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Analyzing Nitrosamines with Hydrogen Carrier Gas: GC/MS/MS Analysis of Nitrosamines in Sartan Drugs

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Introduction

The limited availability of helium has been a concern, leading to a growing interest in switching to alternative carrier gases like hydrogen. Hydrogen offers several advantages over helium[1], including faster run times and improved chromatographic resolution. Helium is commonly used as a carrier gas for analyzing nitrosamine impurities in pharmaceuticals. However, there are concerns that nitrosamines may react with hydrogen, forming unwanted byproducts. To ensure that using hydrogen as a carrier gas does not impact spectral quality, we evaluated its suitability for analyzing eight impurities: N-nitrosodimethylamine (NDMA), N-nitrosomethylethylamine (NMEA), N-nitrosodiethylamine (NDEA), N-nitroso-ethylisopropylamine (NEIPA), N-nitrosodiisopropylamine (NDIPA), N-Nitrosodipropylamine (NDPA), N-nitrosodi-n-butylamine (NDBA), N-Nitrosopiperidine (NPIP).

Hydrogen carrier gas was used with the 7000E and 7010 Series GC/TQ systems equipped with the HydroInert and HES ion sources respectively, assessing spectral quality, linearity, repeatability, recovery, and compliance with nitrosamine analysis regulations.

MassHunter 13 software suite provided the tools for data acquisition and processing to be performed under a unified compliance environment. OpenLab Electronic Content Management (ECM) XT includes native tools to facilitate compliance, including the ability to create users with affiliated permissions, the generation of audit trails, and remote data storage.

Figure 1. 7010D Triple Quadrupole Mass Spectrometer (GC/TQ)

Experimental

The active pharmaceutical ingredients (APIs) and drug products included valsartan, irbesartan, losartan and Olmesartan. A portion of 500 mg of drug substance was weighed accurately into a 15 mL glass centrifuge tube, and 5 mL of internal standard solution (~ 50 ng/mL NDMA-d6 in dichloromethane) was added. These samples were vortexed for 1 min and centrifuged at 4000 rpm for 5 min. The undissolved drug substance settled at the bottom. Approx. 2 mL of the dichloromethane layer was filtered through a 0.45 µm nylon filter and transferred to a GC vial for analysis.

Parameter	Value			
MMI Injection Mode	Pulsed splitless: 15 psi until 0.5 min			
Inlet Temperature	250 °C			
Inlet Liner	Ultra Inert, splitless, single taper, glass wool (p/n 5190-2293)			
Oven Program	40 °C (1.5 min)			
	20 °C/min to 200 °C (0 min)			
	60 °C/min to 250 °C (3 min)			
Total Run Time	13.33 min			
MS Transfer Line	250 °C			
Injection Volume	2 µL			
GC Column	VF-WAXms Helium: 30 m × 0.25 mm × 0.25 µm (p/n CP9205) Hydrogen: 60 m × 0.25 mm × 0.25 µm column (p/n CP9207) and midcolumn backflushing with 2x 30 m × 0.25 mm × 0.25 µm			
Carrier Gas	Hydrogen, 1 mL/min (for HES and HydroInert) or Helium 1.2 mL/min (for HES)			
Mode	Electron impact, 70 eV			
Source and quad Temperature	250 °C Q1 and Q2 = 150 °C			
Collision Gas Flow	Nitrogen at 1.5 mL/min			
Quench Gas Flow	Switched off when using hydrogen carrier gas			
Quant/Qual Transitions (dMRM Based)	Compound	RT in min	MRM Transition	CE
	NDMA-D6	8.437	80 > 50	5
	NDMA	8.448	74 > 44.1	6
			74 > 42.1	24
			43.1 > 42.1	10
	NMEA	8.767	87.9 > 71	4
			87.9 > 42.1	24
			43.1 > 42.1	10
	NDEA	8.969	101.9 > 85.1	4
			101.9 > 56	20
			101.9 > 44.1	14
	NEIPA	9.198	115.9 > 99	6
			115.9 > 44	16
			71 > 56	6
	NDIPA	9.366	130 > 88	6
			130 > 71	16
			130 > 42.1	12
	NDPA	9.832	130 > 113.1	2
			101 > 70	2
			70 > 43.1	6
	NDBA	10.796	158 > 141.1	4
			158 > 99.1	10
			116 > 99.1	4
			84 > 56	22
	NPIP	11.088	113.9 > 97.1	8
			113.9 > 84.1	8
			113.9 > 55	26
			113.9 > 42.1	24

Table 1. 8890 and 7000E and 7010 Series GC/TQ acquisition parameters

Results and Discussion

The full scan spectrum of each of the eight analytes was acquired using helium and hydrogen carrier gas and compared against the NIST library. Excellent match scores (>90) were obtained with hydrogen carrier gas on HES, while good match scores (>80) were obtained with the HydroInert source. Higher average match scores with HES could be attributed to higher response due to enhanced sensitivity.

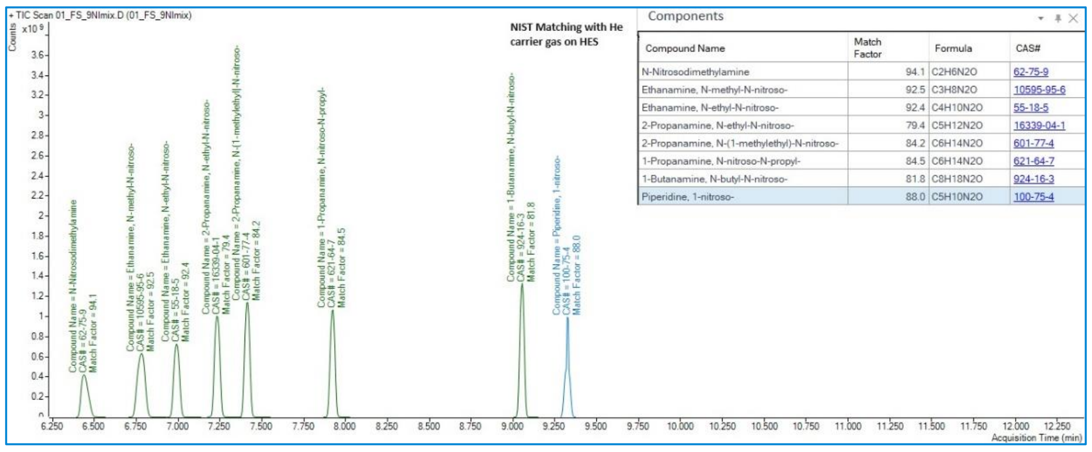

Figure 2. Separation of eight nitrosamine impurities with the 7010 Series GC/TQ using helium carrier gas and 30 m × 0.25 mm × 0.25 µm VF-WAXms column. NIST library match scores ranging over 81-94

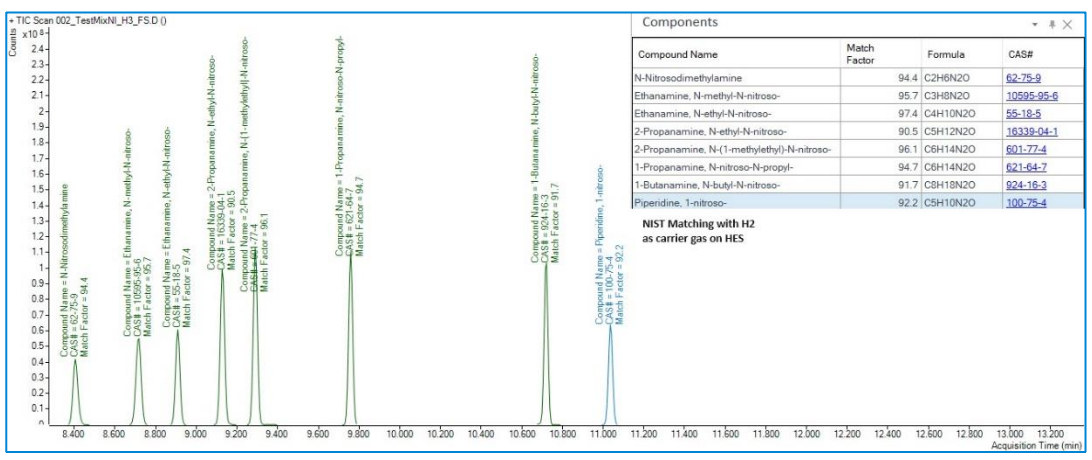

Figure 3. Separation of eight nitrosamine impurities with the 7010 Series GC/TQ (HES source) using hydrogen carrier gas and a 60 m × 0.25 mm × 0.25 µm VF-WAXms column. NIST library match scores ranging over 90-96

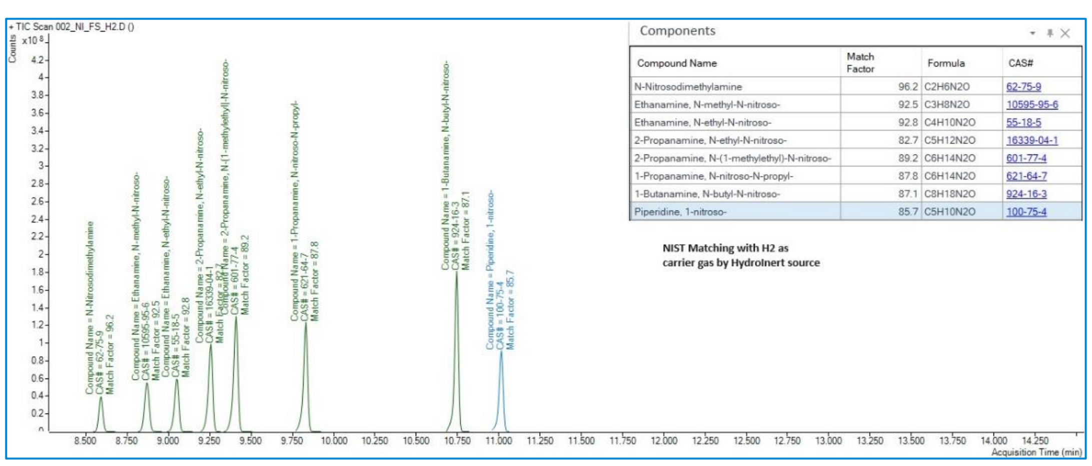

Figure 4. Separation of eight nitrosamine impurities with the 7000E GC/TQ (HydroInert source) using hydrogen carrier gas and a 60 m × 0.25 mm × 0.25 µm VF-WAXms column. NIST library match scores ranging over 82-96

Linearity studies were conducted across a range of concentration. The lowest calibration level was defined as the concentration at which the ion ratios for the qualifier ions met the ion ratio criteria. Using hydrogen carrier gas, detection limits of 3 ppb (3 ng/mL) or lower were achievable with both the HES and HydroInert ion sources.

Compound	Calibration Range (in ng/mL)			USP S/N of quantifier transition at lowest calibration level		
	7010 Series with He carrier Gas	7010 Series with H_2 Carrier Gas	7000E with HydroInert Source	7010 Series with He carrier Gas	7010 Series with H_2 Carrier Gas	7000E with HydroInert Source
NDMA	0.1-50	0.5-50	3-50	>12	>10	>10
NMEA	0.2-50	0.3-50	1-50	>200	>12	>40
NDEA	0.05-50	0.5-50	1-50	>20	>10	>100
NEIPA	0.05-50	1-50	3-50	>50	>80	>90
NDIPA	0.05-50	0.5-50	1-50	>80	>10	>60
NDPA	0.1-50	0.3-50	3-50	>100	>10	>10
NDBA	0.1-50	1-50	3-50	>60	>10	>20
NPIP	0.1-50	1.25-50	3-50	>60	>10	>10

Table 2. Linearity range with different carrier gases with the 7000E and the 7010 Series GC/TQ

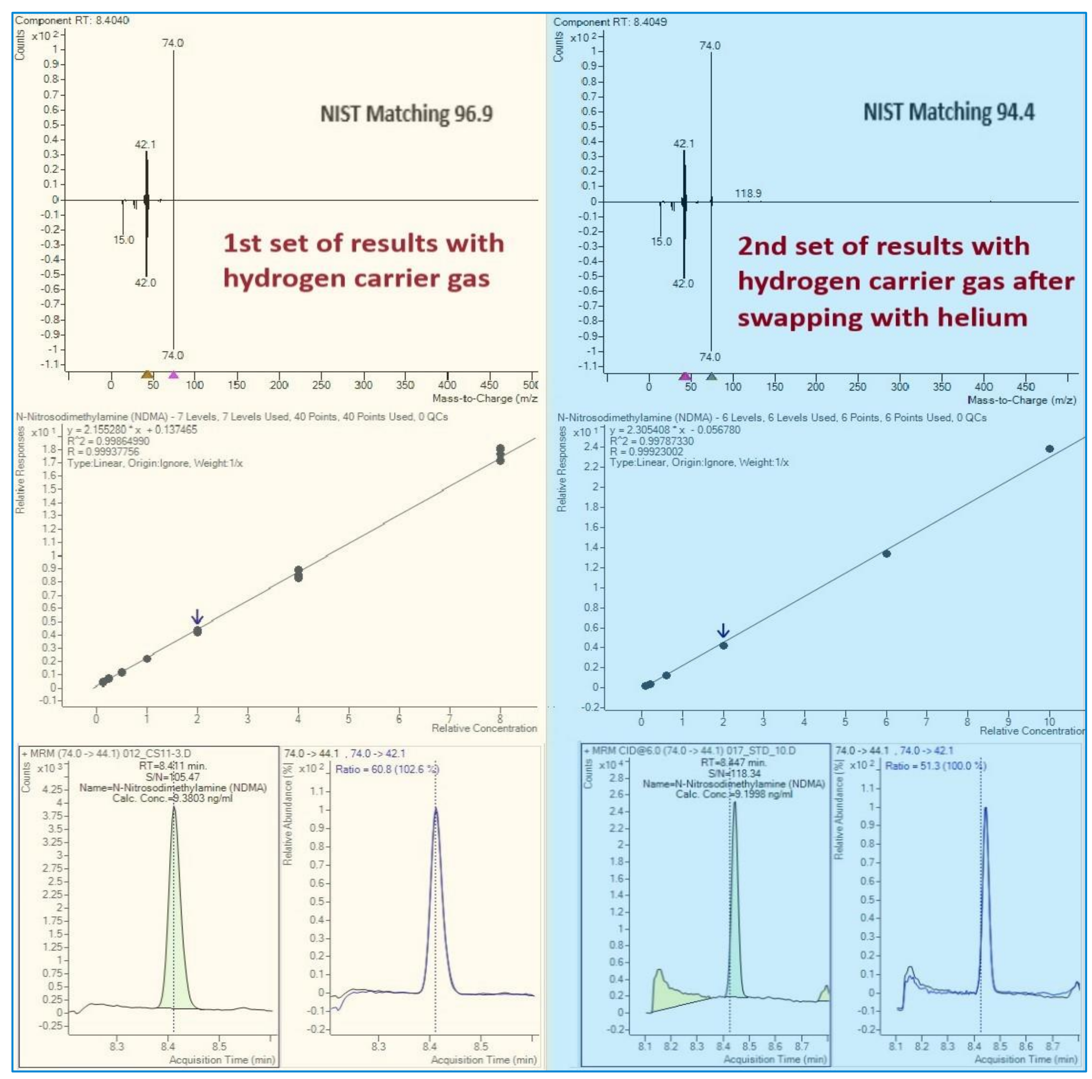

Figure 5. Consistent library match scores, calibration, and ion ratios with 7010 Series GC/TQ using hydrogen carrier gas before and after swapping with helium

The carrier gas was alternated between helium and hydrogen over a period of six months (three exchanges). This ability to maintain spectral fidelity (library match scores >90) consistent calibration response, ion ratios, and sensitivity despite changes in the carrier gas enables a seamless transition between hydrogen and helium.

Results and Discussion

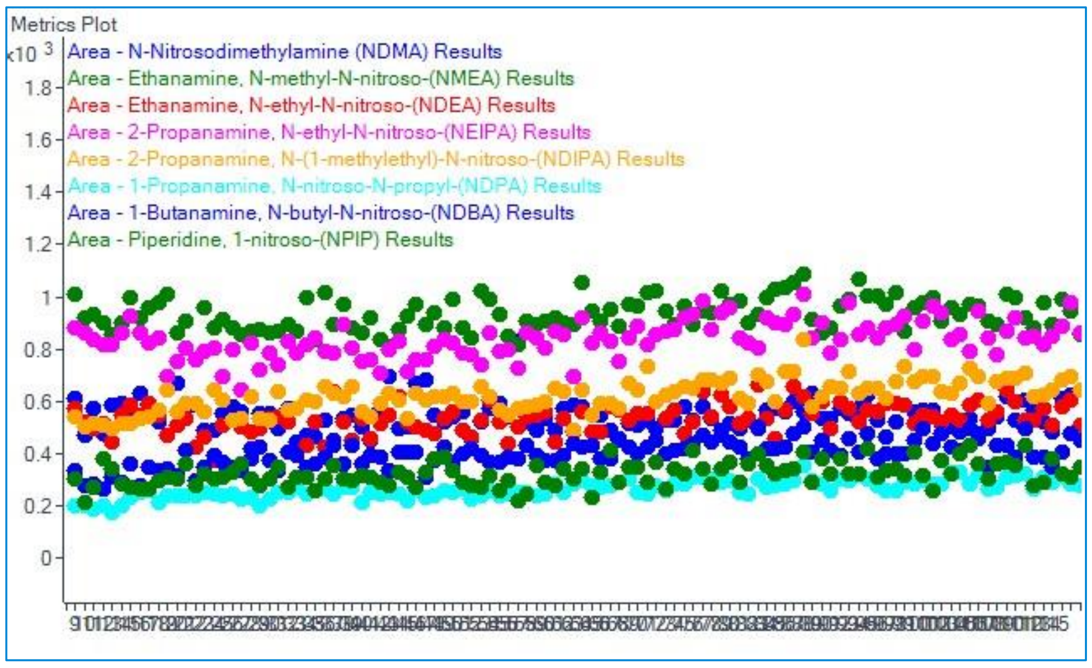

Figure 6. Figure 3. Peak area trend (with 7000E GC/TQ with the HydroInert source) is displayed as output by the metric plot feature of Agilent MassHunter Quantitative software for a recovery sample of nitrosamine impurities at 30 ppb with respect to drug substance.

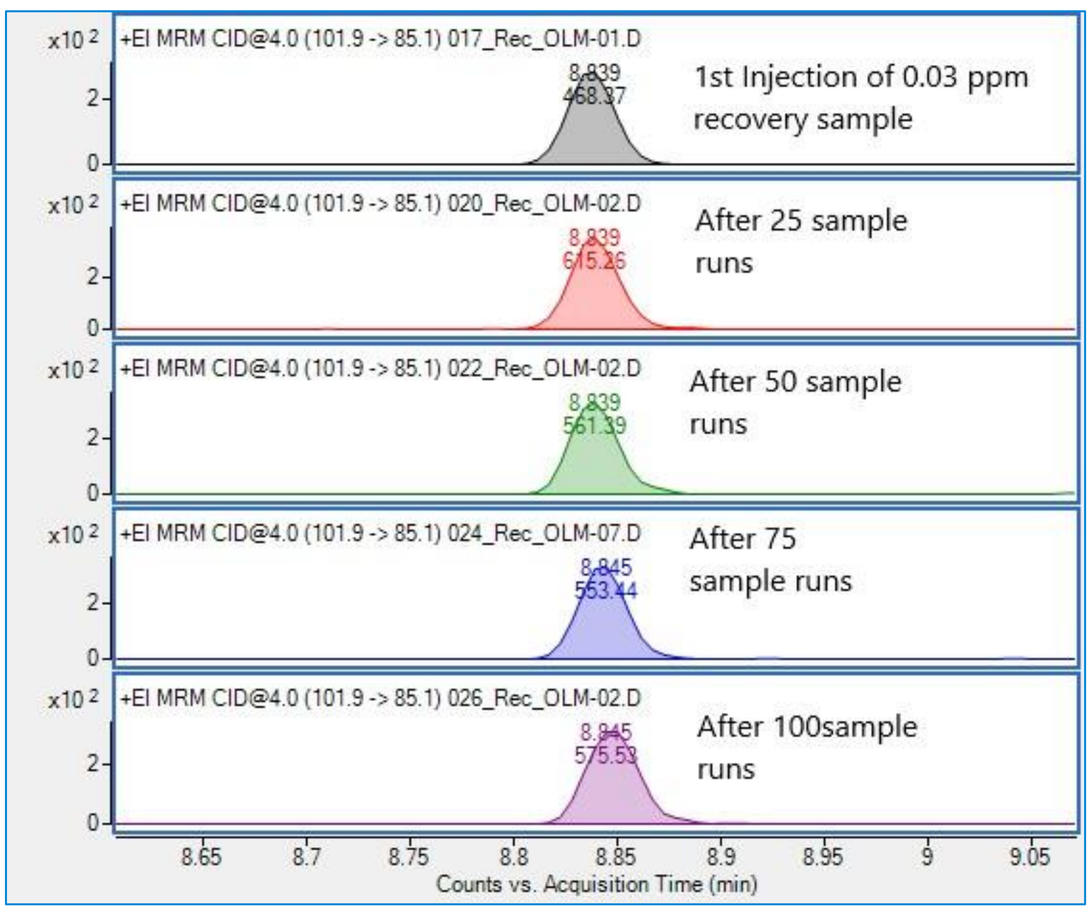

Figure 7. Consistent retention times (RTs) and peak areas after 25, 50, and 100 consecutive sample runs with mid-column backflush configuration (30m x 30m)

The stability of the results was evaluated through 150 consecutive injections using hydrogen as the carrier gas. RSDs calculated based on absolute areas were <10% for all analytes, while those calculated for concentration (after internal standard correction) were <7%. These results indicate a long-term stability of response and demonstrate the method's suitability for routine analysis.

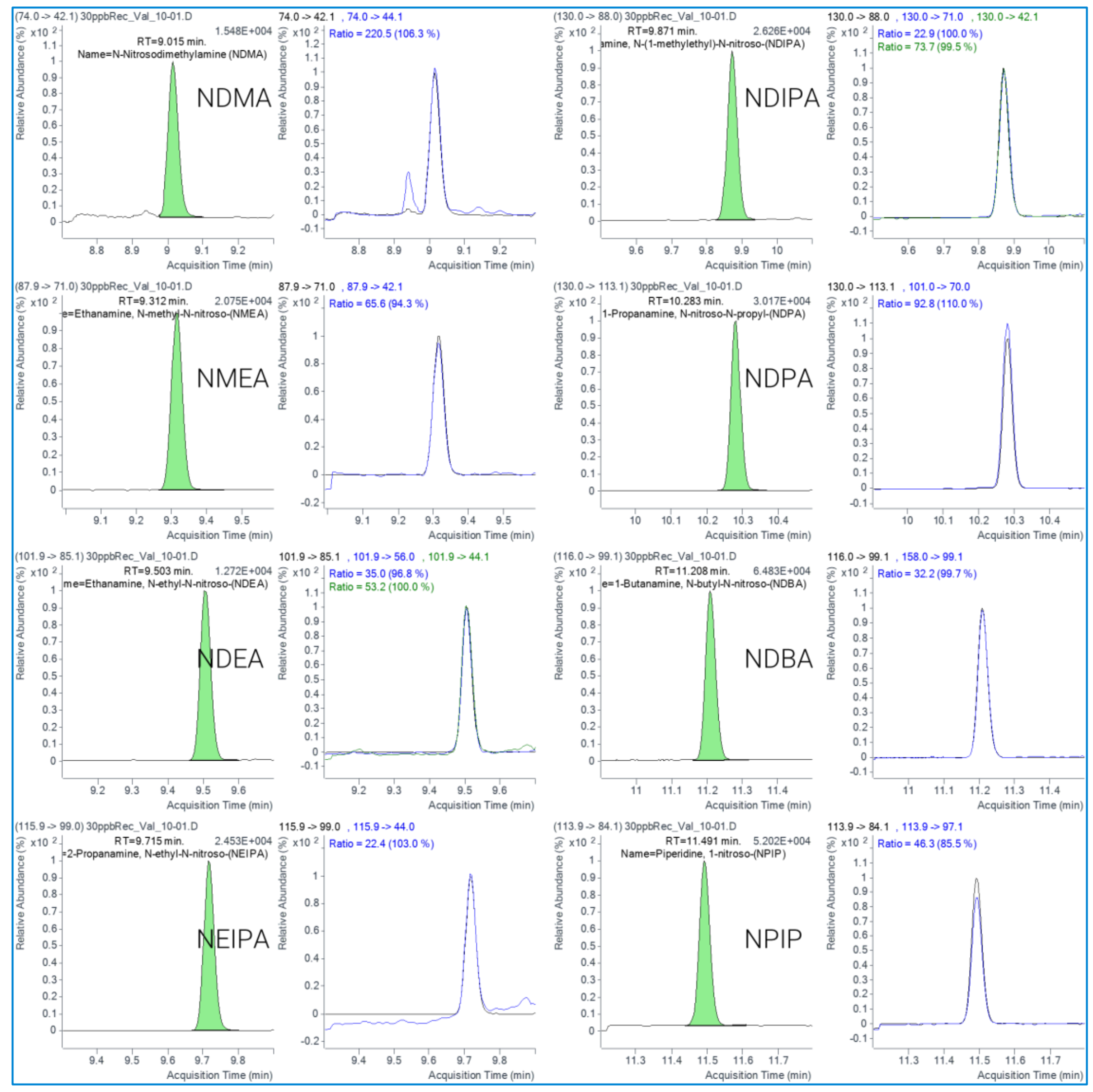

Figure 8. Chromatograms of eight impurities spiked at 30 ng/g Valsartan (7010 Series GC/TQ with the HES source, hydrogen carrier gas)

Conclusions

- The 7000E and 7010 Series GC/TQ systems equipped with the HydroInert and HES, respectively, exhibited exceptional performance in determining eight nitrosamine drug impurities in sartan drug products and substances using hydrogen carrier gas.
- The method was validated at 30 ppb with acceptable recovery and long-term repeatability.
- The 7010 Series GC/TQ system enabled a smooth switch between helium and hydrogen carrier gas without compromising the performance of the methods.
- Both the HydroInert and the HES sources facilitated achieving the necessary detection limits for the tested impurities.

References

[1]Agilent EI GC/MS Instrument Helium to Hydrogen Carrier Gas Conversion, Agilent Technologies user guide, publication number 5994 2312EN, 2020

https://www.agilent.com/en/promotions/asms

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