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NITROSAMINE IMPURITIES IN PHARMACEUTICAL DOSAGE FORM: A REVIEW

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ABSTRACT

The FDA and other international agencies conducted a thorough study of nitrosamine contamination in the impacted APIs and drug products after they were found in various types of drug goods. Nitrosamine impurities are potent, broad acting carcinogens which if present above the safety levels can cause serious harm. This review discusses the background of the nitrosamine reports and its chemistry. Various official and reported analytical methods for quantification of nitrosamine impurities in different drug products and drug substances are mentioned below.

Keywords: Analytical method development, carcinogen, GC-MS, LC-MS/MS, Nitrosamine

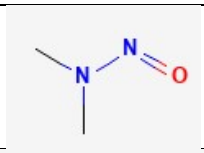
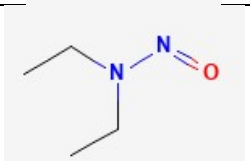
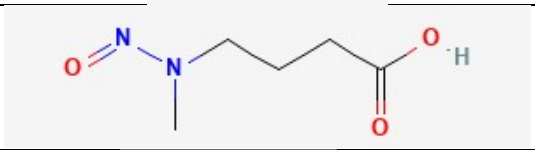
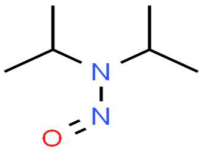
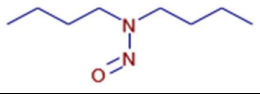
INTRODUCTION [1]

The FDA has been looking into the nitrosamine contaminants found in several medication products. Since 2018, it has been discovered that several medication items contain unsafe amounts of nitrosamines. From 2018 to 2019 various drug products such as valsartan, ranitidine, nizatidine, and metformin were recalled because of observed levels of nitrosamine. Even though nitrosamine impurities have only been found in a small number of drugs, and those batches have been recalled back from the market when impurities were in unacceptable amounts, additional APIs and drug products may also include nitrosamine impurities due to the use of sensitive procedures and materials that may cause them.

DRUG PROFILE OF NITROSAMINE

Most reported nitrosamine impurities:

Table 1: Drug Profile

Impurities	Structure	Molecular weight
N-nitroso dimethylamine, also known by the short form NDMA		**74.08 [2]**
N-nitrosodiethylamine, also known by the short form NDEA		**102.14 [3]**
N-nitroso-N-methyl-4-aminobutanoic acid, also known by the short form NMBA		**146.14 [4]**
N-nitrosodiisopropylamine, also known by the short form NDIPA		**130.19 [5]**
N-nitrosodibutylamine, also known by the short form NDBA		**158.24 [6]**

VARIOUS FACTORS ARE GENERALLY ASSOCIATED WITH THE FORMATION OF NITROSAMINE [1]

Secondary amines, tertiary amines, quaternary amines, and nitrite salts can lead to nitrosamine formation under acidic condition. Research has shown that low yields of nitrosamines can be produced from quaternary amines. The nitrosamines that happen to originate from quaternary amines does not even lower amine impurities. Polymeric and benzylated quaternary amines were more effective precursors as compared to quaternary alkylamines (monomeric) **[7]**. Nitrite salts then make nitrous acid, that reacts with amine and form nitrosamine. The chances of nitrosamine production exceeds if nitrous acid is being used in quenching of residual azide in the presence of precursor amines.

1. **Amines that can form nitrosamines**

A manufacturing process may contain amines for several reasons. The secondary or tertiary amine functional groups may be present in drug substances or in their degradants, intermediates, or beginning materials. As reagents or catalysts, tertiary and quaternary amines can also be purposefully added. Another source of secondary amines is amine solvents, which can degrade under specific reaction circumstances. For instance, N, N-

dimethylformamide can degrade into dimethylamine under certain conditions, such as high reaction temperatures and prolonged reaction times, which can then with nitrous acid to produce NDMA.

2. **Contamination in raw materials received by vendors**

When initial materials and fresh materials from vendors have impurities, nitrosamine impurities might be introduced. Fresh solvents such as ortho-xylene have been contaminated with nitrosamine after getting it from vendors (for example, during movement between different storage vessels).

In some precursor materials (such as sodium azide), sodium nitrite is a recognized contaminant that may be found and can easily react with amines in an acidic environment to produce nitrosamines. Nitrite impurities may be present in raw materials that contain nitrate, such as potassium nitrate. There have been reports of secondary or tertiary amine impurities in various raw and fresh materials and in new solvents such as toluene.

3. **Recovered reagents, catalysts, and solvents**

Because of the availability of leftover amines like trimethylamine, obtained materials such as solvents, reagents, and catalysts may provide a danger of nitrosamine contamination. The formation of nitrosamines during solvent recovery is possible if the recovery procedure includes a quenching part (NA is used to break down any leftover azide).

4. **Quenching process**

When a quenching phase is carried out directly in the main reaction mixture, there is a possibility of nitrosamine production (i.e., when nitrous acid is added to the reaction mixture to break down residual azide).

As a result, nitrous acid can directly interact with any remaining amines in the raw materials used in the manufacturing process. The nitrosamine contaminants may be carried over to the following phases if there are not enough removal or purification procedures in place, or if the processes are not optimised for removing specific impurities of concern. Once they are added, the entire downstream process could become contaminated.

5. **Lack of process optimization and control**

Absence of optimization of the production process for drug substance when reaction parameters like temp, pH, and order in which reagents, and solvents are added are incorrect or badly programmed and fresh materials and aimed in another potential source of nitrosamine impurities. There have been cases where reaction conditions for the same API varied significantly across batches and these differences were also between

varying processing devices housed in the similar facility.

ACCEPTABLE INTAKE [1]

The IARC has classes several nitrosamine impurities as probable or potential human carcinogens due to their severe genotoxic effects on a number of animal species (IARC). FDA issued temporary acceptable limits for these impurities after nitrosamine contamination in ARBs were found. The AI limit is calculated based on daily exposure of impurities that can cause cancer risk when an exposure of over 70 years was seen.

Table 2: Limits of AI for nitrosamine contamination in drugs products suggested by FDA.

Nitrosamine	AI limit (ng/day)
NDIPA	26.5
NMBA	96
NDEA	26.5
NIPEA	26.5
NMPA	26.5
NDMA	96

NITROSAMINE CONTAMINATION IN DRUG PRODUCT [8]

1. Angiotensin II Receptor Blockers

A biphenyl functional group forms the basis of all ARBs and sartans, except for eprosartan. Tetrazole analogues and nontetrazole analogues are the two structural subgroups of ARBs. As in-process impurities, nitrosamines are typically produced during the production of API and are found in ARBs. Co-existing primary amines, secondary amines, and tertiary amines or quaternary ammonium salts interact with nitrosating components to produce nitrosamine contaminations when the synthesis of ARBs occurs, which is the optimal scenario for the nitrosation process. As the amine precursor originates from leftover amides or amines in the organic solvents that are used in the synthesis of API, the chemical structures of ARBs and the contaminating nitrosamines are unrelated. With insufficient control and improper monitoring, nitrosating agents, such as $NaNO_2$, HNO_2, $N2O_3$, and NOX can form from recycled solvents or repurposed activators from various processes.

2. Ranitidine and Nizatidine

Ranitidine's nitrosamine contamination problem is less evident than that of ARBs. Nevertheless, because it acts as an NDMA precursor when water is chlorinated, this H2-blocker is being implicated as a potential source of nitrosamine pollution in water systems. The ranitidine dimethylamine molecule is substituted by the monochloramine (NH_2Cl) in a nucleophilic manner to produce a hydrazine complex, which is then later oxidised to form NDMA. Ranitidine has been identified as the most reactive NDMA precursor in numerous research. Additionally, this medicine

appeared to raise the level of NDMA in urine when taken orally. According to these in vitro and in vivo results that have been reported, ranitidine degradation may be the source of NDMA contamination. Alternately, it's thought that the ranitidine nitro functionality's inherent instability contributes to nitrosation.

3. Miscellaneous

The EMA has revealed that NDMA was found in several batches of the pioglitazone produced by Hetero Labs, India, but at permissible trace levels. Contrarily, Health Canada has announced a voluntary and mandatory recall of metformin made by few businesses, including Apotex Inc., because of NDMA impurities in numerous batches of finished goods that was above the permitted limit. Lots of metformin that were detected by a private laboratory to contain NDMA above the allowable consumption level were examined by FDA laboratories. The agency determined that some, but not all, of the lots contained unacceptable NDMA levels. The agency also discovered that, when NDMA was present, the amounts were typically lower than what the private laboratory had claimed.

Drug-drug interaction (DDI) experiments using rifampicin in healthy volunteers were discontinued in the US in August 2020 due to a problem with drug contamination. For DDI studies, alternate CYP offenders must be considered **[9]**.

QUANTITATIVE ANALYSIS OF NITROSAMINE IN PHARMACEUTICALS [10]

A new general chapter (1469) nitrosamine contamination that was in the pharmacopeial forum PF 46 has been published by the United States Pharmacopeia (USP).

Table 3: Available official methods for analysis of nitrosamine contamination in various drug substances and drug components

Officials	Instruments	Ionization techniques	Impurity	Drug substance/ drug product
FDA	GC-MS (DL)	Triple-quad	NDMA, NDEA	Valsartan
	GC-HS-MS machine	Quadrupole technique	NDMA impurity, NDEA impurity	
	LC-MS/MS machine	HR/triple-quad technique	NDMA impurity	Ranitidine
PALG	GC-HS-MS machine	Single quad technique	NDMA impurity	Sartans drug product
ANSM	HPLC-UV technique	NA	NDMA impurity, NDEA impurity	Sartans drug product
CVUA	UPLC-MS/MS technique	APCI technique	NDMA impurity, NDEA impurity	Sartans drug product
HEALTH CANADA	GC-MS/MS technique	EI technique	NDMA impurity, NDEA impurity	Sartans drug product
SWISSMEDIC	GC-MS machine	EI technique	NDMA impurity, NDEA impurity	Sartans drug product
LGL	GC-HS-MS machine	EI/CI technique	NDMA impurity, NDEA impurity	Sartans drug product
	LC-MS/MS machine	Q-trap technique	NDMA impurity, NDEA impurity	Sartans drug product

Table 4: Summarized report of analytical methods for determining nitrosamine in pharmaceutical products

Sr.no.	Drug name	Method	Specification
1.	Telmisartan [11]	LC-MS/Mass Spectroscopy	Column: Zorbax SB C18 150×3.0mm, 3.5µm Mobile phase A was composed of 0.1% formic acid in water Mobile phase B was made up of 0.1% formic acid in methanol Flow rate: 0.3 ml/min[11]
2.	Azilsartan, valsartan, Telmisartan, Olmesartan, losartan and irbesartan [12]	LC-MS/MS machine	Column: Poroshell HPH- C18 150×4.6mm, 2.7 µm Mobile phase A: 0.1% formic acid added in water Mobile phase B: 0.1% formic acid added in methanol Flow rate: 0.5 ml/min[12]
3.	Candesartan, Olmesartan, Irbesartan and Valsartan[13]	LC-MS/MS technique	Column: Agilent Eclipse XDB-C18 (5m×4.6mm×150mm) Mobile phase A: Water was used Mobile phase B: 0.1% formic acid mixed in methanol Flow rate for it was 0.5ml/min[13]
4.	Losartan, , Olmesartan, telmisartan, irbesartan, , candesartan, and valsartan products[14]	High performance liquid chromatography-tandem mass spectroscopy	Column: X Select HSS T3 (3.5µm, 100 mm, 4.6 mm) Waters Mobile phase: Water (A) and Methanol (B) both containing 0.1% formic acid Flow rate: 0.5 ml/min^{-1}[14]
5.	Telmisartan[15]	ESI-MS/MS	Column: Inert sustain AQ-C18, 250×4.6 mm, 5 µm Mobile phase A: 0.1% formic acid in water Mobile phase B: 0.1% formic acid + Methanol: acetonitrile (2:8) Detection: 220nm[15]
6.	Commercial formulation of metformin and glipizide[16]	UHPLC-APCI-TQ-MS	Column: Kinetex 150×3.0 mm Biphenyl 100 Å, 2.6 µm Mobile phase A: 0.1% w/v formic acid added in water Mobile phase B: 0.1% formic acid mixed in methanol Flow rate for it was: 0.4 ml/min[16]
7.	Valsartan, losartan and irbesartan[17]	LC-MS/MS	Column: Agilent InfinityLab Poroshell 120 EC-C18, 50 mm, 3.0mm, 2.7 µm Mobile phase A that was composed of: 0.1% formic acid mixed in ammonium formate (10mM) aqueous solution Mobile phase B was made up of: 0.1% formic acid mixed in methanol Flow rate of the component was: 0.4 ml/min[17]
8.	Candesartan cilexetil, irbesartan, valsartan, Olmesartan medoxomil, [18]	GC-MS/MS	Column: Agilent VF-Wax ultra-inert capillary (30 mm×0.25mm i.d., 1.0µm) Carrier gas: Helium gas Ionisation source: EI[18]
9.	Azilsartan medoxomil, candesartan cilexetil, irbesartan, losartan, Olmesartan medoxomil, telmisartan, valsartan[19]	GC-MS/MS	Column: Agilent technologies DB-WAX ultrainert (30m×0.25 mm; i.d., 0.25µm) and an Agilent DB-624 (60m× 0.25 mm; i.d., 1.40µm) Carrier gas: Helium gas Ionisation source: EI[19]
10.	Valsartan[20]	LC-MS/MS	Column: Avantor ACE UltraCore C18 superficially porous column in 100×3.0mm and 100 × 2.1 mm dimensions and a 3.5 µm particle size Mobile phase A: 20 mM KH_2PO_4, pH 2.7 (aq.) Mobile phase B: 20 mM KH_2PO_4, pH 2.7 in 7:3 MeCN-H_2O Detection: 254 nm[20]
11.	Rivaroxaban[21]	LC-MS/MS	Column: VD-Spher100 C18 E (150 mm × 4.6 mm, 3µm) Mobile phase: 0.1% formic acid and methanol (1:1 v/v) Flow rate: 0.6 ml/min[21]

12.	**Sitagliptin phosphate monohydrate API[22]**	**LC-MS/MS**	**Column: Agilent-ZORBAX SB-C18 (150 mm × 4.6 mm, 1.8µm) Mobile phase A: 0.01 mol L^{-1} ammonium formate in water Mobile phase B: Acetonitrile Flow rate: 0.4 ml/min[22]**
13.	**Valsartan[23]**	**UPLC-MS/MS**	**Column: Waters XBridge BEH C18 column (150 mm×4.6 mm, 2.5 µm) Mobile phase A: Ammonium acetate aqueous solution (0.01 mol/L) Mobile phase B: Acetonitrile Flow rate: 0.5 ml/min[23]**
14.	**Candesartan cilexetil, irbesartan, losartan, Olmesartan cilexetil, valsartan[24]**	**LC-MS/MS**	**Column: Xselect HSS T3 column (15 cm×3 mm i.d., 3.5 µm) Mobile phase A: 0.1% formic acid in water Mobile phase B: 0.1% formic acid in acetonitrile/methanol (2:8) Flow rate: 0.6 ml/min[24]**
15.	**Valsartan[25]**	**LC-MS/MS**	**Column: Kinetex F5 column (2.6µm, 100×4.6 mm) Mobile phase A: 0.1% formic acid in water Mobile phase B: 0.1% formic acid in methanol Flow rate: 0.6ml/min Detection wavelength: 230 nm[25]**
16.	**Valsartan and losartan[26]**	**Green HPLC**	**Column: RP-C18 symmetry column (75×4.6 mm, 3.5 µm) Mobile phase A: 0.02M AMA adjusted to pH 7.2 Mobile phase B: pure Ethanol Detection wavelength: 230 nm[26]**
17.	**Duloxetine hydrochloride[27]**	**LC-MS/MS**	**Column: X-Bridge Phenyl C18, 100×4.6 mm, 3.5 µm Mobile phase: formic acid and methanol Flow rate: 0.5 ml/min[27]**
18.	**1-methyl-4-nitrosopiperazine in Rifampicin[28]**	**LC-MS/MS**	**Column: ACE UltraCore Super C18 (4.6×50 mm, 2.5 µm) Mobile phase A: Aqueous 1mM ammonium formate Mobile phase B: Methanol Flow rate: 0.5 ml/min[28]**
19.	**Sitagliptin and metformin hydrochloride combination dosage forms[29]**	**LC-MS**	**Column: Atlantis T3 (100×3 mm, 3 µm) Mobile phase A: 0.1% formic acid in water Mobile phase B: 0.1% formic acid in methanol Flow rate: 1 ml/min[29]**
20.	**Lisinopril[30]**	**HPLC-FLD**	**Column: Reversed-phase LC-C18 DB (250×4.6 mm, 5.0 µm) Mobile phase: 20mM phosphate buffer (pH 2.8) and acetonitrile 55:45 v/v Flow rate: 3ml/min[30]**
21.	**Valsartan[31]**	**GC-MS/MS**	**Column: DM-WAX (30m×0.25 mm, 0.5 µm) Carrier gas: Helium Flow rate: 3 ml/min[31]**
22.	**Metformin[32]**	**LC-SRM-MS**	**Column: Hypersil GOLD Phenyl (100×4.6 mm, 3 µm) Mobile phase A: Water+0.1% formic acid Mobile phase B: Methanol+0.1% formic acid Flow rate: 0.5 ml/min[32]**
23.	**Valsartan and irbesartan[33]**	**LC-APCI-MS/MS**	**Column: Poroshell HPH C18 (4.6×150 mm, 2.7 µm) Mobile phase A: 0.2% formic acid in water Mobile phase B: Methanol[33]**
24.	**Metformin[34]**	**LC-HRMS**	**Column: Luna Omega PS C18, 3 µm, 4.6×100 mm, Phenomenex Mobile phase A: 0.1% formic acid in water Mobile phase B: 0.1% formic acid in methanol Flow rate: 0.75 ml/min[34]**
25.	**Ranitidine drug substance and drug product[35]**	**LC-MS**	**Column: ACE C18-AR 3 µm, 150×4.6 mm Mobile phase A: 0.1% formic acid in water Mobile phase B: 100% methanol Flow rate: 0.8 ml/min[35]**
26.	**Losartan[36]**	**HPLC-UV**	**Column: Inertsil ODS 3V (250mm×4.6mm, 5.0 µm)**

			Mobile phase: water: methanol (60:40 v/v) Flow rate: 1.0 ml/min Detection wavelength: 230 nm[36]
27.	**Drug substance and drug products of sartans, ranitidine and metformin[37]**	**SPE GC-MS/MS**	**Column: DB-624 capillary column (60m× 0.25mm id, 1.4 µm) Carrier gas: Helium gas Flow rate: 1.2 ml/min[37]**
28.	**Sitagliptin[38]**	**UPLC-MS/MS**	**Column: Kromasil-100, with C18 column (100 mm×4.6 mm, 3.5 µm) Mobile phase A: 0.12% formic acid in water Mobile phase B: 0.2% formic acid in methanol Flow rate: 0.6 ml/min[38]**
29.	**Midazolam drug substance[39]**	**UPLC-MS/MS**	**Column: ACQUITY UPLC BEH C18 column (2.1mm×100mm, 1.7 µm) Mobile phase A: Ammonium formate aqueous solution (0.1% formic acid) Mobile phase B: Acetonitrile (0.1% formic acid) Flow rate: 0.4 ml/min[39]**
30.	**Ranitidine[40]**	**UPLC-MS/MS**	**Column: Agilent InfinityLab Poroshell HPH-C18, 4.6×150 mm; 2.7 µm Mobile phase A: 0.1% formic acid in water Mobile phase B: 0.1% formic acid in methanol Flow rate: 0.3 ml/min[40]**
31.	**Ranitidine[41]**	**ESI-LC-MS/MS**	**Column: Diamonsil C18 column (4.6mm×150 mm, 5µm) Mobile phase A: 0.1% formic acid in methanol Mobile phase B: 0.1% formic acid in water Flow rate: 1.2 ml/min[41]**
32.	**Metformin hydrochloride, losartan potassium, valsartan, and ranitidine[42]**	**HPLC**	**Column: Phenomex C18 column Mobile phase: water-acetonitrile containing 0.1% formic acid Flow rate: 1 ml/min Detection wavelength: 254 nm[42]**
33.	**Allopurinol[43]**	**GC-HS/MS**	**Column: DB-WAXms capillary column (30m×0.25 mm, 1 µm) Flow rate: 1.5 ml/min[43]**
34.	**Cosmetic products[44]**	**Vortex-assisted dispersive liquid-liquid microextraction prior to gas chromatography-mass spectrometry**	**Column: VF-WAXms (30m×0.25 mm; 0.25 µm) Carrier gas: Helium gas Flow rate: 1 ml/min[44]**

CONTROL OF NITROSAMINE IMPURITIES

On December 9, 2020, a virtual panel discussion was held by the American Association of Pharmaceutical Scientists (AAPS) Chemistry, Manufacturing, and Control (CMC) Community to provide a venue for discussing N-nitrosamine controlling solutions in the pharmaceutical industry and biotechnology industries. People from FDA and other experts of the subject from the industry were on the panel. The acceptable and limit of intake levels for nitrosamine contamination, definitions of "acceptable level of risk," the role of H2O in nitrosamine risk evaluation, contamination control methods based on fate/purge data, expectations for development assessment (early vs. late), uses to oncology programs developed under ICH S9, and regulatory expectations were

some of the topics covered at the meeting **[45]**.

The ICH M7 guideline explains how to control the hazards connected to the probable existence of (possibly) mutagenic impurities (PMIs) within pharmacological ingredients. Following a wave of recalls due to inadequate amounts of the likely carcinogen in pharmaceutical products, the FDA issued recommendations to limit nitrosamine impurities **[46]**.

Additionally, most pharmacopoeias have adopted the idea of the guidelines of quality that is Q3A, Q3B, Q3C, and Q3D from ICH, which offer thorough direction and scientifically encompass a variety of contaminations, including organic as well as inorganic contaminations and residual solvents. The previously discovered mutagen species are difficult to identify and quantify, necessitating extensive research and cutting-edge analytical equipment that can measure minute levels of contaminants.

CONCLUSION

Nitrosamine and N-nitroso compounds are potent broad acting carcinogens. There have been reports of observed nitrosamine levels in various drug substances and drug products. Although quantified within safety levels, it is necessary to assess and quantitate the amount of nitrosamine contamination in the API and formulations. This article aims towards signifying the chemistry and reason for formation of nitrosamine on various stages of development. Various analytical methods that are reported for identifying and quantifying nitrosamine contaminations in drug products are listed in this review which can be helpful for development of method for research purposes.

REFERENCES

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Control of Nitrosamine Impurities in Human Drug- Guidance for Industries, Revision 1, 2021, p.g.no. 1-10.

[2] National Centre for Biotechnology Information (2023). PubChem Compound Summary for CID 6124, N-Nitrosodimethylamine. Retrieved March 23, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/N-Nitrosodimethylamine.

[3] National Centre for Biotechnology Information (2023). PubChem Compound Summary for CID 5921, N-Nitrosodiethylamine. Retrieved March 23, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/N-Nitrosodiethylamine.

[4] National Centre for Biotechnology Information (2023). PubChem Compound Summary for CID 43659, N-Nitroso-N-methyl-4-aminobutyric acid. Retrieved March

23, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/N-Nitroso-N-methyl-4-aminobutyric-acid.

[5] National Centre for Biotechnology Information (2023). PubChem Compound Summary for CID 11758, N-Nitrosodiisopropylamine. Retrieved March 23, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/N-Nitrosodiisopropylamine.

[6] National Centre for Biotechnology Information (2023). PubChem Compound Summary for CID 13542, N-Nitrosodibutylamine. Retrieved March 23, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/N-Nitrosodibutylamine.

[7] Kemper JM, Walse SS, Mitch WA. Quaternary amines as nitrosamine precursors: a role for consumer products. Environmental Science & Technology. 2010 Feb 15;44(4):1224-31.

[8] Li K, Ricker K, Tsai FC, Hsieh CJ, Osborne G, Sun M, Marder ME, Elmore S, Schmitz R, Sandy MS. Estimated cancer risks associated with nitrosamine contamination in commonly used medications. International journal of environmental research and public health. 2021 Sep 8;18(18):9465.

[9] Van Haarst A, Smith S, Garvin C, Benrimoh N, Paglialunga S. Rifampicin Drug–Drug–Interaction Studies: Reflections on the Nitrosamine Impurities Issue. Clinical Pharmacology & Therapeutics. 2022 May 20.

[10] https://www.usp.org/sites/default/files/usp/document/stakeholder-forum/pnp/highlights-of-1469-nitrosamine-impurities.pdf

[11] Chidella KS, Dasari VB, Anireddy J. Ultra-Sensitive LC-MS/MS Method for the Trace Level Quantification of Six Potential Genotoxic Nitrosamine Impurities in Telmisartan. American Journal of Analytical Chemistry. 2021 Jun 10;12(6):227-40.

[12] Gopireddy RR, Maruthapillai A, Mahapatra S. A Multi-Analyte LC–MS/MS Method for Determination and Quantification of Six Nitrosamine Impurities in Sartans like Azilsartan, Valsartan, Telmisartan, Olmesartan, Losartan and Irbesartan. Journal of Chromatographic Science. 2022 Jul 14.

[13] González R, Torrado G, Arribas JM, Peña MA. Development of an analytical method for the determination and quantification of n-nitrosodimethylamine in

olmesartan by HPLC-MS/MS. Microchemical Journal. 2022 Aug 1; 179:107402.

[14] Monteiro MA, de Lima PC, Novotny TS, Santana DS, Lima ME, Dantas AS, dos Santos LO, de Souza MN, Maranho RL, Ochs SD. Development and Validation of Methods Based on High-Performance Liquid Chromatography-Tandem Mass Spectrometry for Determining N-Nitrosamines Impurities in Sartan Pharmaceutical Products for Monitoring Program. Available at SSRN 4057039.

[15] Yarala MR, Gummadi S. Determination of Potential Genotoxic Impurities (Orthophenylene Diamine Dihydrochloride), 4'-Bromomethyl-2-Cyanobiphenyl, 4'(Dibromomethyl)[1, 1'-Biphenyl]-2-Carbonitrile in Telmisartan by ESI-MS/MS. Journal of Chromatographic Science. 2021 Dec 30.

[16] Solanki R, Patel C, Patel R, Maradiya A, Parikh S, Gayakvad B. UHPLC-APCI-TQ-MS analytical method to quantify nitrosamine impurities in the commercial formulation of metformin and glipizide. Journal of Liquid Chromatography & Related Technologies. 2022 Sep 28:1-0.

[17] Khorolskiy M, Ramenskaya G, Vlasov A, Perederyaev O, Maslennikova N. Development and validation of four nitrosamine impurities determination method in medicines of valsartan, losartan, and irbesartan with HPLC-MS/MS (APCI). Iranian Journal of Pharmaceutical Research: IJPR. 2021;20(3):541.

[18] Liu J, Xie B, Mai B, Cai Q, He R, Guo D, Zhang Z, Fan J, Zhang W. Development of a sensitive and stable GC-MS/MS method for simultaneous determination of four N-nitrosamine genotoxic impurities in sartan substances. Journal of analytical science and technology. 2021 Dec;12(1):1-8.

[19] Chang SH, Ho HY, Zang CZ, Hsu YH, Lin MC, Tseng SH, Wang DY. Screening of nitrosamine impurities in sartan pharmaceuticals by GC-MS/MS. Mass Spectrometry Letters. 2021;12(2):31-40.

[20] James M, Edge T. Low-Level Determination of Mutagenic Nitrosamine Impurities in Drug Substances by LC–MS/MS. LCGC Europe. 2021 Jul 12;34(7):267-76.

[21] Baksam VK, Saritha N, Devineni SR, Jain M, Kumar P, Shandilya S, Kumar P. A Critical N-Nitrosamine Impurity of Anticoagulant Drug, Rivaroxaban: Synthesis, Characterization, Development of LC–MS/MS Method for Nanogram Level Quantification. Chromatographia. 2022 Jan 1:1-0.

[22] Wichitnithad W, Nantaphol S, Noppakhunsomboon K, Rojsitthisak P. An update on the current status and prospects of nitrosation pathways and possible root causes of nitrosamine formation in various pharmaceuticals. Saudi Pharmaceutical Journal. 2022 Dec 24.

[23] Wang Z, Hu S, Wu X, He Z, Ke C, Hu M. A highly sensitive LC-MS/MS method for determination and quantification of a recently identified N-nitrosamine impurity in the sitagliptin phosphate monohydrate active pharmaceutical ingredient. Analytical Methods. 2023.

[24] Li S, Dong L, Tang K, Lan Z, Liu R, Wang Y, Wang R, Lin H. Simultaneous and trace level quantification of two potential genotoxic impurities in valsartan drug substance using UPLC-MS/MS. Journal of Pharmaceutical and Biomedical Analysis. 2022 Apr 1; 212:114630.

[25] Chang SH, Chang CC, Wang LJ, Chen WC, Fan SY, Zang CZ, Hsu YH, Lin MC, Tseng SH, Wang DY. A multi-analyte LC-MS/MS method for screening and quantification of nitrosamines in sartans. Journal of Food and Drug Analysis. 2020;28(2):292.

[26] Xu Q, Li Q, Belsky JL, Min D, Biba E, Gump E, Simpson JT. Development and Validation of a Single Quadrupole LC/MS Method for the Trace Analysis of Six Nitrosamine Impurities in Valsartan. MS Method for the Trace Analysis of Six Nitrosamine Impurities in Valsartan. 2021.

[27] Abd El-Hay SS, Elhenawee M, Maged K, Ibrahim AE. Cost-effective, green HPLC determination of losartan, valsartan and their Nitrosodiethylamine impurity: Application to pharmaceutical dosage forms. Royal Society Open Science. 2022 Jun 1;9(6):220250.

[28] Gopireddy RR, Maruthapillai A, Tamilselvi M. Determination of potential nitrosamines NDMA, NDIPA and N-Nitroso Duloxetine in Duloxetine Hydrochloride by

LC-MS/MS using APCI source. Materials Today: Proceedings. 2022 Jan 1;68:A7-20.

[29] Tao X, Tian Y, Liu WH, Yao S, Yin L. Trace Level Quantification of 4-Methyl-1-Nitrosopiperazin in Rifampicin Capsules by LC-MS/MS. Frontiers in Chemistry. 2022 Feb 14; 10:30.

[30] Mallavarapu R, Katari NK, Siddhani VK, Marisetti VM, Rekulapally VK, Vyas G, Jonnalagadda SB. Development and validation of rapid ultra-high performance liquid chromatography with tandem mass spectroscopic method for the quantification of N-nitrosodimethyl amine and N-nitrosodiethyl amine in sitagliptin and metformin hydrochloride immediate and extended-release formulations. Journal of Separation Science. 2022 Aug;45(16):3067-81.

[31] Tsanaktsidou E, Kanata L, Almpani S, Zacharis CK, Markopoulou CK. Development and Validation of an HPLC-FLD Method for the Determination of NDMA and NDEA Nitrosamines in Lisinopril Using Pre-Column Denitrosation and Derivatization Procedure. Separations. 2022 Nov 4;9(11):347.

[32] Tummala SR, Amgoth KP. Development of GC-MS/MS Method for Simultaneous Estimation of Four Nitrosoamine Genotoxic Impurities in Valsartan. Turkish Journal of Pharmaceutical Sciences. 2022 Aug 1;19(4).

[33] Yang H, Moy E, Volny M, Martins C, Du M, Elmasri W, Tadey T. Highly sensitive and robust LC-MS/MS solution for quantitation of nitrosamine impurities in metformin drug products.

[34] Mavis ME, Gursu GG, Cagatay NU. Development of A Sensitive LC-APCI-MS/MS Method for Simultaneous Determination of Eleven Nitrosamines in Valsartan and Irbesartan with A Simple Extraction Approach. Journal of Chromatography B. 2023 Jan 13:123593.

[35] Yang J, Marzan TA, Ye W, Sommers CD, Rodriguez JD, Keire DA. A cautionary tale: quantitative LC-HRMS analytical procedures for the analysis of N-Nitrosodimethylamine in metformin. The AAPS Journal. 2020 Jul; 22:1-8.

[36] Rao GS, Ramadevi D, Rao BM, Rajana N, Basavaiah K. Novel

stability indicating LC-MS method for N-Nitroso dimethyl amine genotoxic impurity quantification in ranitidine drug substance and drug product. Journal of Applied Pharmaceutical Science. 2022 Jul 5;12(7):106-14.

[37] Patil S, Chadar R, Prasad A, Koppula P, Koppula S. Quantification and Validation of a HPLC-UV Method for Simultaneous Analysis of Nitrosamine Impurities (NDMA, NDEA and NDIPA) in Losartan. Journal of Pharmaceutical Research. 2021 Oct;20(4):44.

[38] Lim HH, Oh YS, Shin HS. Determination of N-Nitrosodimethylamine and N-Nitrosomethylethylamine in drug substances and products of sartans, metformin and ranitidine by precipitation and solid phase extraction and gas chromatography–tandem mass spectrometry. Journal of pharmaceutical and biomedical analysis. 2020 Sep 10; 189:113460.

[39] Chittireddy HN, Kumar JS, Bhimireddy A, Shaik MR, Khan M, Adil SF, Khan M, Aldhuwayhi FN. Development and Validation for Quantification of 7-Nitroso Impurity in Sitagliptin by Ultraperformance Liquid Chromatography with Triple Quadrupole Mass Spectrometry. Molecules. 2022 Dec 5;27(23):8581.

[40] Chen D, Luo L, Shen D, Huang L, Zeng L, Wang J. A Simple and Sensitive UPLC–MS/MS Method for the Simultaneous and Trace Level Quantification of Two Potential Genotoxic Impurities in Midazolam Drug Substance. Chromatographia. 2022 Nov 23:1-7.

[41] Angrish P, Mani C, Banerjee S. Development of a Validated Method of Testing for NDMA in Ranitidine. Pharmaceutical Technology. 2020 Oct 3;44(10):42-7.

[42] Liu J, Zhao Z, Yang X, Jin Y, Liu X, Wang C, Zhang Z. Determination of N-nitrosodimethylamine in Ranitidine Dosage Forms by ESI-LC-MS/MS; Applications for Routine Laboratory Testing. Iranian Journal of Pharmaceutical Research: IJPR. 2021;20(4):255.

[43] Kirakosyan, V.G., Vardapetyan, S.M., Varderesyan, L.H. and Tsaturyan, A.H., 2021. Development Of A Rapid And Efficient Method For Quantitative

Determination Of N-Nitrosodimethylamine Impurity By High-Performance Liquid Chromatography In Metformin Hydrochloride, Losartan Potassium, Valsartan And Ranitidine Medicinal Raw Materials And Its Products. Proceedings of the YSU B: Chemical and Biological Sciences, 55(3 (256)), pp.296-299.

[44] Shaikh T, Gosar A, Joglekar A, Mahatre S. Development Of Headspace Gas Chromatography-Mass Spectrometry (Gchs-Ms) Method For The Determination Of Trace Level N-Nitrosomorpholine (Nmor) Impurity In Allopurinol.

[45] Schettino L, Benedé JL, Chisvert A. Determination of nine prohibited N-nitrosamines in cosmetic products by vortex-assisted dispersive liquid–liquid microextraction prior to gas chromatography-mass spectrometry. RSC Advances. 2023;13(5):2963-71.

[46] Roberts SW, Lennard A, Mohan G, Bernstein J, Cauchon NS, Cole S, Curristin N, Huynh-Ba K, Kolz CN, Murti C, Tang K. Meeting Report: N-Nitrosamine Impurity Control Strategies in the Pharmaceutical and Biotechnology Industries.

[47] Burns MJ, Teasdale A, Elliott E, Barber CG. Controlling a cohort: use of mirabilis-based purge calculations to understand nitrosamine-related risk and control strategy options. Organic Process Research & Development. 2020 Jun 30;24(8):1531-5.