GC-MS Method for the determination of NDMA and NDEA in Sartan (Valsartan, Losartan, Candesartan, Irbesartan, Olmesartan) APIs (developed on a Shimadzu GC-MS QP 2020plus):

GC Parameter:	Inj. temp.: 240 °C Split ratio: 10 Col. flow: 1.52 mL/min (He) Col. temp.: 60 °C (hold 2 min), 15 °/min → 130 °C (hold 3 min) 25 °/min → 240 °C (hold 10 min)
MS Parameter:	Ion source temp.: 230 °C Interface temp.: 240 °C Det. voltage: 1.5 kV (absolute) NDMA: Ch.1: 74.0 m/z; Ch.2: 42.0 m/z NDEA: Ch.1: 102.0 m/z; Ch.2: 44.0 m/z Max. area ratio deviation: ± 30 %
Headspace parameter (AOC-5000):	Sample-Vol.: 1.00 mL Incubat. temp.: 130 °C; Incubat. time: 20 min Agitator speed: 500 rpm; on time: 99 sec Syringe temp.: 140 °C GC runtime: 38:00 min
Column:	Restek Rtx-624 with guard-column (30 m x 0.32 mm I.D., 1.8 µm)
Solvent:	NMP (1-Methyl-2-pyrrolidon, ≥ 99,5 %, Merck 8.06072.1000)
Reagents:	NDMA (N-Nitrosodimethylamine), LGC standards DRE-C15604000, 0.1 g NDEA (N-Nitrosodiethylamine), Sigma Aldrich 73861-10ML, 10 mL

Stock solution (NDMA) = 80 µg/mL in MeOH

For example, weigh 5 mg of NDMA in a 2.0 mL volumetric flask and dilute to volume with methanol (c = 2,500 µg/mL). Dilute 0.32 mL in a 10.0 mL volumetric flask with NMP (c = 80 µg/mL).

Spiking solution (NDMA) = 40 µg/mL in NMP

Dilute 2.5 mL of Stock solution (NDMA) to 5.0 mL with NMP. (c = 40 µg/mL)

Stock solution (NDEA) = 100 µg/mL in MeOH

For example, weigh 5 mg of NDEA in a 50.0 mL volumetric flask and dilute to volume with methanol (c = 100 µg/mL).

Spiking solution (NDEA) = 50 µg/mL in NMP

Dilute 2.5 mL of Stock solution (NDMA) to 5.0 mL with NMP (c = 50 µg/mL).

Reference sample amount: 400 mg API

1. Linearity

Solution to be used	**Vol. [mL]**	**filled up with solvent [mL]**	**conc. [µg/mL]**	**ppm**	**resulting solution**
NDMA stock sol. NDEA stock sol.	0.5 0.15	 20	NDMA: 2 NDEA: 0.75	2.5 1	Standard 1
NDMA stock sol. NDEA stock sol.	0.2 0.1	 20	NDMA: 0.8 NDEA: 0.5	1 0.6	Standard 2
Standard 1	1	4	NDMA: 0.5 NDEA: 0.188	0.6 0.2	Standard 3
Standard 1	1	10	NDMA: 0.2 NDEA: 0.075	0.25 0.1	Standard 4
Standard 2	1	10	NDMA: 0.08 NDEA: 0.05	0.1 0.06	Standard 5

⇒ **result: R^2 (NDMA) = 0.9996**

⇒ **result: R^2 (NDEA) = 0.9993**

2. LOQ/LOD

Limit of quantitation/Limit of detection (LOQ/LOD):

	LOQ	LOD	Limit (320 mg Valsartan)
NDMA	0.10 ppm	0.01 ppm	0.300 ppm
NDEA	0.080 ppm	0.02 ppm	0.082 ppm

3. Sample preparation

Sample solution (real samples):

Weigh 400 mg API in a 20 ml headspace vial. Add 0.5 mL of solvent and crimp immediately. Prepare two sample solutions.

Prepare a third sample following the above procedure, but add 4 µL of each spiking solution (NDMA = 0.16 µg ≙ 0.4 ppm; NDEA = 0.2 µg ≙ 0.5 ppm). Recovery should be within 70 - 130 % for NDMA and within 70 – 150 % for NDEA.

Remarks:

The method is only suitable for API products.

It is recommended to check each sample for possible matrix interferences at the respective retention times for NDMA and NDEA. If any interference is present (area ratio > 30 %), the sample should be analysed by an alternative technique (e. g. LC-MS/MS).