APPLICATIONS

Analysis of NDMA and NDEA in Sartan Drugs and Drug Products by GC-MS on a Zebron™ ZB-624*PLUS*™

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Overview

N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) are Class 2A carcinogens that have been found to be present as impurities in several different generic drug substances and drug products. NDMA is highly toxic and is a known carcinogen in lab animals, and along with NDEA has been classified as a probable human carcinogen. Accurate identification and quantification of these impurities is essential to assure quality and safety of the drug substance and drug product. Valsartan and other related sartan medicines are used to treat patients with hypertension (high blood pressure), and those with heart failure or who have had a recent heart attack. Sartans work by blocking the action of angiotensin II, a hormone that constricts blood vessels and causes blood pressure to rise.

In the summer of 2018, the U.S. Food and Drug Administration (FDA) issued a recall for several drug products containing Valsartan, due to the potential presence of the impurities NDMA and NDEA. The European Medicines Agency (EMA) also acted quickly to ban the importation of Sartans from certain manufacturers in China and India after these impurities were found to be present. All this attention has also resulted in additional products being voluntary recalled by the manufacturers for drug products containing other sartans (Irbesartan and Lorsartan). NDMA and NDEA are not expected impurities and are believed to have been introduced into the drug products because of the specific sequence of manufacturing steps and chemical reactions used to make the drug substance; the specific source of these impurities is still under investigation.

Results and Discussion

A single point calibration for NDMA and NDEA at 20 ppb was generated by spiking 10 µL of 200 µg/mL standard solution into headspace vial with 1.0 mL DMSO (equal to 0.02 µg of NDMA and NDEA) with signal-to-noise ratio of 140 for NDMA and 222 for NDEA. A DMSO blank gave no appreciable peak area at the retention times for NDMA and NDEA. For NDMA m/z 74, 42, and 43 were monitored (SIM), with m/z 74 used for quantitation; and for NDEA m/z 102, 56, and 57 were monitored, with m/z 102 used for quantitation. S/N was 140 for NDMA and 222 for NDEA, respectively, for the 20 ppb standard concentration. LOQ was estimated (S/N = 10:1) at 1.5 ppb for NDMA and 0.9 ppb for NDEA; and LOD was estimated (S/N = 3:1) at 0.4 ppb for NDMA and 0.3 ppb for NDEA.

Two Valsartan tablets from different manufacturing lots were analyzed separately by crushing each 500 mg tablet and mixing in 1 mL of DMSO in a 20 mL headspace vial. Tablet 1 was determined to contain 5 ppb NDMA and 264 ppb NDEA; Tablet 2 was determined to contain 10 ppb NDMA and 139 ppb NDEA.

Conclusions

A headspace extraction was performed for Valsartan formulations in DMSO solvent to analyze for the presence of NDMA and NDEA at ppb levels. The Zebron ZB-624*PLUS* GC column coupled with GC-MS detection provided the required sensitivity for ppb level quantification. The ZB-642*PLUS* affords the resolution and minimal baseline bleed necessary for detecting ppb concentrations of these genotoxic substances in formulated drug products and drug substances. Traditional 624 chemistry has a drawback of stationary-phase bleed at high temperature, and does not perform well on GC-MS. The integrity of the G43 (624 phase) stationary phase in the ZB-624*PLUS* is reinforced through crosslinking of the polysiloxane backbone, allowing for use at higher temperatures than traditional G43 phases, without the risk of column bleed and baseline noise that would otherwise compromise analyses at low ppb levels. The ZB-624*PLUS* comfortably retains selectivity of G43 stationary phase for quantification of tertiary amine of NDMA and NDEA.

NOTE: FDA and EMA have separately published GC-MS/MS and LC-MS/MS methods for analysis of NDMA and NDEA in sartan medicines. As this situation evolves to include additional identified impurities (e.g. N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) recently found in losartan potassium tablets), it is expected that these analysis methods will be revised. It is recommended to monitor the FDA and EMA websites for updates to this evolving situation.

GC Conditions

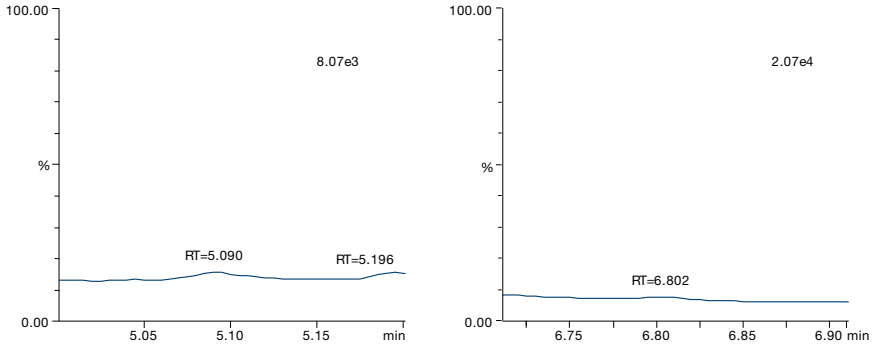
Column: Zebron ZB-624*PLUS*
Dimensions: 30 meter x 0.25 mm x 1.40 µm
Part No.: 7HG-G040-27
Injection: Split 10:1 @ 150 °C
Headspace 1 mL sample in 20 mL vial
NOTE: Detailed Headspace conditions below
Recommended Liner: Zebron PLUS Straight Z-Liner™
Liner Part No.: AG2-4B03-05 (for Shimadzu® systems)
Carrier Gas: Helium @ 36.1 cm/sec
Oven Program: 60 °C for 1 min, to 240 °C at 20 °C/min for 1 min
Detector: MSD @ 250 °C
SIM: (m/z 74, 42, and 43 for NDMA)
(m/z 102, 56, and 57 for NDEA)
Instrument: Shimadzu GCMS-QP2020 NX with HS-20 (headspace)
Ion Source: 250 °C
Emissions Current: 150 µA
Transfer Line Temperature: 250 °C
Detector Voltage: 1.3 kV
Sample: Standard is 20 ppb in DMSO (0.02 µg into 1 mL)
1. NDMA
2. NDEA

Headspace Conditions (Shimadzu HS-20)

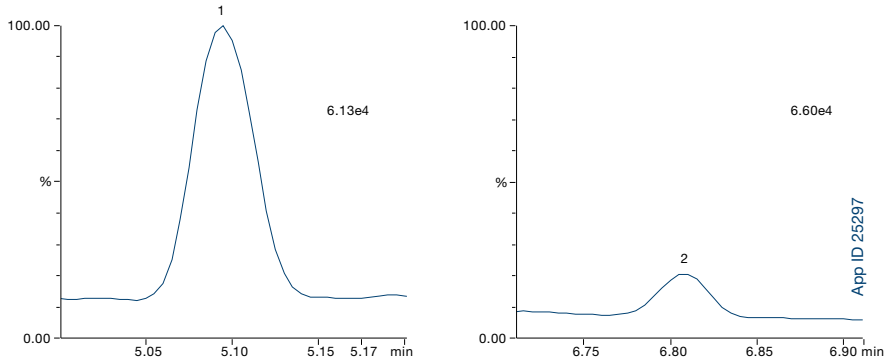
Mode	Loop
Shaking Level:	2
Vial Capacity:	20 mL
Oven Temp:	145 °C
Equilibrating Time:	15 min
Sample Pressurization:	80 kPa
Pressurizing Time:	3.0 min
Pressuring Equilibration Time:	0.1 min
Load Time:	0.5 min
Load Equilibration Time:	0.1 min
Injection Time:	0.5 min
Needle Flush Time:	5 min
Sample Line Temp:	150 °C
Transfer Line Temp:	150 °C

Data Courtesy of Shimadzu Europa GmbH, Dr. Hendrik Schulte, Product Specialist GC-MS

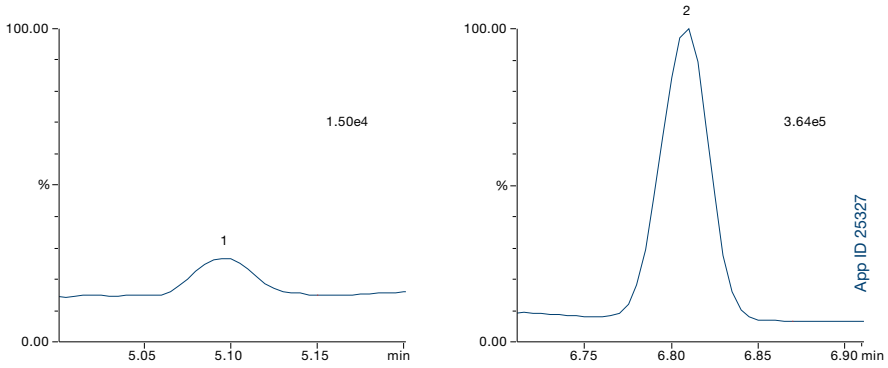
DMSO Blank



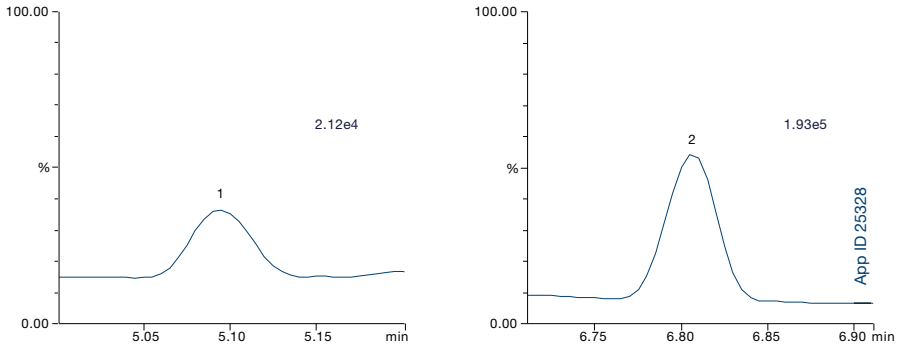
NDMA and NDEA by GC-MS on a Zebron™ ZB-624*PLUS* (20 ppb Standards)



NDMA by GC-MS on a Zebron ZB-624*PLUS* (Valsartan Tablet #1)



NEMA by GC-MS on a Zebron ZB-624*PLUS* (Valsartan Tablet #2)



Ordering Information

Zebron™ ZB-624*PLUS*™ GC Columns			
ID(mm)	**df(µm)**	**Temp. Limits °C**	**Part No.**
20-Meter			
0.18	1.00	-20 to 300/320	7FD-G040-22
30-Meter			
0.25	1.40	-20 to 300/320	7HG-G040-27
0.32	1.80	-20 to 300/320	7HM-G040-31
0.53	3.00	-20 to 300/320	7HK-G040-36
60-Meter			
0.25	1.40	-20 to 300/320	7KG-G040-27
0.32	1.80	-20 to 300/320	7KM-G040-31
0.53	3.00	-20 to 300/320	7KK-G040-36

Note: If you need a 5 in. cage, simply add a (-B) after the part number, e.g., 7HG-G040-27-B. Some exceptions may apply. Agilent 6850 and some SRI and process GC systems use only 5 in. cages. 0.18 mm, 0.25 mm, and 0.32 mm are MS certified.

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