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Application News

NO. GC-22-ADI-061

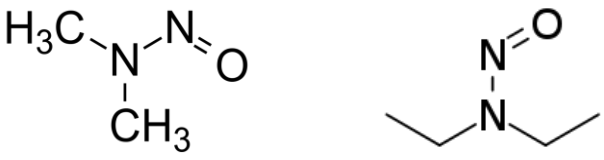
GCMS-QP2020 NX, HS-20

Analysis of N-Nitrosodimethylamine (NDMA) & N-Nitrosodiethylamine (NDEA) in pharmaceutical substance by HSGCMS

Introduction

N-Nitrosodimethylamine (NDMA) & N-Nitrosodiethylamine (NDEA) are simplest of Dialkylnitrosamines. They are continued to be released as a by-product and contaminant from various industries and from municipal wastewater treatment plants. Major releases of NDMA, NDEA have been from the manufacture of pesticides, rubber tires, alkyl amines, and dyes. Similarly, these compounds are produced as a byproduct in the manufacturing of Active Pharmaceutical Ingredients (API's). These compounds are classified as a Group 2A carcinogen (probable human carcinogen) by the World Health Organization.

Recently, some drug products were discovered to have been contaminated with NDMA & NDEA. It is believed to have been introduced into the finished products as a result of the manufacturing process of the drug substance. This contamination, was far exceeding the regulatory exposure limits specific to drug products. Consequently, medical agencies across Europe as well as the US Food and Drug Administration (USFDA) withdrew all affected drug products from the market. Hence it is very essential to have a sensitive, accurate, reliable & robust method by using suitable analytical technique. The USFDA Office of Testing and Research (OTR) has developed an Headspace Gas Chromatography Mass Spectrometry (HSGCMS) method to detect the presence of NDMA in drug substance. In this experiment the pharmaceutical API's namely Valsartan, Losartan & Olmesartan-Medoximil prone to contamination with NDMA and NDEA is analyzed by referring USFDA OTR HSGCMS method. Refer figure 1 for structure of NDMA & NDEA



NDMA **NDEA**

Figure 1: Structure of NDMA & NDEA

Experimental

This study was conducted using a Shimadzu GCMS-QP2020 NX with HS-20 Headspace autosampler. The instrument was operated in constant linear velocity mode, equipped with a Shimadzu Stabilwax capillary column providing the best chromatographic resolution, symmetrical peak shapes, and enhanced sensitivity for target analytes. A commercial mixture of NDMA & NDEA was used to prepare calibration curves ranging from 2.5 – 10 µg/L. The standards were prepared in N,N-Dimethyl sulfoxide. The instrument operating conditions are shown in Table 1.

Table 1: GCMS-QP2020 NX Operating Conditions

Instrument Details	Shimadzu GCMS-QP2020 NX with HS-20		
GC Parameters			
Column Details	SH-Stabilwax, 30 m, 0.32 mm ID, 0.25 µm df		
Injection Mode	Splitless		
Flow Control Mode	Linear Velocity		
Detector	Mass spectrometer		
Carrier Gas	Helium		
Column Flow	1.60 mL/min		
Linear Velocity	45.6 cm/sec		
Temp. Program	Ramp Rate (ºC/min)	Temp. (ºC)	Hold Time (min)
	-	40.0	2.0
	10	120.0	0.0
	25	230.0	5.6
Diluent	N, N-Dimethyl sulfoxide		
HS Parameters			
Mode	Loop (1 mL)		
Oven Temp.	120 ºC		
Sample Line Temp.	125 ºC		
Transfer Line Temp.	130 ºC		
Shaking Level	5		
Pressurizing Gas Pressure	103 kPa		
Equilibrating Time	15.0 min		
GC Cycle Time	30.0 min		
MS Parameters			
Ion Source Temp.	200 ºC		
Ionization Mode	EI		
Mode	SIM		
SIM Ions	NDMA	NDEA	
	74, 42 & 43	102, 57, 56 & 44	
Detector Voltage	Set relative to tune + 0.8 kV		
Electron Voltage	70 eV		

Linearity of the Calibration Curve:

A four-point calibration curve of NDMA & NDEA from 2.5 to 10 µg/L was analyzed using the conditions described in Table 1. The retention times, correlation coefficient & LOQ established from S/N and % RSD are shown in table 2. The calibration curves established for both components with (r^2) greater than 0.999 for calibration levels 2.5, 5.0, 7.5 & 10.0 ppb shown in Figure 2. Figure 3 & 4 depicts chromatographic overlay of all the linearity levels and 6 replicates of 5.0 ppb linearity solution respectively.

Table 2: LOQ summary

Component	R.T. (min)	LOQ (2.5 ppb)		r^2
		S/N	% RSD	
NDMA	7.58	134	4.0	0.999
NDEA	8.63	118	8.2	0.999

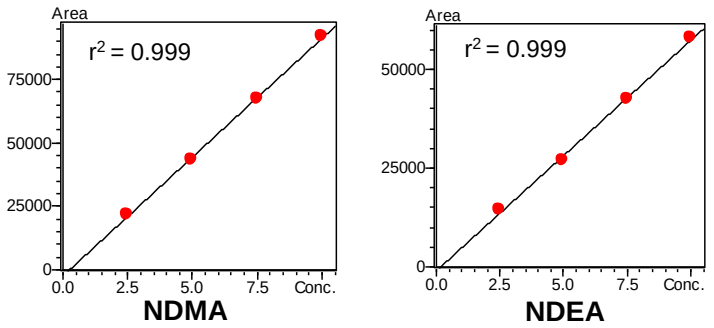


Figure 2: Calibration Curves from 2.5 ppb to 10 ppb

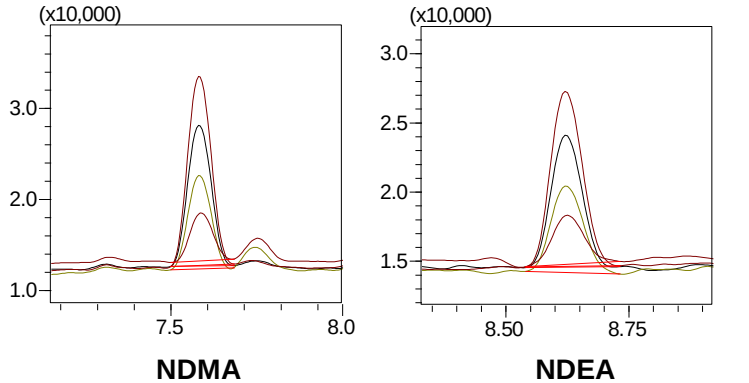


Figure 3: Chromatographic overlay from 2.5 ppb to 10 ppb

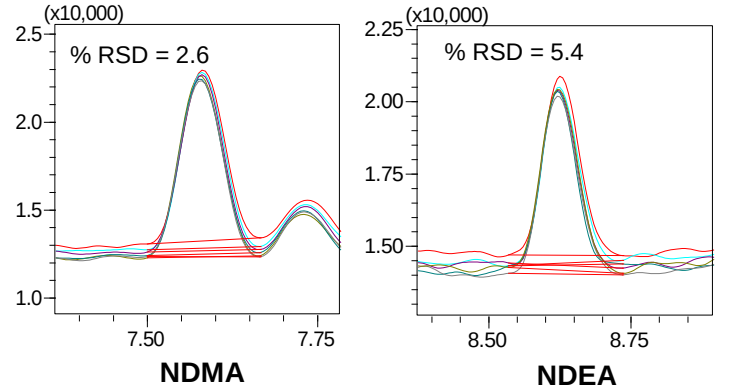


Figure 4: Chromatographic overlay of 6 replicates of 5 ppb

Sample Analysis:

Three API samples namely Valsartan, Losartan & Olmesartan-Medoxomil were individually weighed in a 20 mL headspace vial to which added 2 ml of DMSO as diluent to make 5 % w/v solution.

Spiked Recovery Test:

Samples of individual API's were weighed in a 20 ml headspace vial which were spiked with 2 ml 2.5 ppb, 5.0 ppb & 10.0 ppb NDMA & NDEA standard solutions respectively and were subjected for HSGCMS analysis.

Table 3, 4 & 5 shows results of the sample analysis and accuracy study for 3 API's.

Valsartan API				
Conc.	Sample Amount (ppb)		% Recovery	
	NDMA	NDEA	NDMA	NDEA
2.5 ppb	ND	130.4	108.6	104.6
5.0 ppb			99.9	96.5
10.0 ppb			100.5	114.2

Losartan API				
Conc.	Sample Amount (ppb)		% Recovery	
	NDMA	NDEA	NDMA	NDEA
2.5 ppb	ND	74.1	95.0	113.4
5.0 ppb			96.1	107.9
10.0 ppb			99.8	107.7

Olmesartan-Medoxomil API				
Conc.	Sample Amount (ppb)		% Recovery	
	NDMA	NDEA	NDMA	NDEA
2.5 ppb	ND	130.4	103.4	114.4
5.0 ppb			89.8	88.7
10.0 ppb			98.3	102.7

Conclusion:

- Trace level quantitation was done by referring USFDA OTR method and the results obtained are accurate, reliable & reproducible.
- Ultra Fast scanning, and ASSP™ features enabled sensitive, selective, fast, reproducible, and linear method of analysis.

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