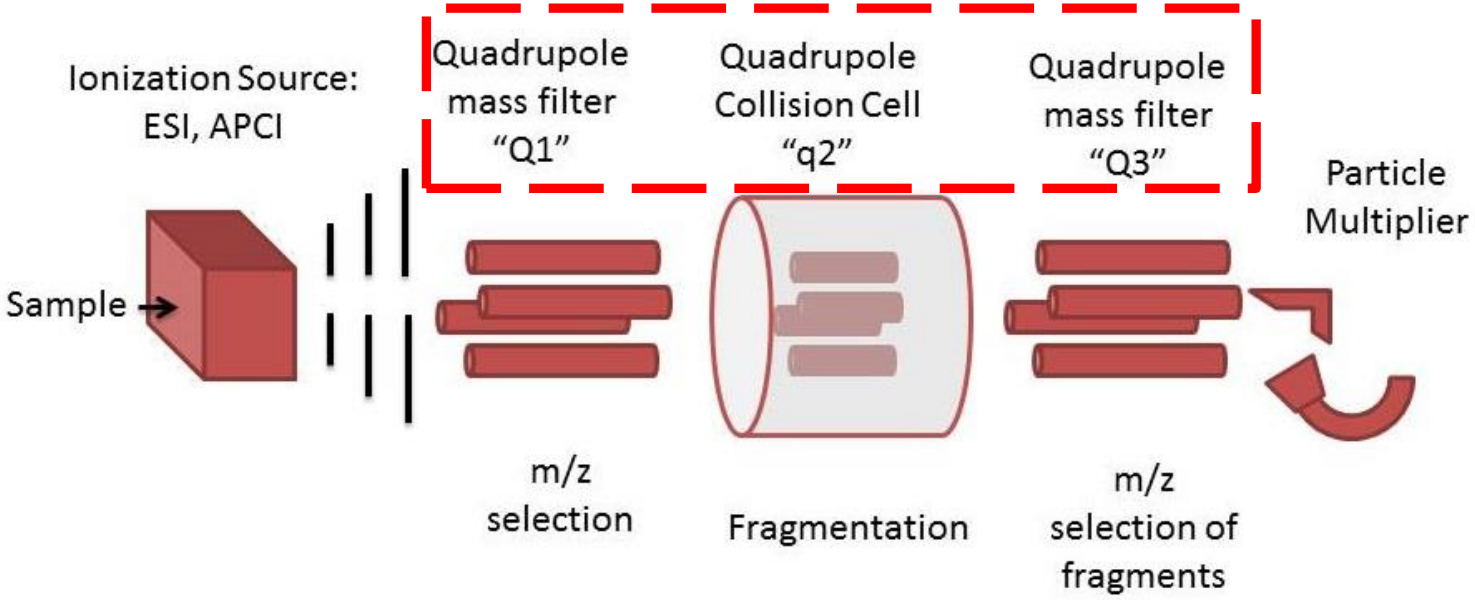
Triple Quadrupole Mass Spectrometer; QQQ



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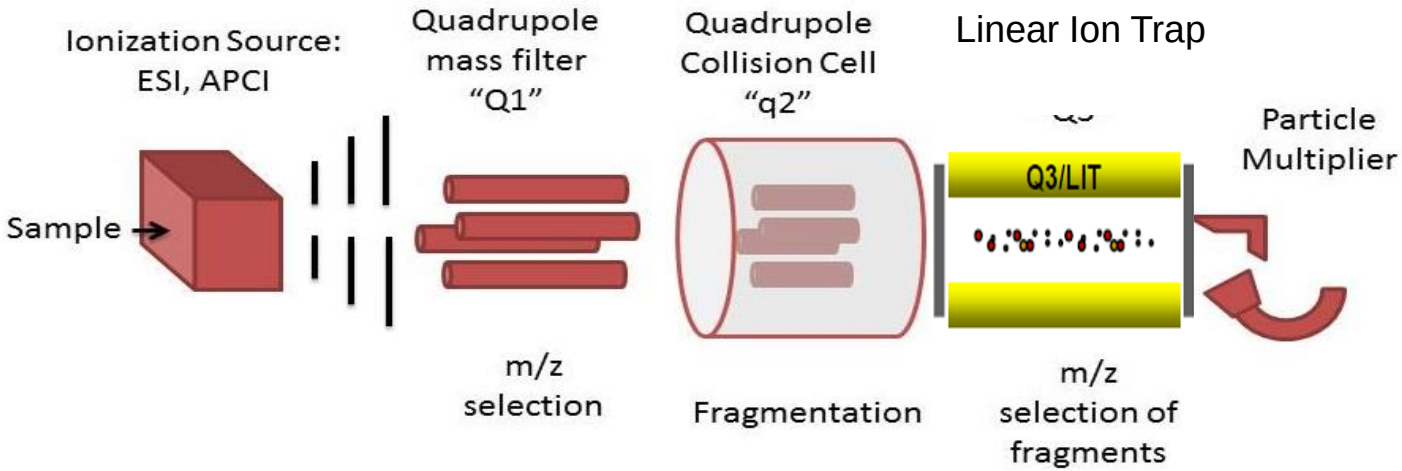
Triple Quadrupole Linear Ion Traps Mass Spectrometer; QTRAP



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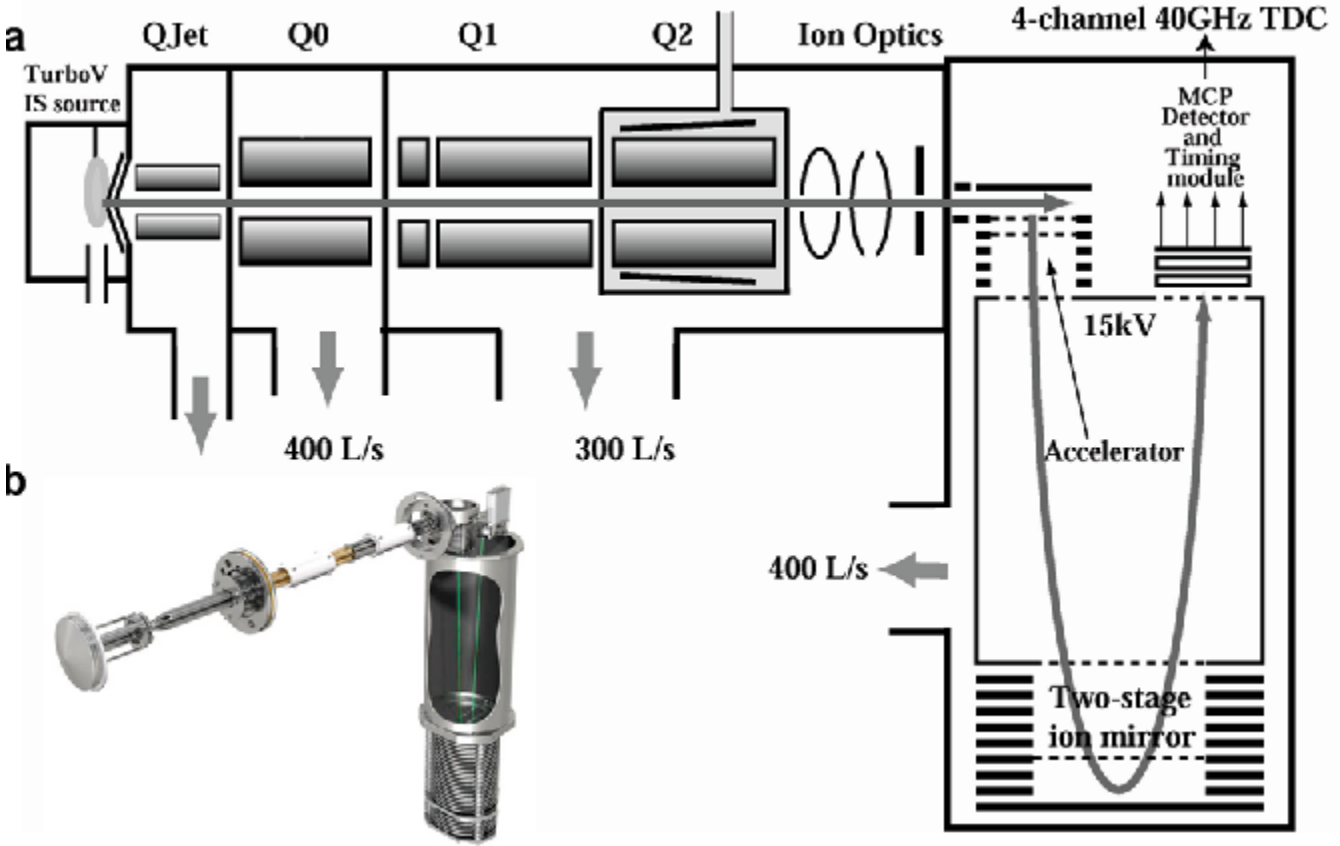
Quadrupole Time of Flight (QTOF)



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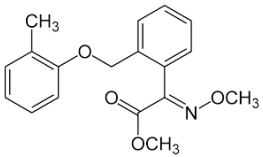
Advantages of high-resolution mass spectrometry

- QTOF can distinguish between compounds of similar mass
  - X500R = 30,000 resolution, 300 Da compound, ∆m = 0.01 Da

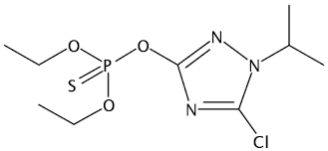
- QTOF can accurately measure molecular weight to *several decimal places*
  - 300 Da compound, 5 ppm mass error = 0.0015 Da

High-resolution mass spectrometry
can distinguish these pesticides!

Kresoxim-methyl
$C_{18}H_{19}NO_4$
Mass = 313.1214 Da



Isazophos
$C_9H_{17}ClN_3O_3PS$
Mass = 313.0417 Da



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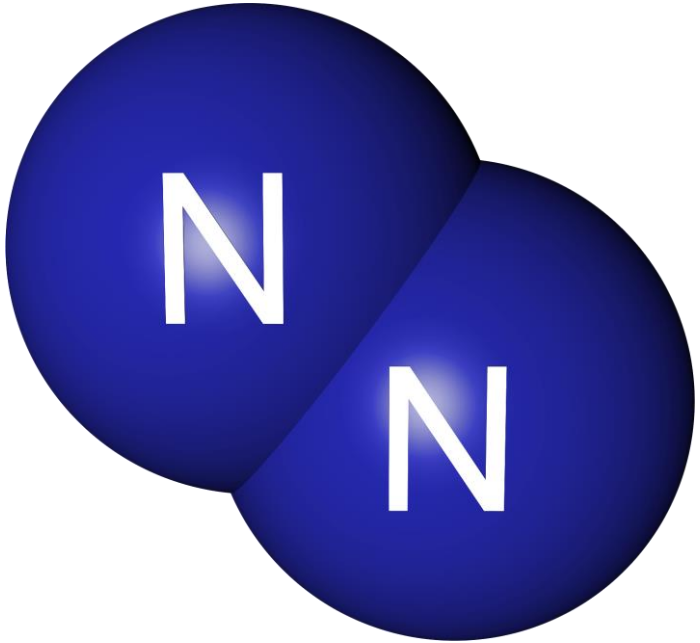
FRAGMENTATION



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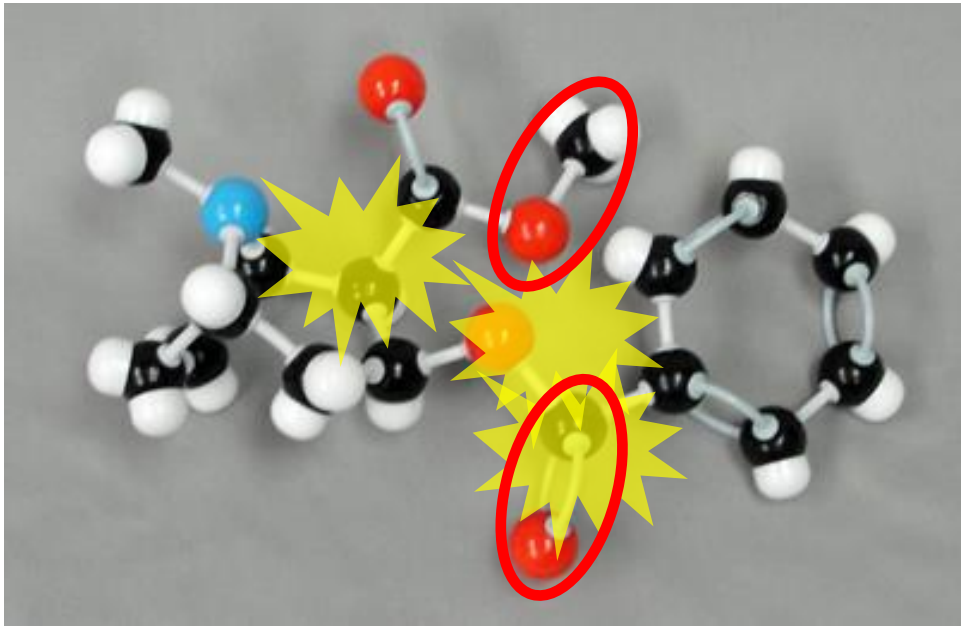
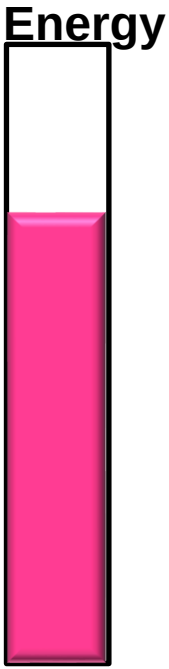
Fragmentation





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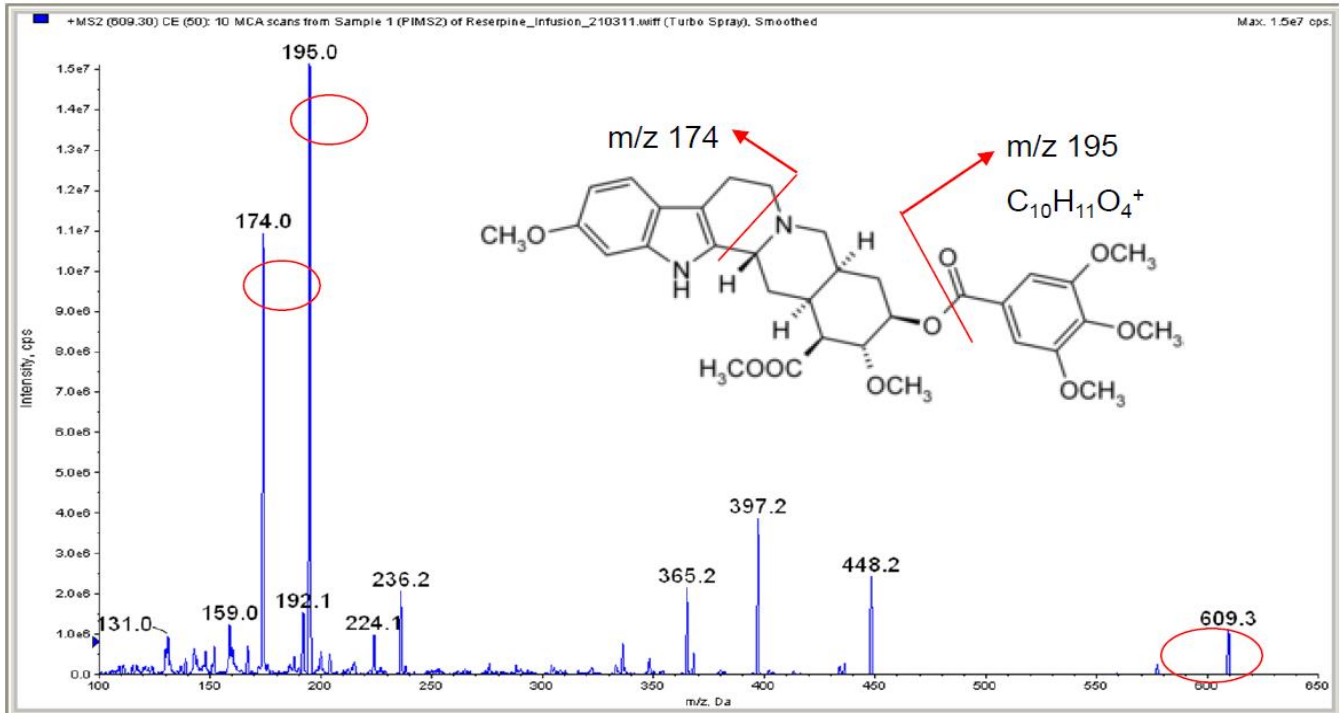
Example : Reserpine MSMS



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Evaluation: FDA

Triple quadruple evaluation

SCIEX Triple Quad 6500+ and QTRAP 6500+ systems

SCIEX 7500 system

High-resolution evaluation

X500 QTOF system

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High resolution systems

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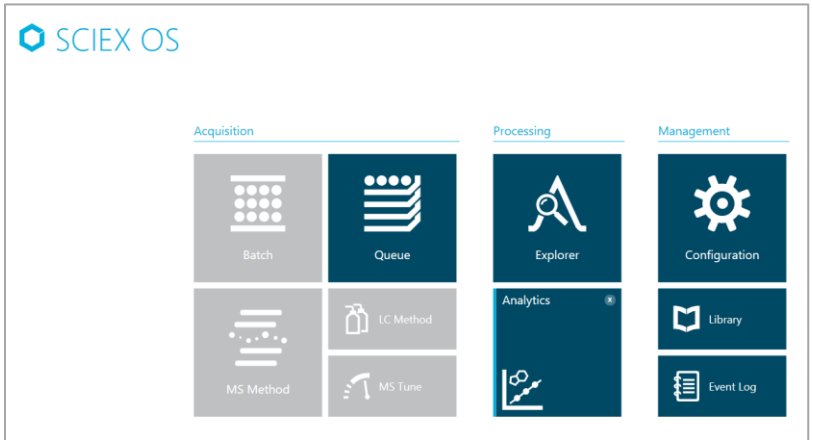
Search for unknowns

BATCH-BATCH INSPECTION USING LC-HRMS

- Characteristics of the X500 QTOF system
- Reliable, easy to calibrate
- SWATH acquisition
- SCIEX OS software



X500R QTOF system

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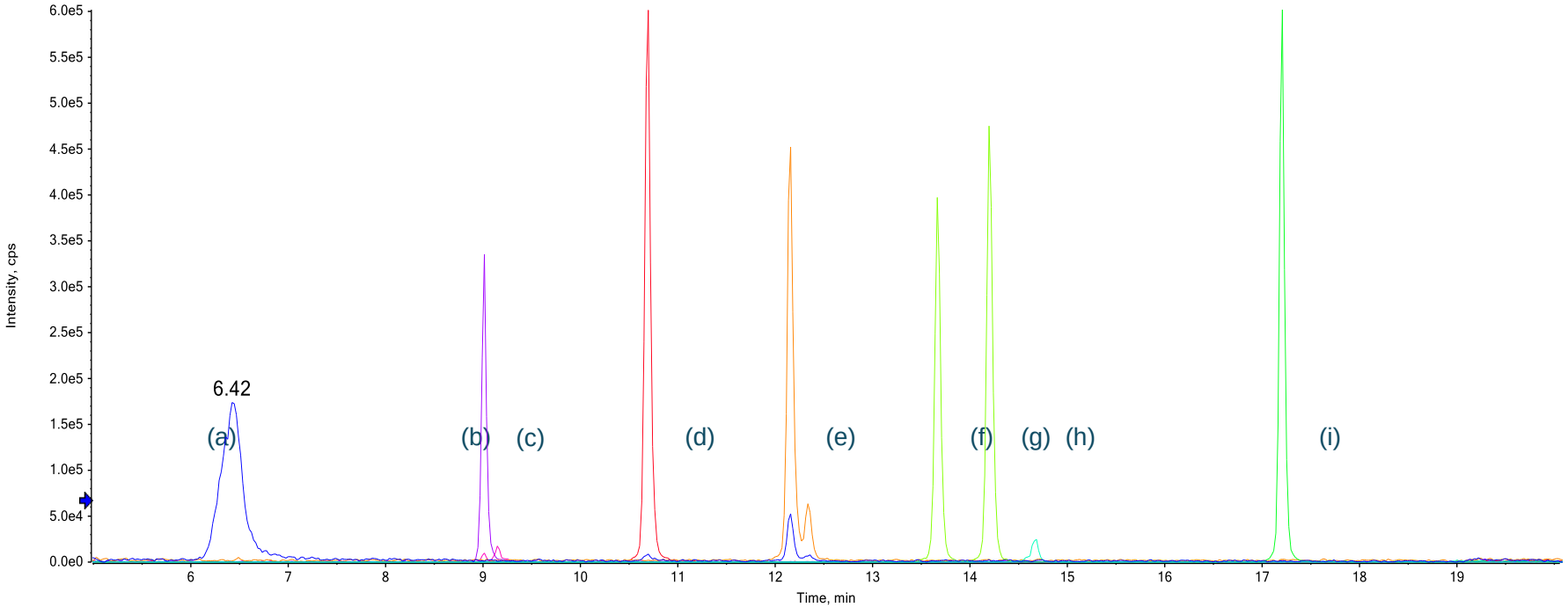
Chromatogram of metformin analysis



(a) NDMA; (b) NMO; (c) NMBA; (d) NDEA; (e) NEIPA; (f) NDIPA; (g) NDPA; (h) NMPA; (i) NDBA

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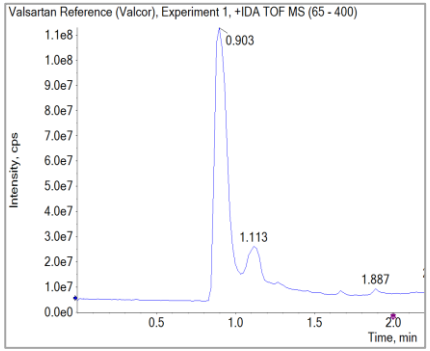
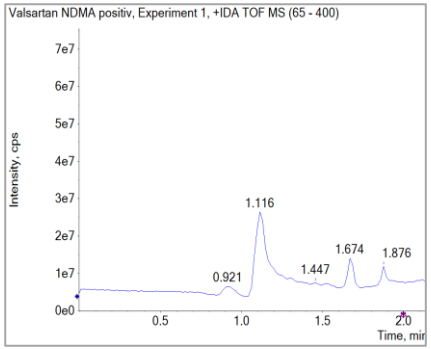
Search for unknowns

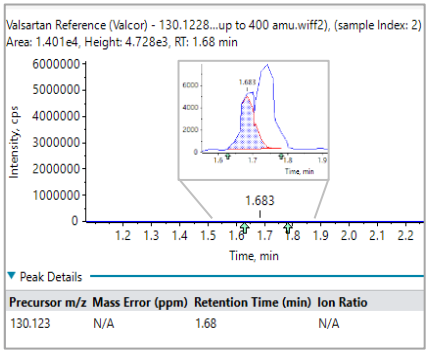
BATCH-BATCH INSPECTION USING LC-HRMS

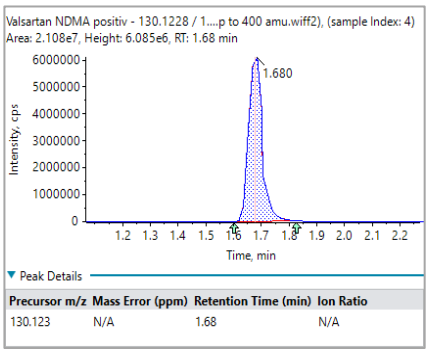
REFERENCE

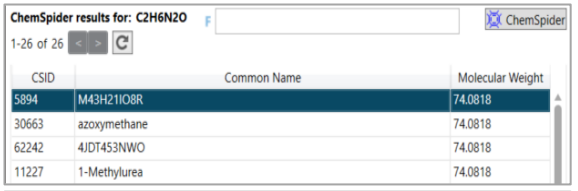
SAMPLE

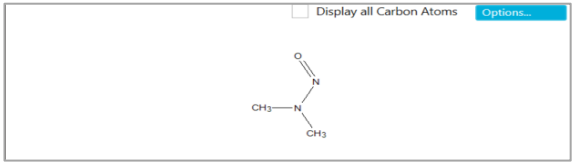


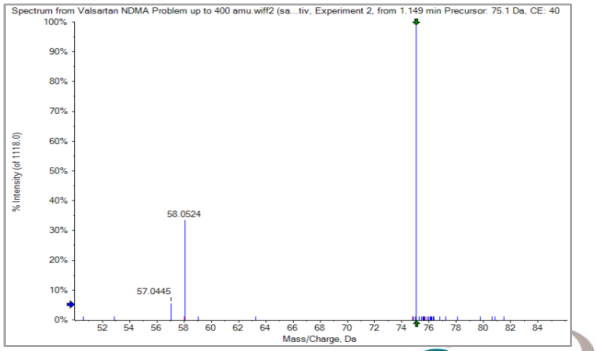












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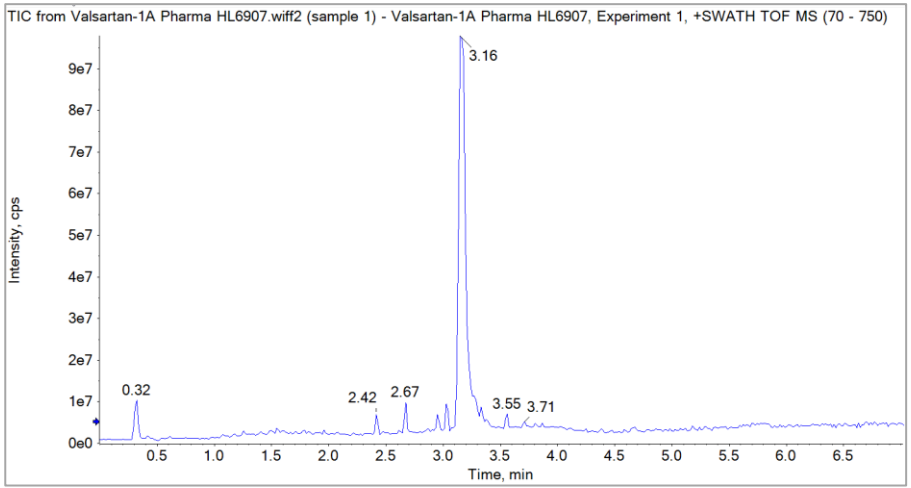
Search for unknowns using SWATH acquisition

ELECTROSPRAY IONIZATION (ESI)



Index	Component Name	Expe... RT	Area	Height	Retenti... Time	Precur... Mass	Area Ratio of comparison
6272	130.1221 / 1.97	1.97	1.679e6	5.851e5	1.97	130.122	1666.100
6479	323.1619 / 2.19	2.19	4.929e4	1.740e4	2.19	323.162	146.070
9617	336.2512 / 3.87	3.87	2.349e5	4.805e4	3.87	336.251	91.827
7885	456.2013 / 2.96 [M+Na]+	2.96	3.012e5	1.061e5	2.97	456.201	90.882
9906	282.2792 / 4.80 [M+NH4]+	4.80	6.413e5	2.075e5	4.80	282.279	86.068
7879	416.2088 / 2.96	2.96	3.588e5	1.244e5	2.97	416.209	69.522
9489	419.2271 / 3.64	3.64	5.066e5	1.790e5	3.57	419.227	52.319
7884	434.2185 / 2.96 [M+H]+	2.96	1.582e6	5.473e5	2.97	434.218	49.198
9378	308.2206 / 3.42	3.42	4.191e4	9.304e3	3.42	308.221	49.155
9495	291.1492 / 3.65	3.65	1.248e7	1.138e6	3.18	291.149	46.702
6057	711.3074 / 1.80						
9792	733.4978 / 4.43						
9841	734.5054 / 4.63						
9840	716.4942 / 4.63						
9774	733.5007 / 4.32						
5629	427.2185 / 1.51 [M+H]+						
9836	713.4772 / 4.60						
9837	731.4863 / 4.60						
6242	675.3559 / 1.93						
5887	544.2970 / 1.71						
8646	185.0808 / 3.06 [M+H]+						
5957	714.3238 / 1.74						
6173	727.3375 / 1.86						
6076	676.3737 / 1.82						
6350	720.3670 / 2.05 [M]+						
8219	345.1560 / 3.03 [2M+H]+	3.03	1.660e4	4.242e3	3.10	345.157	12.050
5268	457.2295 / 1.18 [M+H]+	1.18	4.623e4	1.209e4	1.18	457.230	11.979
6110	683.3115 / 1.83	1.83	5.807e5	3.851e4	1.84	683.311	11.730
9754	298.2741 / 4.14	4.14	2.937e4	6.957e3	4.13	298.274	11.656
6049	662.3253 / 1.80 [M+NH4]+	1.80	1.067e5	2.139e4	1.81	662.325	11.599
9120	277.2163 / 3.12 [M+H]+	3.12	1.798e4	6.098e3	3.10	277.216	11.592
5552	552.2353 / 1.47	1.47	2.808e4	4.249e3	1.46	552.235	11.527
8474	207.0916 / 2.96 [M+NH4]+	2.96	1.627e5	5.795e4	2.97	207.092	11.518
8482	313.1292 / 3.03 [M+CH3OH+H]+	3.03	3.514e4	4.059e3	3.06	313.129	11.505
5844	713.3217 / 1.67	1.67	3.649e5	2.259e4	1.63	713.322	11.442
5302	102.0909 / 1.21	1.21	5.094e4	1.781e4	1.21	102.091	11.322
8909	199.0976 / 3.12 [M+CH3OH+H]+	3.12	1.880e5	4.317e4	3.09	199.098	11.296
9206	418.2248 / 3.25 [M+H]+	3.25	3.616e7	7.820e6	3.18	418.225	11.281
6497	530.2816 / 2.20 [M+NH4]+	2.20	5.393e4	1.345e4	2.21	530.282	11.256
5357	207.0920 / 1.28	1.28	3.402e4	1.231e4	1.29	207.092	11.228
5987	458.2606 / 1.77 [M+NH4]+	1.77	1.452e5	4.560e4	1.78	458.261	11.083
5787	639.2845 / 1.62 [M+Na]+	1.62	2.959e4	1.054e4	1.62	639.284	11.006
5628	444.2451 / 1.50 [M+NH4]+	1.50	1.753e5	5.929e4	1.50	444.245	10.966
5684	249.1336 / 1.53 [M+CH3OH+H]+	1.53	2.593e4	4.159e3	1.53	249.134	10.825
5983	187.0963 / 1.77 [M+H]+	1.77	1.925e4	6.205e3	1.78	187.096	10.818
8895	113.0595 / 3.09 [M+CH3OH+H]+	3.09	1.996e4	5.008e3	3.09	113.059	10.759
5804	661.3399 / 1.64	1.64	7.519e4	8.005e3	1.63	661.340	10.727
5861	109.1010 / 1.70	1.70	1.793e4	5.676e3	1.70	109.101	10.698

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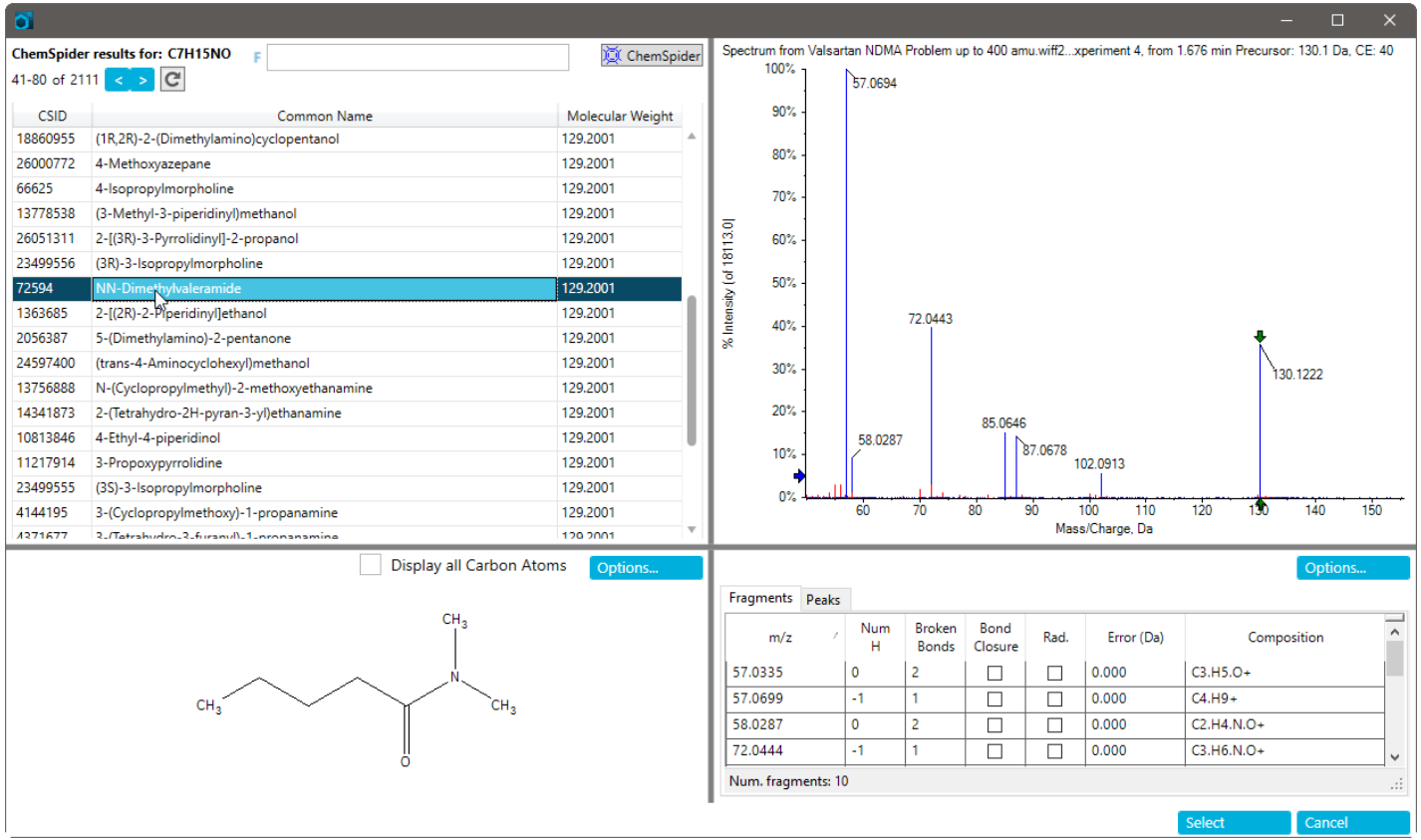
ChemSpider and auto-fragmentation tool in SCIEX OS software 1.7



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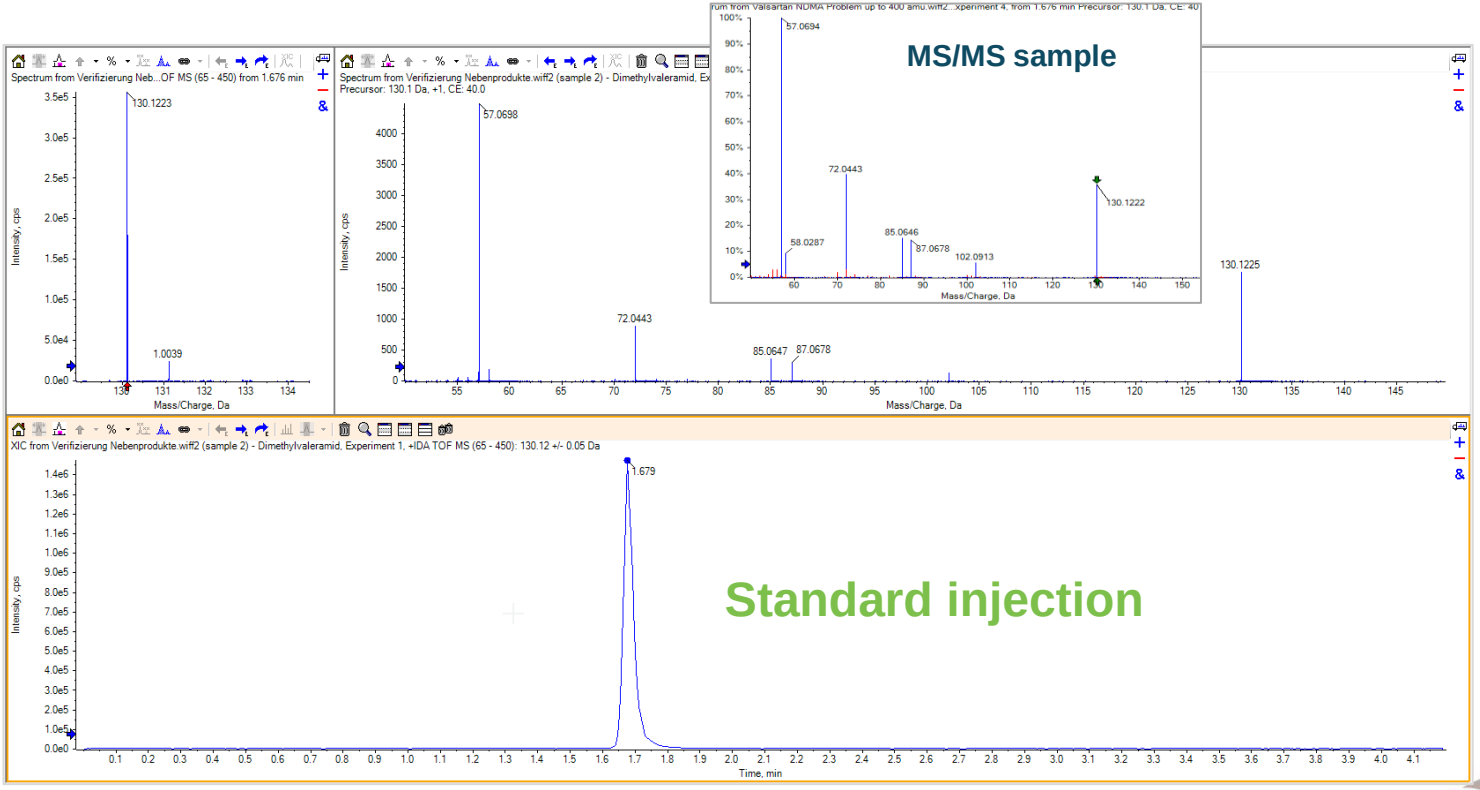
Compound identification by standard addition



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QTRAP system

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Nitrosamine compounds analyzed

QTRAP 6500+ SYSTEM

Compound Name	CAS Number	Molecular Formula
N-Nitrosodimethylamine (NDMA)	62-75-9	C_2H6N_2O
N-Nitrosodibutylamine (NDBA)	924-16-3	$C8H18N_2O$
N-Nitrosodi-n-propylamine (NDIPA)	621-64-7	$C6H14N_2O$
N-Nitrosomethylethylamine (NMEA)	10595-95-6	$C3H8N_2O$
N-Nitrosodiethylamine (NDEA)	55-18-5	$C4H10N_2O$
1-Nitrosopyrrolidine (NPYR)	930-55-2	$C4H8N_2O$
1-Nitrosopiperidine (NPIP)	100-75-4	$C_5H_{10}N_2O$
4-Nitrosomorpholine (NMOR)	59-89-2	$C_4H_8N_2O_2$

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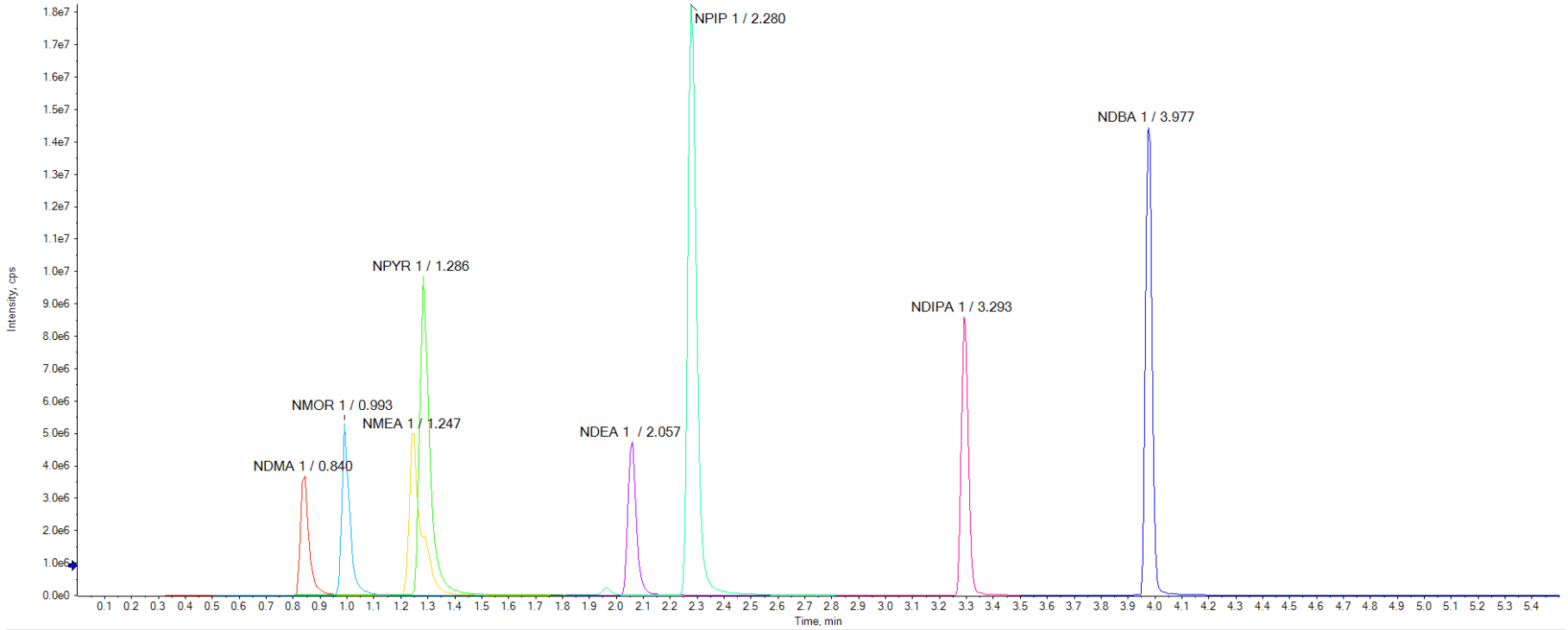
Positive XIC and HPLC separation



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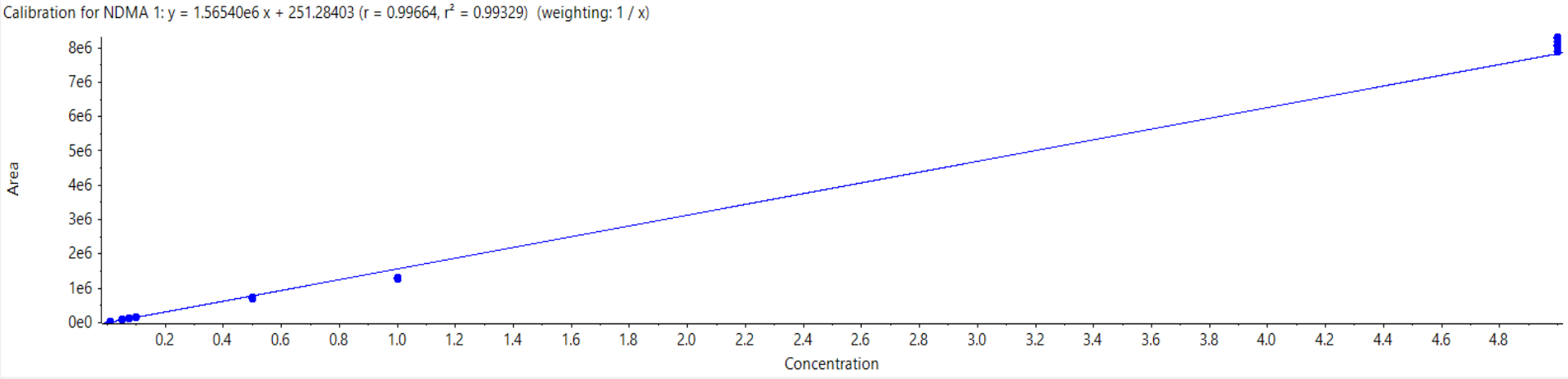
Calibration and accuracy

- All calibration curves for both quantifier and qualifier transition have an r value >0.99
- Accuracies at each level of the calibration curve for all analytes between 70% and 130%
- Calibration curve range between 10 pg/mL and 5,000 pg/mL (50-5,000) pg/mL for NMEA and NPYR)



Note: calibration curve concentration in ng/mL

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LOD and LOQ results

- A limit of quantification (LOQ) of 10.00 pg/mL of 2.50 pg/mL achieved for the majority of compounds
- 2 compounds have a slightly raised LOQ and LOD of 50.00 pg/mL and 10.00 pg/mL respectively
- &CV achieved for all compounds (6 injections) at both LOQ and 10x LOQ is well within acceptable limits or trace analysis.

Compound Name	LOQ (pg/mL)	LOD (pg/mL)	%CV at LOQ	%CV at 10x LOQ
N-Nitrosodimethylamine (NDMA)	10.00	2.50	4.61	3.23
N-Nitrosodibutylamine (NDBA)	10.00	2.50	3.06	1.29
N-Nitrosodi-n-propylamine (NDIPA)	10.00	2.50	2.60	2.04
N-Nitrosomethylethylamine (NMEA)	50.00	10.00	3.24	1.31
N-Nitrosodiethylamine (NDEA)	10.00	2.50	5.19	1.69
1-Nitrosopyrrolidine (NPYR)	50.00	10.00	2.43	0.63
1-Nitrosopiperidine (NPIP)	10.00	2.50	2.20	0.95
4-Nitrosomorpholine (NMOR)	10.00	2.50	4.68	2.03

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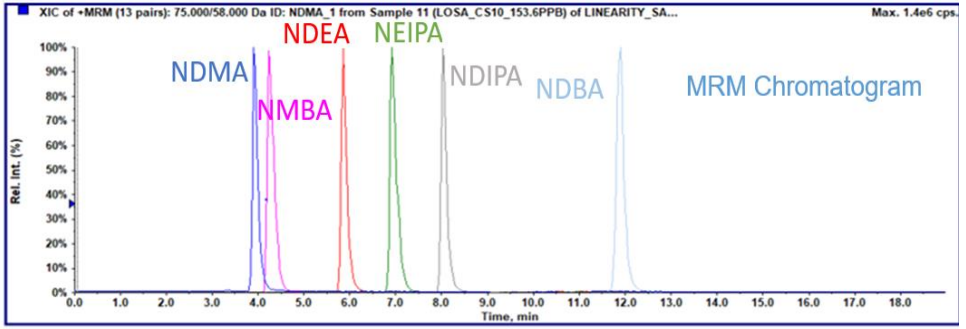
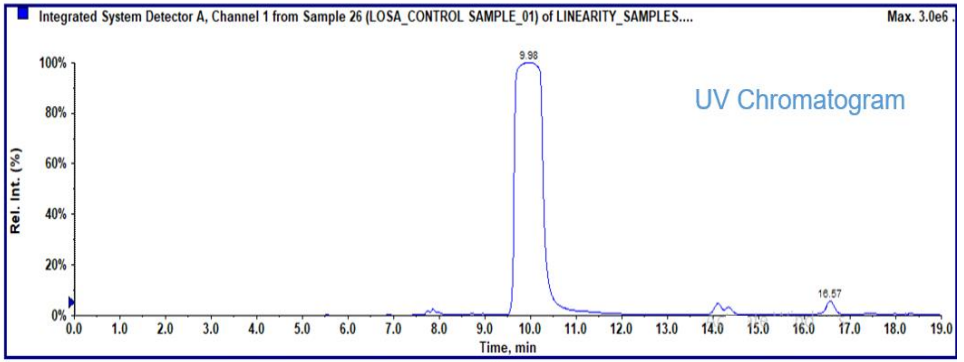
Chromatography for nitrosamine analysis in sartan family

NITROSAMINES IN LOSARTAN

- MRM signals for 6 nitrosamines

	LLOQ: 0.4 ng/mL or 0.01 ppm Losartan		Threshold: 1.2 ng/mL or 0.03 ppm Losartan	
Analyte	**%CV**	**Avg Accuracy**	**%CV**	**Avg Accuracy**
NDMA	*9.21*	*89.36*	*4.15*	*81.81*
NMBA	*8.36*	*79.77*	*4.47*	*78.01*
NDEA	*2.83*	*98.72*	*4.10*	*90.85*
NEIPA	*3.00*	*94.46*	*4.31*	*82.93*
NDIPA	*2.19*	*88.64*	*4.54*	*77.22*
NDBA	*4.83*	*111.01*	*2.54*	*98.38*





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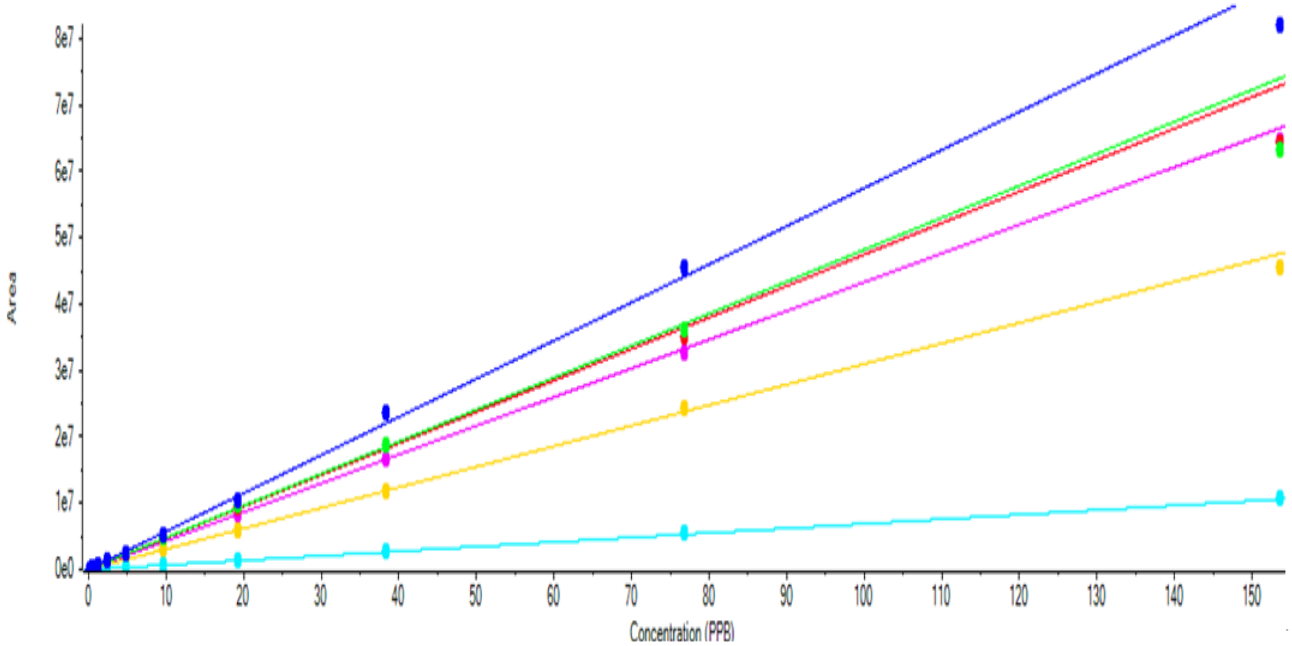
Representative calibration curves

NITROSAMINES IN LOSARTAN

- Calibration curves ranging from 0.2 ng/mL to 153.6 ng/mL for all nitrosamines evaluated correspond to 0.005 - 3.8 µg/g with respect to losartan
- In all cases, linearity is demonstrated with an r value >0.99



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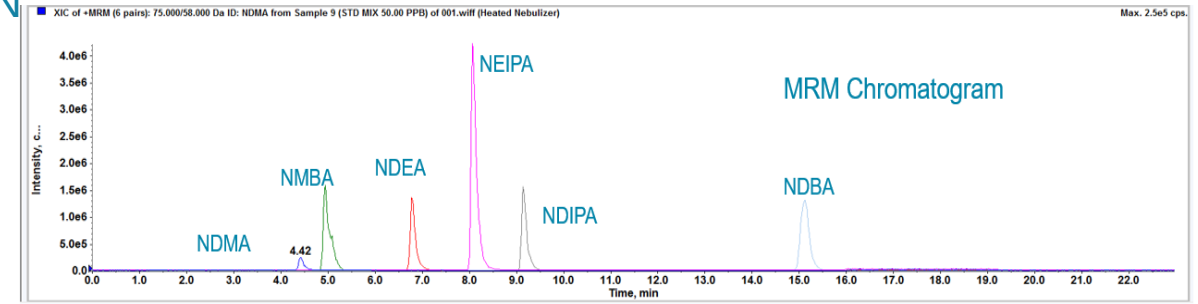
Chromatography for nitrosamine analysis in sartan family

NITROSAMINES IN VALSARTAN

- MRM signals for 6 nitrosamines
- All the compounds showed correlation values r >0.99
- Recovery in the matrix was also evaluated at the LOD at the LOQ and at the daily exposure limit specified by the FDA (0.03 ppm in the API)



	LLOD 0.005ppm n=6		LLOQ 0.01 ppm n=6		Spec Level 0.03 ppm n=6	
Analyte	**%CV**	**Accuracy**	**%CV**	**Accuracy**	**%CV**	**Accuracy**
NDMA	9.41	104.5	*2.96*	*94.3*	*3.78*	*95.6*
NMBA	8.08	106.9	5.38	100.9	3.22	97.3
NDEA	6.58	104.7	0.94	103.1	3.41	100.2
NEIPA	4.45	95.5	1.61	96.8	2.57	102.4
NDIPA	6.73	102.3	6.17	90.3	3.82	82.8
NDBA	9.69	94.5	9.15	100.8	3.18	97.8

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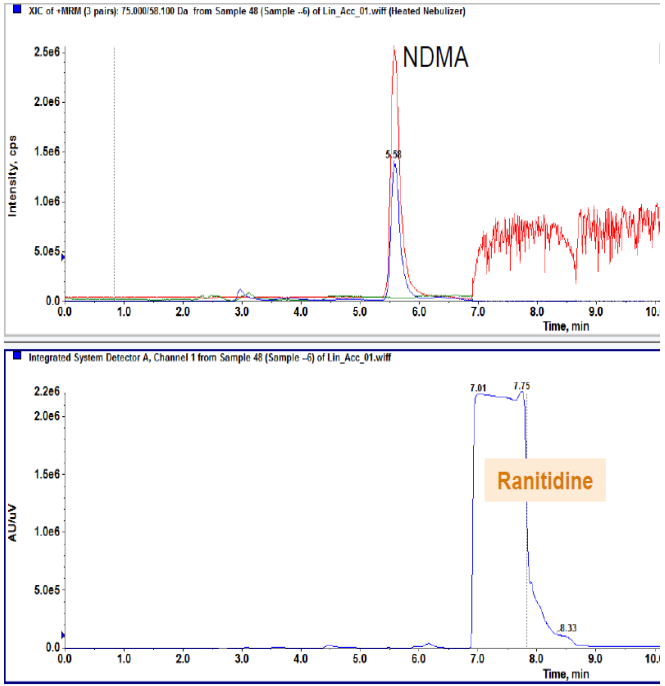
Chromatogram for ranitidine analysis

NDMA IN RANITIDINE

- MRM signals for NDMA - 2 transitions are monitored

Sample	Concentration in 50 mg/mL Ranitidine	Avg. Accuracy %	Precision %RSD	Recovery %
LOD (0.01ppm)	*0.5 ng/mL*	*101%*	*1.5*	*80-120*
LLOQ (0.03ppm)	*1.5 ng/mL*	*102.8*	*2.5*	*80-120*
Spec Level (0.09ppm)	*4.5 ng/mL*	*104.1*	*1.4*	*80-120*



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Enhanced product ion scan

SEARCH IN LIBRARIES USING THE QTRAP SYSTEM

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QTRAP system technology

WHAT IS A QTRAP SYSTEM?

- In a QTRAP system, a linear ion trap (LIT) is added to the Q3 of a typical triple quadruple instrument
- This allows for a multitude of additional workflows beyond basic MRM applications for better specificity and quantitative performance

Scan Type	Triple Quad	QTRAP
Precursor	•	•
MRM	•	•
Neutral Loss	•	•
Product Ion	•	•
Enhanced MS (EMS)		•
Enhanced Multiply Charged (EMC)		•
Enhanced Resolution		•
Enhanced Product Ion		•
MS^3 (MS/MS/MS) and MRM^3		•

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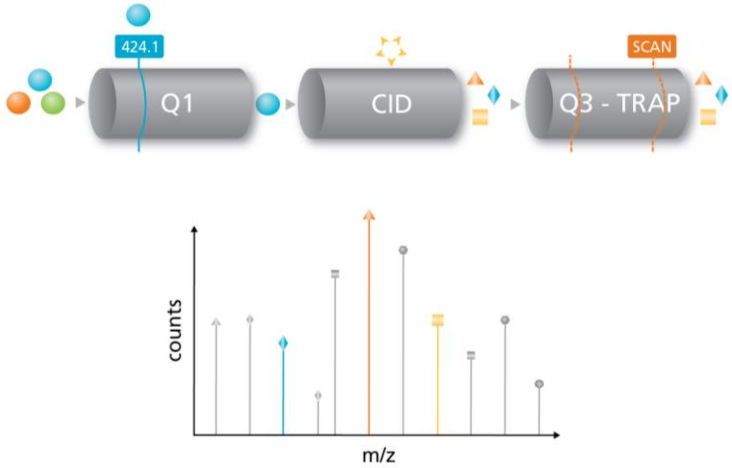
What is an enhanced product ion scan?

FAST AND SENSITIVE MS/MS SCAN

- Precursor ions are filtered in Q1
- The ions are then fragmented in the LINAC collision cell
- Trapping is performed in Q3 (fixed or dynamic fill time)
- Trapped ions are scanned to give a full MS/MS spectra
- This scan can be performed alongside typical MRM analysis to provide a further level of confirmation to your analysis
- If a library of target compounds is present, this can be used to provide a library match and hit score, which provides further confidence in the specificity of the analysis without having to perform multiple injections



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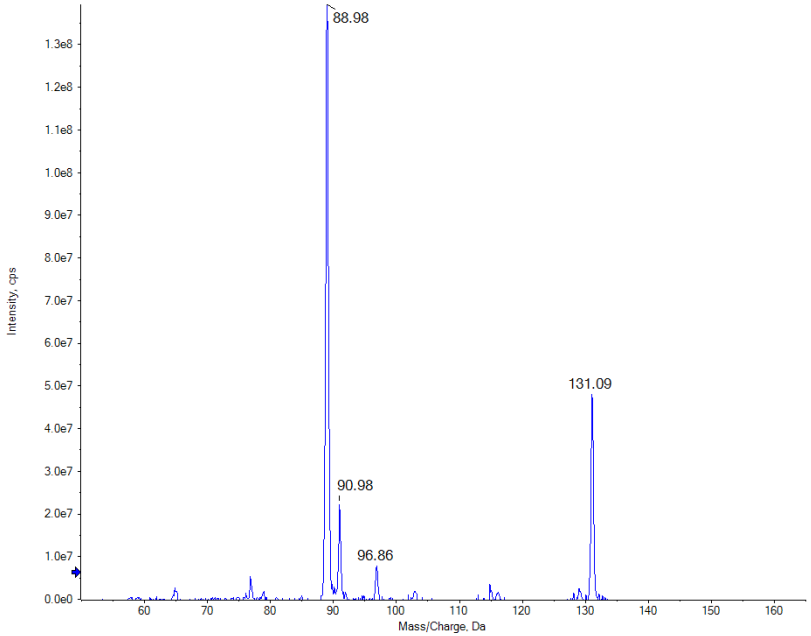
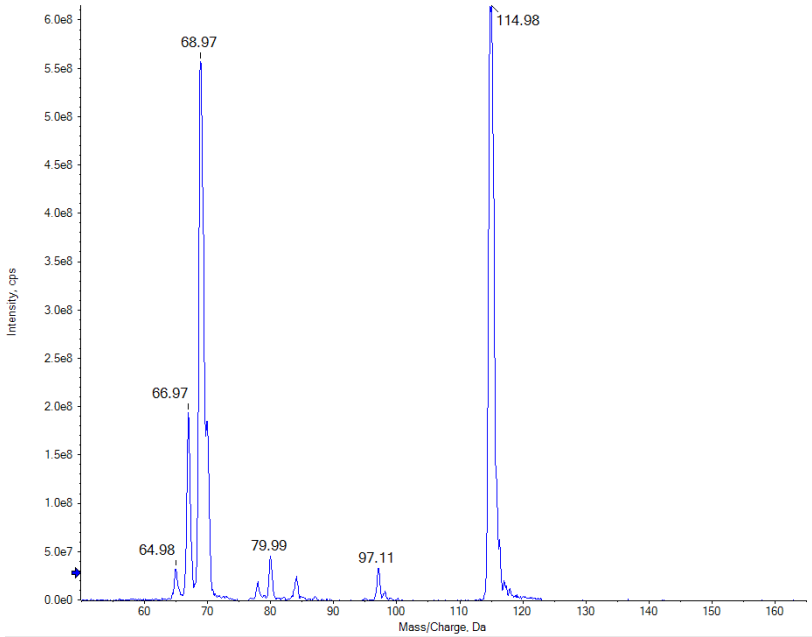
Enhanced product ion scan QTRAP system

NDIPA



NPIP



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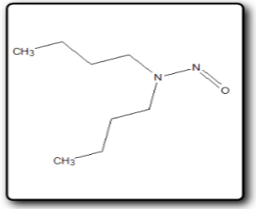
Library entry example: NDBA

NDBA 1

Identifier	
CAS Index	924-16-3
Formula	C8H18N2O
Molecular Weight	158.24163
Monoisotopic Mass	158.14191
Libraries	Nitrosamines
Classes	
Synonyms	



Compound information

▼ Additional Information

Comments

▼ Library Search Thresholds

▼ Retention Times

Default	LC Model	Name	Retention Time

▼ Transitions

Precursor m/z	Polarity	CE	CES	Ion Source	Scan Type	CAD Gas Type	CAD Gas Value	Data File	Date Modified
▼ QTRAP 6500+ Low Mass									
159.1	Positive	35	15		Enhanced Prodion Scan				12/9/2019 3:02:43 PM

MS/MS spectra

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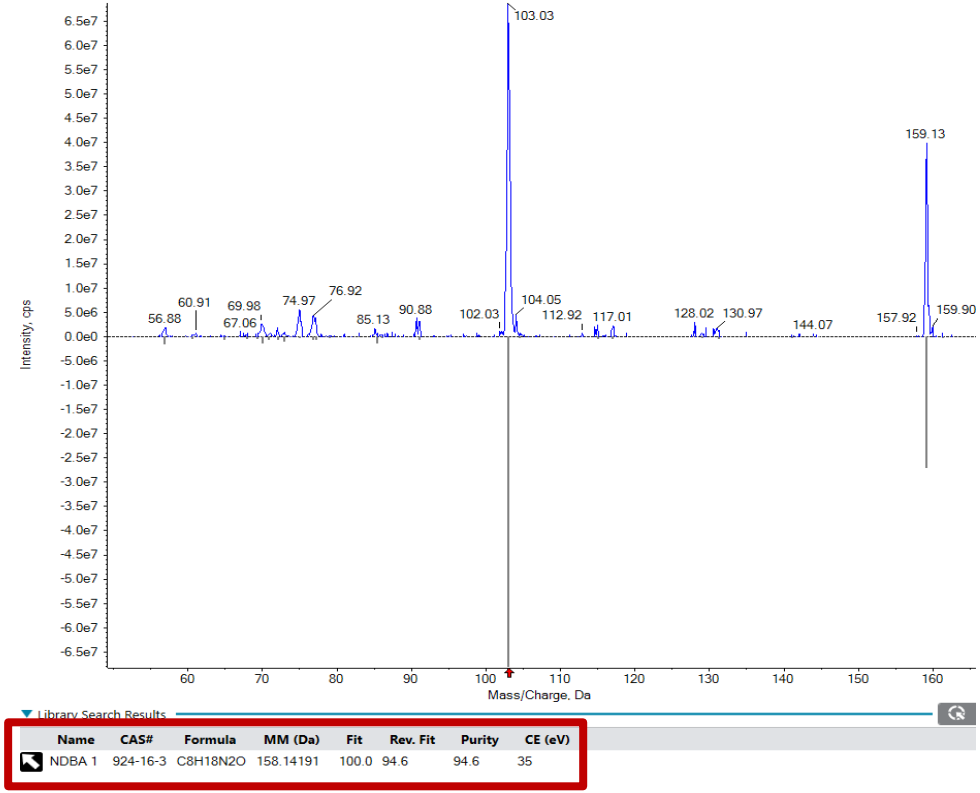
Library search functionality: NDBA



- By using a nitrosamine library, we can perform confirmation to ensure the specificity of our analyte.
- In this case, NDBA has been identified with a purity of 94.6% based on library spectra
- Therefore, this provides confidence in the assignment of the analyzed peak and can exclude any artifact peaks that may occur

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Achieved LOD, LOQ and linearity

API Load ~100 mg	Methanol Diluent	Impurity	NDMA	NDEA	NEIPA	NDIPA	NDPA	NMPA	NDBA	NMBA	NMO[$]
	USFDA Method Limits[##]	LOD (ppm)	0.005	0.002	0.003	0.001	0.001	0.002	0.001	0.002	NAV
		LOQ (ppm)	0.01	0.02	0.02	0.02	0.005	0.005	0.005	0.005	NAV
		Linearity (ppm)	0.01 – 0.1	0.02 – 0.1	0.02 – 0.1	0.02 – 0.1	0.005 – 0.1	0.005 – 0.1	0.005 – 0.1	0.005 – 0.1	NAV
	Methanol Diluent	**Impurity**	**NDMA**	**NDEA**	**NEIPA**	**NDIPA**	**NDPA**	**NMPA**	**NDBA**	**NMBA**	**NMO[$]**
	Limits Achieved on QTRAP® 5500+ System	LOD (ppm)	0.005	0.002	0.001	0.001	0.001	0.001	0.001	0.001	0.001
		LOQ (ppm)	0.01	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
		Linearity (ppm)	0.01 - 2	0.005 - 2	0.005 - 2	0.005 - 2	0.005 - 2	0.005 - 2	0.005 - 2	0.005 - 2	0.005 - 2
	Methanol Diluent	**Impurity**	**NDMA**	**NDEA**	**NEIPA**	**NDIPA**	**NDPA**	**NMPA**	**NDBA**	**NMBA**	**NMO[$]**
	Limits Achieved on X500B System	LOD (ppm)	0.005	0.001	0.001	0.001	0.001	0.005	0.001	0.001	0.005
		LOQ (ppm)	0.01	0.01	0.01	0.01	0.005	0.01	0.005	0.005	0.01
		Linearity (ppm)	0.01 - 1	0.01 – 1	0.01 – 1	0.01 - 1	0.005 - 1	0.01 - 1	0.005 – 0.5	0.005 - 1	0.01 - 1

API Load ~25 mg	Water/Acidified Water	Impurity	NDMA	NDEA	NEIPA	NDIPA	NDPA	NMPA	NDBA	NMBA	NMO[$]
	Limits Achieved on X500B System	LOD (ppm)	0.005	0.002	0.002	0.002	0.002	0.005	0.002	0.002	0.005
		LOQ (ppm)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
		Linearity (ppm)	0.01 - 2	0.01 – 2	0.01 – 2	0.01 – 2	0.01 – 2	0.01 – 2	0.01 – 2	0.01 – 2	0.01 - 2

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Conclusions

QTRAP AND HRMS LC-MS/MS SYSTEMS

- Any of our systems has the necessary sensitivity to determine the values requested by regulatory authorities
- Extensive sample preparation is not required
- Selective, sensitive and reproducible methods for the detection and quantification of various APIs are presented and can be transferred to your laboratory immediately
- HRMS systems will help enable timely detection of nitrosamines and their precursors
- QTRAP systems allow additional contaminations to be explored by searching libraries, and aid matrix effect elimination MRM^3

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Tech notes

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Drug Discovery and Development

Método Altamente Selectivo y Sensible para la Cuantificación de Nitrosaminas en Sustancias Farmacológicas en Valsartán

Cuantificación con el sistema SCIEX Triple Quad™ 5500+ LC-MS/MS - QTRAP® Ready acoplado al sistema ExionLC™ AD

Aman Sharma[1], Sandeep Choudhary[1], M Chandrasekar[1], Manoj Pillai[1]
SCIEX, India

Valsartán y otros medicamentos relacionados a la familia "sartán" se usan para tratar pacientes con hipertensión (presión arterial alta) y aquellos con insuficiencia cardíaca o que han sufrido un ataque cardíaco. El mecanismo de acción de los "sartanes" es bloquear la acción de la Angiotensina-II, una hormona que contrae los vasos sanguíneos y hace que aumente la presión arterial.

En julio de 2018, la US FDA emitió un aviso de retiro del mercado para una gran cantidad de medicamento genérico usado para el bloqueo del receptor de Angiotensina-II, Valsartán, fabricado en instalaciones de China, debido a la niveles inaceptables de contaminación por el compuesto genotóxico n-nitrosodimetilamina (NDMA). En los siguientes años, se han emitido cientos de retiros

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Drug Discovery and Development

Analysis of nitrosamine impurities in a metformin drug substance and drug product

Using the SCIEX X500 QTOF System

Sandeep Choudhary[1], Rajendra Prasad Thatipamula[1], Jack Steed[2], Pankaj Partani[1], Jianru Stahl-Zeng[3], Manoj Pillai[1]
[1]SCIEX CoE, India; [2]SCIEX, UK, [3]SCIEX, Germany

Metformin, a biguanide developed from galegine, is an oral antihyperglycemic agent most widely used in the treatment of type 2 diabetes. Chemically, it is a hydrophilic base which exists at physiological pH as the cationic species (>99.9%). It is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4, with the pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The tablets are available under various brand names for oral administration containing 500 mg, 750 mg or 1000 mg of metformin hydrochloride.[1]

Nitrosamines, the chemical compounds containing nitroso functional group, are classified by the ICH M7(R1) Guideline as class one impurities, "known mutagenic carcinogens", based on both rodent carcinogenicity and mutagenicity data. They are categorized by the International Agency for Cancer Research as

Additionally, the FDA has provided "guidance for industry" regarding "control of nitrosamine impurities in human drugs".[4]

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Drug Discovery and Development

Analysis of Genotoxic Nitrosamines in Losartan and Ranitidine Active Pharmaceutical Ingredients

On the SCIEX QTRAP® 4500 LC-MS/MS System with ExionLC™ AD System

Sandeep Choudhary, Aman Sharma, M Chandrasekar, Manoj Pillai
SCIEX, India

In recent years, there have been several high profile drug recalls of angiotensin II receptor blocking saratan class drug (valsartan, losartan, irbesartan), due to contamination of the final drug products with potentially genotoxic nitrosamine compounds, including n-nitrosodimethylamine (NDMA). More recently in September of 2019, the US FDA announced the discovery of low levels of NDMA in the H2 blocker ranitidine, generic for Zantac, which is sold as an over-the-counter medication used to treat heartburn and GERD. This resulted in the recall by some manufacturers of this product, and the recommendation of some regulating agencies (Health Canada) that all products containing this medication be recalled. Drug product contamination and subsequent recalls pose obvious health risks to consumers, and

26.5 ng/day for n-nitrosodiethylamine (NDEA) to 96 ng/day for NDMA. Because the daily dosage of a drug can vary, an

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