EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 12
Issue: 5
Year: 2025

MITIGATING N-NITROSAMINE IMPURITIES IN PHARMACEUTICALS: DETECTION, RISK AND REGULATORY MEASURES

Yogeshwari M. Kadam*, Hemant P. Alhat, Sarika H. Alhat and Shashikant N. Dhole

PES Modern College of Pharmacy (For ladies), Moshi, Pune.

***Corresponding Author: Yogeshwari M. Kadam**
PES Modern College of Pharmacy (For ladies), Moshi, Pune.

Article Received on 22/03/2025 **Article Revised on 12/04/2025** **Article Accepted on 02/05/2025**

ABSTRACT
A nitrosamine impurity partially nitrosamine derived from secondary amine, posses significant risk due to their established carcinogenic properties. These organic compound health garnered attention, particularly after their detection in various medication, including angiotensine II receptors blockers and anti-diabetic drugs, prompting recalls and regulatory scrutiny. The formation of nitrosamines is attributed to reactions involving amides, carbamates, and nitrites during pharmaceutical manufacturing processes. Advance analytical techniques such as HPLC-HRMS and GCMS are crucial for detecting these impurities, ensuring that their levels remain complaint with safety standards set by regulatory agencies like the FDA, ICH and USP. To mitigate risks, comprehensive guidelines have been established, focusing on rigorous risk assessments and the need for stringent controls over raw materials and manufacturing processes. Ongoing research and cooperation between regulatory authorities and the pharmaceutical sector are crucial for maintaining the safety and effectiveness of medicinal products.

KEYWORDS: Nitrosamines, Impurities, Advance analytical methods, Regulatory guidelines.

INTRODUCTION

N-nitrosamine impurities are organic substances identified by the presence of a nitroso (N-N=O) functional group. In the field of organic chemistry, "nitroso" signifies that this group is attached to an organic structure. Nitroso compounds are divided into several categories, including C-nitroso compounds (like nitroso alkenes, R-N=O), S-nitroso compounds (such as nitroso thiols, RS-N=O), N-nitroso compounds (which include nitrosamine, RN(-R)N=O) and O-nitroso compounds (such as alkyl nitrites, RO-N=O).[1] Nitrosamine are known carcinogenic impurities formed through reactions involving secondary amine, amides, carbamates, and nitrides or other nitrogenous agents.[2] These compounds can be found in a range of products such as beverages, food items, pesticides and tobacco. They gained considerable focus in 2018 after being detected in pharmaceutical products.[3] Studies have established a link between nitrosamines and development of cancer in several organs including the liver esophagus, nasal passages, lungs, bladder, tongue, forestomach, and pancreas. The specific development of these tumor depend on both the type of N-nitrosamines and species tested.[4] Due to their significant mutagenic and carcinogenic properties, N-nitrosamines are categorized as a "concern group" by the International Council for Harmonisation of Pharmaceutical Guidelines. Emphasizing the importance of evaluating and controlling DNA-reactive impurities in pharmaceutical is crucial to minimizing the potential risk of cancer.[5]

Direction of nitrosamine as unwanted contamination in drug component and final products

Table 1: Overview of nitrosamine: Chemical name, Acronyms, Cas numbers, Formulas and Molecular weights.

Acronyms	Name of chemicals	Empirical Formula	Molecular Mass g/mol	CAS#
NDBA	Nitrosodibutylamine-A-Butyl-V-nitroso-1-butanamine	$C_8H_{18}N_2O$	158.25	924-16-3
NDMA	Nitrosodimethylamine-A-Methyl-7V-nitrosomethanamine	$C_2H_6N_2O$	74.08	16-75-9
NMBA	Nitrosomethylaminobutyric acid-4-[Methyl (nitroso) amino] butanoic acid	$C_5H_{10}N_2O3$	14.15	61445-5-4
NDEA	Nitrosoiethylamine A-Isopropyl-A-	$C_4H_{10}N_2O$	102.14	55-18-6

	Nitroethanamine			
NEIPA	Nitrosoethylisopropylamine-W-ethyl-A-nitoso-2-amine-propanamine	$C_5H_{12}N_2O$	116.16	16339-04-1
NMPA	Nitrosomethylphenylamine-A-methyl-A-nitrosophenylamine	$C_7H_8N_2O$	136.15	614-00-6
NDIPA	Nitrosodiisopropylamine-A-isopropyl-A-nitrosoisopropylamine	$C_6H_{14}N_2O$	130.19	601-77-4

History and Occurrence of nitrosamine impurites

The FDA begin its investigation into nitrosamine impurity in drug in 2018. These impurities have been identified in several type of medications including angiotensin-II receptor blockers, Histamine-2 blockers (such as ranitidine and nizatidine), antidiabetic medications like metformin and sitagliptine, antibiotic like rifampin and rifapentine, smoking cessations drugs such as varenicline, Sitagliptine.[6] The issue of nitrosamine contamination has become a significant global concern expanding beyond angiotensin receptor blocker (ARBs), regulatory agencies such as the EMA and the U.S. FDA have reported instances of NDMA contamination in various medications. including ranitidine, nizatidine and metformin. Recently, attention has also turned to newly identified nitrosamine impurities. Specifically1-methyl-4-nitrosopiperazine has been detected in rifampin, while 1-cyclopentyl-4-nitrosopiprazine (CPNP) has been found in rifampentine. This ongoing scrutiny highlights the needs of vigilance in monitoring pharmaceutical safety.[7, 8, 9, 10, 11, 12]

Table 2: Categories of Drug Impurities and Their Corresponding Action or Outcomes.[6]

Date	Drug/ Category	Impurity	Action/Outcome
June 2018	Valsartan (Angiotensin-II Blocker)	NDMA	FDI discovered NDMA in numerous lots manufacturer recall affected batchs, leading to drug shortages.
September 2019	Ranitidine (Zantac), Nizatidine	NDMA	FDI recommended voluntary recalls of product exceeding acceptable NDMA levels; noted stability testing concern regarding NDMA level increasing overtime
April 2020	Ranitidine	NDMA	FDI requested withdrawal of all ranitidine in product from the US market
December 2019	Metformin	NDMA	FDA identified NDMA in some samples requested voluntary recall of specific loss with level acceptable intake limit
August 2020	Rifampin, Refapentine	MNP, CPNP	FDA allowed distribution of affected drug while manufacturer work to reduce or eliminate impurities preventing shortage
July 2021	Varenicline (Chantix)	N-nitroso-varenicline	FDA permitted distribution of varenicline above recommended acceptable intake limit but below interim limit) until impurities could be reduced; levels were lowered by August 2021.
August 2022	Sitagliptine	NTTP	FDA encouraged manufacturers to report sitagliptin products exceeding recommended levels of NTTP, evaluating distribution on a case by case basis

Nitrosamine impurity found in drugs

Recently there have been concerns regarding finished pharmaceutical product containing impurity that exceed regulatory acceptance levels.[13] Authorities have discovered the presence of nitrosamine contamination in multiple bioactive substance and regulated medication, resulting in unforeseen withdrawal of drugs such as ranitidine, metformin, nizatidine, sitagliptin, valsartan and varenicline because of elevated concentrations of these contamination.[14, 15]

Table 3: Overview of impurities found in drug products.

Product Name	Properties	Therapeutic Class	Common Used
Valartans	Empirical Formula-$C_{24}H_{29}N_5O_3$ Molecular weight - 435.519 g/mol Melting point - 105-110℃ White Powder Highly dissolve in solvent such as ethanol, methanol, and acetonitrile, Limited solubility in water	Angiotensin II receptor antagonists	Manage high blood pressure[14, 15, 16, 3]

Ranitidine hydrochloride	Empirical Formula-$C_{13}H_{22}HN_4O_3SHCL$ Molecular weight - 314.41 g/mol Melting point - 134℃ White or light yellow crystals. Readily dissolves in water. Poorly soluble in anhydrous alcohol. Minimally soluble in dichloromethane.	H2-receptor antagonists	Inhibiting acid secretion caused by gastrin. To treat Zollinger-Ellison syndrome and peptic ulcers. They also help prevent stress ulcer and the recurrence of gastric and duodenal ulcers[17, 18]
Metformin hydrochloride	Empirical Formula- $C_4H_{11}N_5$ Molecular weight - 165.62 g/mol Melting point - 232℃ White crystalline powder Dissolves quickly n water. Barely dissolves in acetone, chloroform, dichloromethane, and ether.	Type II Diabetes	Decreasing glucose production in the liver Lowering glucose absorption in the gastrointestinal tract [19, 20]
Nizatidine	Empirical Formula-$C_{12}H_{21}N_5O_2S_2$ Molecular Weight- 331.46 g/mol Melting point - 130-132℃ Off-white crystalline powder Soluble in water	H2-receptor antagonists	Reduces gastric acid secretion Managing gastroesophageal reflux disease, peptic ulcers, and duodenal ulcers[21]
Refampicine	Empirical Formula- $C_{43}H_{58}N_4O_{12}$ Molecular weight - 822.9402 g/mol Melting point - 183-188℃ Highly soluble in Methyl chloride, dimethyl sulfoxide, tetrahydrofuran, chloroform, ethyl acetate and methanol with limited solubility in water (PH<6) acetone and carbon tetrachloride.	Anti microbacterias	Diverse mycobacterial infections and gram positive bacterial infection treatment of tuberculosis (TB)[14, 22]
Famotidine	Empirical Formula- $C_8H_{15}N_7O_2S_3$ Molecular Weight - 337.445 g/mol Melting point - 163.5℃ White or pale yellow crystals Dissolves well in glacial acetic acids, slightly dissolves in methanol, and exhibits minimal solubility in ethanol and water.	H2-receptor antagonists	Manage conditions like duodenal ulcer, benign stomach ulcer, GERD (gastroesophageal reflux disease), and Zollingers-Ellison syndrome[14,23]
Varenicline	Empirical Formula- $C_{13}H_{13}N_3$ Molecular weight - 211.268 g/mol Melting point - 138.5℃ Appears as a white to off- white or pale yellow solid; readily dissolves in water	Cholinergic receptor agonist partical cholinergic nicotinic agonist	Treat aids in smoking cessation and as as a nasal spray, treat dry eye disease symptoms[14, 24, 25]
Sitagliptin	Empirical Formula-$C_{16}H_{15}F_6N_5O$ Molecular Weight- 407.31 g/mol Melting point - 114.1-115.7℃ White to off white, viscous liquid	Dipeptidyl Peptidase 4 (DPP4) inhibitor	Treat diabetes, prediabetes, intestinal inflammation, impaired glucose tolerance, hepatitis and inflammatory liver diseases[14, 26]
Atorvastatin calcium	Empirical Formula-$(C_{33}H_{35}FN_{205})_2CaH_2O$ Molecular weight - 1209.42g/mol Melting point - 176℃ Pale white to light off-white crystalline solid. Minimal solubility in acenonitrile and pH 7.4 phosphate buffer Easily dissolves in methanol and slightly in ethanol	HMG-CoA Reductase inhibitor	Inhibiting cholesterol production in the lever, decreasing the risk of developing cardiovascular diseases[27, 28, 29]

Advanced analytical methods are employed to detect nitrosamine impurity

Analytical technique are essential in the pharmaceutical industry and research laboratories ensuring the production of safe and effective medications chemical analysis can be broadly categorized into two types quantitative and qualitative analysis focus on determining the composition of a substance while quantitative analysis is a concern with the measuring the concentration of specific bioactive compound, markers or impurities a variety of analytical methods are utilized for these purpose including UV Spectroscopy, FTIR, HPLC, LCMS/MS, GCMS/MS with headspace, LC-FTIR, LC-NMR, CE-MS, CE-NMR, SFC-MS, LC-FT, NMR these techniques are widely applied in both qualitaive and quantitative evaluations of pharmaceutical product research institute particularly in academic setting often have access to cutting aged analytical technologies before pharmaceutical products such as active pharmaceutical ingredient is approved for market release it must meet strict purity standard with impurity not exceed 0.05%.[30]

To detect nitrosamines in certain medications, several analytical methods can be used, such as chromatography coupled with mass spectrometry, UV spectrophotometry or nitrogen chemiluminescence detection (NCD). The United States Pharmacopeia (USP) provides guideline for manufacturers to identify nitrosamine impurity particularly for common compound like NDMA, NDEA, NDIPA, NEIPA, NMBA. Four key analytical methods are recommended for this testing.

1. High Performance Liquid Chromatography integrated with High Resolution Mass Spectrometry (HPLC - HRMS): This method is adviced for detecting a range of nitrosamines, including, NDEA, NDBA, NDMA, NMBA, NEIPA and NDIPA
2. Gas Chromatography integrated with Mass Spectrometry (GC - MS/MS): This technique can be utilized to identify NEIPA, NDIPA, NDMA and NDEA.
3. HPLC tendon mass spectrometry this method is also recommended for analyzing nitrosamine such as NDMA, NDEA, NDIPA and NMBA.
4. Gas Chromatography integrated with Tandem Mass Spectrometry (GC - MS/MS): GC - MS/MS is suggested for identification of NDMA, NDEA, NDIPA and NMBA.[2]

Table 4: Nitrosamine compounds: Chemical Information and Analytical detection methods.

Product Name	Technique	Analytical method	Impurities
Water	PLCPC-UV	Using post-column UV photolysis and Griess reaction in high-performance liquid chromatography, N-nitrosamine and other related nitroso compounds in water are analysed	NMOR, NDEA, NPYR, NPIP, NDPA, N-Nitro, NDELA, NDMA, NDBA, NMEA, NMOR[31]
Groundwater	LC-MS	Triple quadrupole mass spectroscopy in conjunction with ultra high-performance liquid chromatography allowed for the simultaneous detection of nine different types of N-nitrosamine compounds in groundwater	NMor, NPIP, NPYR, NDBA, NMEA, NDEA, NDPA, NDphA and NDMA[32]
Food	HPLC-UV-FLD	Analytical research on a new technique using terbium-doped carbon dots and HPLCUV-FLD coupling to determine the amount of nitrosamine in food	NDBA, NMor, NPYR, NPIP, NDEA[33]
Sartans	HPLC	Nitrosamine analysis with a special stationary phase technique	NPIP, NDPA, NDBA, NMEA, NPYP, NDEA, NMOR, NDBA and NDPHA[34]
	LC/MS	Nitrosamine impurity determination with the Ultivo Triple Quadrupole LS/MS	N-test-butyl-N-ethylnitrosamine, NMBA, NDMA, NEIPA, NDEA, NDBA, NPIP, NMEA, NPYR, NMPHA, NDIPA, NMIPA[35]
	LC-MS	Using Liquid Chromatography and Tandem Mass Spectrometry, the genotoxic contaminant N-nitroso-N-methyl-4-aminobutyric acid was quantified in four sartan compounds.	NMBA, NDMA, NDEA, NDBA[36]
	LC-MS/MS	LC-MS/MS method for NDEA and NDMA testing of film coated tablets containing sartan	NDMA, NDEA NDEA and NDMA[37]
		Utilizing the High Resolution Agilant 6546 LC/Q-	NDEA, NPYR,

		TOF for nitrosamine impurity determination	NEIPA, NMPHA, NDMA, NDBA, NDIPA, NMBA, NMEA, and NMIPA[38]
		A LC-MS/MS multi-analytic technique for detection and quantitation of nitrosamine in sartans medication	NDPHA, NDMA, NMEA, NMEA, NDPA, NMOR, NPIP and NDEA[39]
		The Six nitrosamine contamination in sartans medication including Telmisartan, Azilsartan, Olmesartan, Losartan, Valsartan and Irbasartan were identified and quantified using the multianalytic LCMS/MS method.	NDEA, NDMA, NDIPA, NDBA, NMBA, NEIPA[40]
Valsartan	HPLC	Using the liquid chromatographic method, six nitrosamine impurities in valsartan were simultaneously estimated.	NDBA, NMBA, NDEA, NDIPA, NEIPA, NDMA[41]
	HPLC	N-Nitrosodimethylamine impurity in Valsartan drug substance and its Formulations: Fast and effective high-Performance Liquid Chromatography analysis	NDMA[42]
	HPLC-MS/MS	HPLC-MS/MS for the Rapid Detection of Genotoxic impurities	NPYR, NDEA, NPIP, NDELA, NDPA, NMOR, NDBA, NDMA[43]
Losartan	HPLC-UV	The HPLC-UV technique for the simultaneous detection of nitrosamine contamination such as NDIPA, NDMA and NDEA in Losartan: Qualification and Validation	NDMA, NDEA, NDIPA[44]
Losartan and Valsartan	HPLC	Applications of economical and environmentally friendly HPLC method in analysis of Losartan, Valsartan and their nitrosodiethylamine impurity in pharmaceutical formulations.	NDEA[45]
Losartan, Valsartan and other ARBs	LC-HRMS	Pharmaceutical nitrosamine impurity detection using an LCHRMS-based analytical platform: contemporary analytical methods satisfy regulatory requirements	NEIPA, NDMA, NDEA, NMBA NDBA and NDIPA[46]
Olmesartans	HPLC-MS/MS	Creation of an HPLC-MS/MS analytical technique for measuring and identifying N-nitrosodiethylamine in Olmesartans	NDEA[47]
Telmisartan	LC-MS/MS	an Ultra-Lensitive LC-MS/MS technique can be employed to quantified Six possible Genotoxic Nitrosamine contamination in Telmisartan at the trace level using	NDEA, NEIPA, NDIPA, NDBA, NMBA[48]
Metformin	HPLC-MS	Impact of Hypromellose and Metformin on the formulation drug product on the production of N-nitrosodimethylamine in prolonged-released tablets of Metformin hydrochloride	NDMA[49]
	LC/MS	Eight nitrosamine contaminants in metformin were simultaneously identified utilizing the Agilent 6470 Triple Quadrupole LCMS-9030.	NDMA, DEA, NEIPA, NMBA, NDPA, NMPA, NBBA[50]
	LC-MS	Have DMF? NDMA and DMF are separated and identified chromatographically using an LCMS-9030	NBMA[51]
	LC-HRMS	Nitrosamine contaminants in Metformin Active Pharmaceutical Ingredients and finished drug product were simultaneously analysed with Shimadzu LCMS-8050 Triple Quadrupole-MS	NDIPA, NDEA, NMPA, NMBA, NDMA, NEIPA, NMBA, NDPA and NDBA[52]
	LC-MS	High Resolution Mass Spectroscopy utilizing a	NDBA, NDEA,

		widely available Liquid Chromatography Method to quantify six nitrosamine compounds and a N,N-Dimethylformamide in a medication called Metformin.	NMBA, NEIPA, NDMA and NDIPA[53]
	LC-HRMS	Analytical platform based on LC-HRMS to identify nitrosamine in pharmaceutical: Contemporary analytical methods fulfill regulatory requirements.	NEIPA, NDPA, NDMA, NDEA, NDBA,NMPA, NDIPA and NMBA[54]
	LC-ESI-RMS	The Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) method can be used to measure NDMA content in Metformin active ingredient and drug formulation.	NEIPA, NDMA, NDPA, NMPA, NDIPA, NDEA, NMBA and NDBA[55]
Ranitidine	LC/MS	Analysis of NDMA impurity levels in Ranitidine determination using agilant 6470 Tripole Quadrupole LC/MS system.	NDMA[56]
	LC-MS	Intense Sensitivity measurement of Genotoxic Nitrosamine contamination in Ranitidine Drug Formulations using Water-Based LC-MS: Evaluation with the Xevo TQ-XS Tendem Quadrupole Mass Spectrometer and UPLC I-Class for Enhanced Accuracy	NEIPA, NDMA, NDBA, NDEA, NMBA and NDIPA[57]
	LC-MS/MS	Using ESI-LC-MS/MS to determine N-nitrosodimethylamine in Ranitidine Dosage Forms for Typical Laboratory Testing	NDMA[58]
Lisinopril	HPLC-FLD	Creation and Verification of an HPLC-FLD technique incorporating a preliminary denitrosation steps and derivatisation for the identification of NDMA and NDEA contaminants in Lisinopril	NDEA, NDMA[59]
Enalapril Maleate	HPLC-FD	The creation and approval of a semi-quantitative approach to detect presence of N-nitrosamines in the drug substance Enalapril Maleate using derivatisation and HPLC detection with a fluoriometric detector	NDEA, NDMA[60]
Chloroquine and Hydroxychloroquine	LC-HRMS	Analytical Platform Based on LC-HRMS to Identify Nitrosamines in Pharmaceuticals: Contemporary Analytical Methods Fulfil Regulatory Requirements	NEIPA, NDPA, NDBA, NDMA, NDEA, NMPA and NMBA[61]
Propranolol	LC-MS/MS	A sensitive and repeatable measurement of N-nitrosopropranolol in propranolol medicinal product and substance	NDMA[62]
Biopharmaceuticals	LC-MS/MS	A new technique for NH2-MIL-101(Fe) assisted dispersive Micro-Solid phase Extraction- Based N-Nitrosamine Impurity Monitoring combined with Biopharmaceuticals LC-MS/MS	NDEA, NEIPA, NPIP, NMPA, NDIPA, NMPA, NDPA, NDBA, NDBA, MeNP, NPYR, NMOR, and NDBzA[63]

Regulatory guideline

Impurities are defined in various official pharmacopoeias and regulatory guidelines with slight variations in wording. These definitions are specified by organizations like Indian Pharmacopeia (IP), European Pharmacopeia (EP), United States Pharmacopeia (USP) and U.S. Food and Drug Administration (USFDA)

Indian Pharmacopeia (IP)

The 2022 edition of Indian Pharmacopiea (IP) introduced a new general chapter, 5.11 "nitrosamine impurities' on page 1210 volume I. This chapter provide guidance to stakeholders and is specifically referenced in monographs for certain APIs. It provides guidance on how to accurately identify, assess and manage nitrosamine contamination in both pharmaceutical ingredients and goods. Possible sources of nitrosamine formation include the API, starting or intermediates materials that includes secondary amine groups or tertiary amine groups as well as amine impurities in tertiary or quaternary amines used during API synthesis (e.g., triethylamine with traces of diisopropylamine). Under some circumstances, the drugs substance may degrade and nitrosamines like ranitidine may develop. Nitrosamine can occur as a result of contaminants in the final drug products container closure system, particularly

when subjected to nitrosating chemicals such nitrites or nitrocellulose.

Presence of impurities in raw materials from the supplier

Nitrosamine impurities may develop in raw materials or solvents that are contaminated (e.g., o-xylene, toluene, methylene chloride) during shipping or transfer. Cross-contamination may occur if materials are produced at sites with existing nitrosamine contamination. To produce nitrosamines sodium nitrite can react with amines in acidic environments, particularly when nitrogen-containing heterocycles, like secondary and tertiary amine impurities, are present in certain materials and solvents.

Sources of contamination: Recovered Solvents, Catalysts and Reagents

Due to residual amines such a trimethylamine or di-isopropylethylamine, recovered solvents, catalysts and reagents may pose a danger of nitrosamine contamination. Raw material may become contaminated if equipment is not adequately cleaned between different customers or materials, or if cleaning procedures are not validated to effectively remove all potential impurities.

Nitrosamine risk Assessments and Control strategy development

To ensure nitrosamine impurities remain within acceptable intake levels, drug product manufacturers must implement controls to assess the potential for nitrosamine formation or contamination. Manufacturers can refer to ICH Q9 Quality Risk Management guidelines for industry. The sources of nitrosamine contamination that are most likely to occur should be examined in the risk assessment. These sources include the raw materials, excipients, manufacturing process, production method and the route taken by the drug substance synthesis. If the risk evaluations suggests or testing detects the occurances of nitrosamines in the therapeutic substance, therapeutic product or other materials, a control measure must be established. This strategy must ensure nitrosamine levels comply with acceptable intake limits and align with current regulatory requirements.

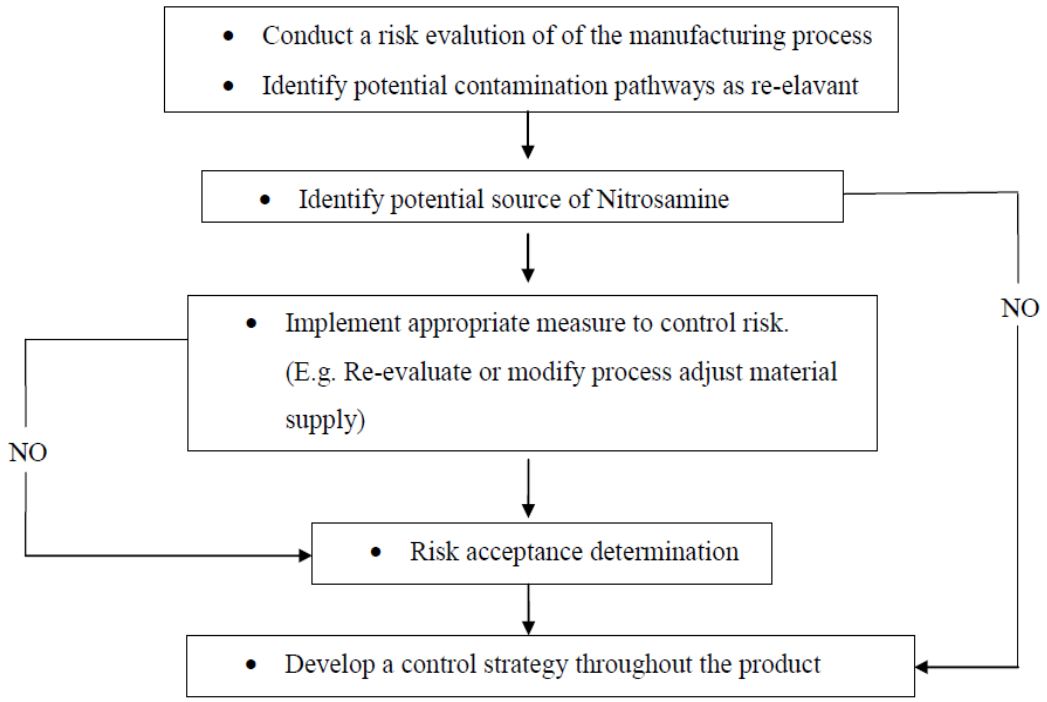

Figure 1: Nitrosamine impurity control strategy overview.

Limit of nitrosamine intake

The acceptance intake refers to the daily exposure level to nitrosamines that is considered to present a negligible health risk, usually linked to a 1 in 1,00,000 chance of cancer over a 70-year period. However since nitrosamine are highly potent carcinogens, this threshold may not be applicable and acceptance intake level should be determined case by case using specific safety data. Toxicologist often use the median tumorigenic dose (TD50) to estimate safe intake levels, relaying on rodent carcinogenicity data to calculate AI and assess cancer risk.

Table 5: Acceptance intake limit of nitrosamine impurity.

Nitrosamine impurities	Acceptance Intake Limits (ng/day)
NMBA	96
NDMA	96
NIPEA	26.5
NDEA	26.5
NDIPA	26.5
NMPA	26.5

Absence of process refinement and supervision: Nitrosamine contamination can arise from poorly optimized manufacturing processes, where factors like temperature, pH and reagent addition sequences are not well controlled. Absence of process optimization and control: A risk estimation should recognize all potential origins of nitrosamines such as the bioactive substance, water, diluents, inactive ingredients, manufacturing process, packaging and stability.

International Council for Harmonization (ICH): The ICH defines an impurity as any element in the dug substance that is not the chemical entity specified as the drug substance.

U. S. Food and Drug Administration (FDA): The FDA defines an impurity in a drug substance or product as any component that is not the intended product, a related substance or an excipient including buffer ingredients. Impurities may be introduced during the manufacturing process or may originate from the product itself. They may include substances such as starting materials, reagents, catalyst, raw materials or intermediates and can develop during synthesis, storage or shipment. The FDA method employs specialized, expensive equipment like LC-HRMS to detect nitrosamine impurities. It is intended to analyze nitrosamines, although regulations are limited to four of them. As the analysis lacks a sophisticated system, high resolution mass spectrometers may not be necessary.

United State Pharmacopoiea (USP): Chapter <1089> titled "Impurities in drug substance and drug product" generally defines an impurity as any substance found in a drug substance that is not the active ingredient specified as the drug substance. In drug products, an impurity refers to any component that is not part of the formulation ingredients. Nitrosamine impurities are a significant concern in the pharmaceutical industry because of their potential to cause mutations and cancer. Global health authorities have compiled a list of these impurities, which includes detailed chemical information for each. According to the ICH M7 guidelines, N-nitroso compound are classified as Class 1 mutagens, indicating their ability to cause DNA damage and increase the risk of cancer. The ICH M7 framework helps assess and contrl these impurities to limit carcinogenic risk in pharmaceuticals.[64, 65, 66]

N-nitrosamine impurities in drug formulation: Sources, formlation Mechanisms and Contributing factors from Excipients and Preservative

A significant problem in medication development is the creations of N-nitrosamine contaminants from inactive ingredients and preserving agents. Excipients may include nitrosating agents such as nitrites, which can interact with secondary amines to produce nitrosamines.[67] N-nitrosamine impurities in pharmaceuticals can arise from various sources, including contaminants is excipients, solvent and the degradation or interaction of excipient with the drug. Active Pharmaceutical Ingredients (APIs) can also break down during the manufacturing process. Excipients, which are more complex and sourced from a variety of origins including animals, synthesis, mining, chemicals, plants and biotechnology frequently contributing to the development of impurities trace levels of nitrosatig impurities, including nitrites and nitrates can be present in common excipients.[68] These include ingredients like pregelatinized starch, sodium starch glycolate, polyvinylpyrrolidone, sodium CMC and cross-linked polyvinylpyrrolidone, and lactose. Aldehde in pharmaceutical excipients can catalyst nitrosation with secondary amines, forming nitrosamines. Formaldehyde is produced when PEG 300 and polysorbate 80 polymers degrade. Additionally, some plant-derived cellulose excipients may contain furfural aldehyde resulting from the production process.[69, 70, 71] Excipients such as formaldehyde, formic acid and peroxides have the potential to interact with active pharmaceutical ingredients (APIs), emphasizing the need to carefully understand the manufacturing of excipients. Additionally, preservatives may lead to the production of N-nitrosamines if the produce nitrosating compounds. The manufacturing process, particularly under acidic conditions or elevated temperatures, can encourage the formation of N-nitrosamines, especially when di-substituted amines are involved. Oxidation during drying further increases this risk, as seen in metformin talets, where excipient nitrate and nitrite content, combined with processing conditions, contributes to N-nitrosamine formation.[72]

Computational Tools and Methods for assessing n-nitrosamine impurities in pharmaceuticals

Various software tools are available that utilize computational methods to predict or verify the existence of N-nitrosamine contamination, helping to assess the evolution of their development and potential risks in pharmaceuticals. Quantum mechanical and chemical

techniques are commonly used in the development of pharmaceutical and cosmetic products to evaluate the cancer-causing potential and DNA reactivity on N-nitroso impurities, a process called as Computer-Aided Discovery and Redesign (CADRE). An automated online tool has been created to assess the risk levels of N-nitrosamine compounds using SMILES notation and providing a fast evaluation method to detect high risk N-nitrosamine impurities. A computational risk assessment approach is also employed to evaluate the probability of N-nitrosamine and other genotoxic impurities forming during manufacturing of bioactive ingredients. The Food and Drug Administration has developed a molecular similarity approach to recognized alternative compounds for evaluating the carcinogenic risk of N-nitrosamine contamination.

Key recommendations for managing n-nitrosamine impurities in pharmaceuticals

1. Based on current research and industry practices, the following recommendations are proposed:
2. Further Research: Explore innovative approaches to study N-nitrosamine impurities.
3. Advanced Detection Tools: Develop more sensitive and selective analytical instruments.
4. Improved Analytical Methods: Refine techniques for detecting N-nitrosamines.
5. Control raw Materials: Avoid chemicals that form nitrosamines during synthesis.
6. Prioritize Research: Government should fund studies on N-nitrosamine impurities, focusing on their sourced, detecting and health risks.
7. Regulatory Attention: Strengthen oversight and guidelines for N-nitrosamines.
8. Collaborative Efforts: Foster partnerships between regulators, researchers and manufacturers.
9. Enhanced Detection: Develop cutting-edge techniques such as GC-MS, CE-MS, LC-MS for quantifying N-nitrosamine impurities.

CONCLUSION

In conclusion, the detection of N-nitrosamine contamination in formulations has become a pivotal global challenge/significant global concern due to their known carcinogenic properties and potential health risks. These impurities are generated through different reactions that involve secondary amines, carbamates, amides, nitrites, or other nitrogen-containing compounds. The identification of N-nitrosamine in finished pharmaceutical products has resulted in the sudden recall of medications such as sartans, metformin, silagliptine, vareniciline, ranitidine and nizatidine because of elevated amount of impurities, emphasizing the importance of careful monitoring to ensure pharmaceutical safety. Analytical method like HPLC, HPLC-PCUV, HPLC-UV-FLD, HPLC-MS/MS, LC-MS/MS, LC/Q-TOF, LC-MS, HPLC-UV, HPLC-FD LC/MS, LC-HRMS and HPLC-FLD are vital for both qualitative and quantitative analysis of pharmaceutical products ensuring the creation of safe and effective medications. Regulatory authorities such as the Indian Pharmacopoeia (IP), European Pharmacopoeia (EP), United State Pharmacopoeia (USP) and U.S. Food and Drug Administration (USFDA), have issued guidelines for the identification, evaluation and management of nitrosamine contamination in pharmaceutical components and products stressing the need for control measures to monitor and limit nitrosamine levels. Additionally, the establishment of maximum allowable doses for nitrosamine is crucial to mitigate potential health risk and ongoing research and collaboration between regulators, researchers and manufacturing are essential to further address this issue and enhance pharmaceutical safety.

REFERENCES

1. Manchuri KM, Shaik MA, Gopireddy VS, Sultana N, Gogineni S. Analytical Methodologies to Detect N-Nitrosamine Impurities in Active Pharmaceutical Ingredients, Drug Products and Other Matrices. Chemical Research in Toxicology, 2024; 19, 37(9): 1456-83.
2. Cioc RC, Joyce C, Mayr M, Bream RN. Formation of N-nitrosamine drug substance related impurities in medicines: a regulatory perspective on risk factors and mitigation strategies. Organic Process Research & Development, 2023; 21, 27(10): 1736-50.
3. Malihi F, Wang T. An improved analytical method for quantitation of nitrosamine impurities in ophthalmic solutions using liquid chromatography with tandem mass spectrometry. Journal of Chromatography Open, 2022; 1, 2: 100037.
4. Sedlo I, Kolonić T, Tomić S. Presence of nitrosamine impurities in medicinal products. Archives of Industrial Hygiene and Toxicology, 2021; 30, 72(1): 1.
5. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, 2021; 6. Available at: https://www.ema.europa.eu/en/documents/ scientific-guideline/ich-guideline-m7r1-assessment-controldna-reactive-mutagenic-impurities-pharmaceuticals-limit_ en.pdf
6. Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration, 2021.
7. U.S. Food & Drug Administration. Statement alerting patients and health care professionals of NDMA found in samples of ranitidine, 2019. Statement Available at: https://www.fda.gov/news-events/press-announcements/statement-alertingpatients-and-health-care-professionals-ndma-found-samples-ranitidine. Accessed December 1, 2020.
8. European Medicines Agency. EMA to review ranitidine medicines following detection of NDMA, 2019. Press Release. Available at:

https://www.ema.europa.eu/en/ news/ema-review-ranitidine-medicines-following-detection-ndma. Accessed December 1, 2020
9. U.S. Food & Drug Administration. Questions and answers: NDMA impurities in metformin products, 2020. Q&A. Available at: https://www.fda.gov/drugs/drugsafety-and-availability/questions-and-answers-ndma-impurities-metformin-prod ucts. Accessed December 1, 2020
10. European Medicines Agency. EMA update on metformin diabetes medicines, 2019. Press Release. Available at: https://www.ema.europa.eu/en/news/ema-updatemetformin-diabetes-medicines. Accessed May 11, 2020.
11. U.S. Food & Drug Administration. Laboratory analysis of ranitidine and nizatidine products, 2019. Laboratory Tests. Available at: https://www.fda.gov/drugs/drugsafety-and-availability/laboratory-tests-ranitidine. Accessed December 1, 2020.
12. U.S. Food & Drug Administration. FDA works to mitigate shortages of rifampin and rifapentine after manufacturers find nitrosamine impurities, 2020. Update. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-worksmitigate-shortages-rifampin-and-rifapentine-after-manufacturers-find-nitrosa mine. Accessed December 1, 2020
13. Shaik KM, Sarmah B, Wadekar GS, Kumar P. Regulatory updates and analytical methodologies for nitrosamine impurities detection in sartans, ranitidine, nizatidine, and metformin along with sample preparation techniques. Critical reviews in analytical chemistry, 2022; 2, 52(1): 53-71.
14. Vikram HP, Kumar TP, Kumar G, Beeraka NM, Deka R, Suhail SM, Jat S, Bannimath N, Padmanabhan G, Chandan RS, Kumar P. Nitrosamines crisis in pharmaceuticals− Insights on toxicological implications, root causes and risk assessment: A systematic review. Journal of Pharmaceutical Analysis, 2024; 1, 14(5): 100919.
15. Siddiqui N, Husain A, Chaudhry L, Alam MS, Mitra M, Bhasin PS. Pharmacological and pharmaceutical profile of valsartan: a review. Journal of Applied Pharmaceutical Science, 2011; 30: 12-9.
16. European Medicines Agency (Dec), Questions and answers n Information on nitrosamines for Marketing authorization holders", 2019. EMA/CHMP/428592/2019 Rev. 2 https://www.ema.europa.eu.
17. Pahwa R, Sharma S, Kumar V, Kohli K. Ranitidine hydrochloride: An update on analytical, clinical and pharmacological aspects. J Chem Pharm Res, 2016; 8(7): 70-80.
18. Joseph J et al. Ranitidine Ban – A Review. International Journal of Pharmaceutical Sciences Review and Research. Dec, 2019; 59(2): 52-55.
19. Flatie Alemu A, Tegegne AA, Getaw NS. Evaluation of Seven Different Brands of Metformin Hydrochloride Tablets Available in the Market in Gondar City, Ethiopia. Drug, Healthcare and Patient Safety, 2024; 31: 19-28.
20. Keire DA, Bream R, Wollein U, Schmaler-Ripcke J, Burchardt A, Conti M, Zmysłowski A, Keizers P, Morin J, Poh J, George M. International regulatory collaboration on the analysis of nitrosamines in metformin-containing medicines. The AAPS journal, 2022; 21, 24(3): 56.
21. Singh S, Dadabhau GD, Singh K. a systematic review of antiulcer drug its pharmacodynamic & pharmacokinetic properties: Nizatidine. European chemical bulletin, 2022; 11(8): 1159-64.
22. Khadka P, Dummer J, Hill PC, Katare R, Das SC. A review of formulations and preclinical studies of inhaled rifampicin for its clinical translation. Drug delivery and translational research, 2023; 13(5): 1246-71.
23. National Center for Biotechnology Information PubChem Compound Summary for CID 5702160, Famotidine, 2025.
24. National Center for Biotechnology Information PubChem Compound Summary for CID 170361, 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, 2025.
25. National Center for Biotechnology Information. PubChem Compound Summary for CID 5310966, Varenicline, 2025.
26. National Center for Biotechnology Information. PubChem Compound Summary for CID 4369359, Sitagliptin, 2025.
27. Kim MS, Jin SJ, Kim JS, Park HJ, Song HS, Neubert RH, Hwang SJ. Preparation, characterization and in vivo evaluation of amorphous atorvastatin calcium nanoparticles using supercritical antisolvent (SAS) process. European journal of pharmaceutics and biopharmaceutics, 2008; 1, 69(2): 454-65.
28. Sonje VM, Kumar L, Meena CL, Kohli G, Puri V, Jain R, Bansal AK, Brittain HG. Atorvastatin calcium. InProfiles of drug substances, excipients and related methodology, 2010; 1, 35: 1-70. Academic Press.
29. National Center for Biotechnology Information. PubChem Compound Summary for CID 60823, Atorvastatin, 2025.
30. Shaik KM, Sarmah B, Wadekar GS, Kumar P. Regulatory updates and analytical methodologies for nitrosamine impurities detection in sartans, ranitidine, nizatidine, and metformin along with sample preparation techniques. Critical reviews in analytical chemistry, 2022; 2, 52(1): 53-71.
31. Lee M, Lee Y, Soltermann F, Von Gunten U. Analysis of N-nitrosamines and other nitro (so) compounds in water by high-performance liquid chromatography with post-column UV photolysis/Griess reaction. Water research, 2013; 15, 47(14): 4893-903.
32. Chen S, Zhang Y, Zhao Q, Liu Y, Wang Y. Simultaneous determination for nine kinds of N-

nitrosamines compounds in groundwater by ultrahigh-performance liquid chromatography coupled with triple quadrupole mass spectrometry. Int J Environ Res Public Health, 2022; 19(24): 16680.
33. Ding, Z.; Cai, M.; Gan, W.; Yuan, P.; Wei, L.; Cheng, X. Analytical Methods Studies on a Novel Method for the Determination of Nitrosamines in Food by HPLC-UV-FLD Coupling with TerbiumDoped Carbon Dots. Food Chem, 2023; 405: 134894.
34. Analysis of Nitrosamines Using Unique Stationary Phase Technology - Feb 01 2022 - Joseph J. Pesek, Maria T. Matyska, Tanya Hiltz - Life Science News Articles - Labmate Online. https://www. labmate-online.com/article/chromatography/1/microsolvtech nology-corp/analysis-of-nitrosamines-using-unique-stationaryphase-technology/3098 (accessed 2024-01-20).
35. Mani, C.; Banerjee, S. Determination of Nitrosamine Impurities Using the Ultivo Triple Quadrupole LC/MS. Application Note: Pharmaceuticals; Agilent Trusted Answers, 2019.
36. Xie, B.; Guo, D.; Mai, B.; Fan, J. Determination of Genotoxic Impurity N-Nitroso-N-Methyl-4-Aminobutyric Acid in Four Sartan Substances through Using Liquid Chromatography-Tandem Mass Spectrometry. Molecules, 2022; 27(21): 7498.
37. Str, W. Test Method for the Determination of NDMA and NDEA by LC-MS/MS in Sartan Containing Film Coated Tablets. Chemisches und Veterinaruntersuchungsamt¨ (CVUA) Karlsruhe, 2018; 1− 7.
38. Mani, C.; Banerjee, S. Determination of Nitrosamine Impurities Using the High-Resolution Agilent 6546 LC/Q-TOF. Application Note: Small Molecule Pharmaceuticals; Agilent Trusted Answers, 2021.
39. Chang, S. H.; Chang, C. C.; Wang, L. J.; Chen, W. C.; Fan, S. Y.; Zang, C. Z.; Hsu, Y. H.; Lin, M. C.; Tseng, S. H.; Wang, D. Y. A MultiAnalyte Lc-Ms/Ms Method for Screening and Quantification of Nitrosamines in Sartans. J. Food Drug Anal, 2020; 28(2): 292−301.
40. Gopireddy, R. R.; Maruthapillai, A.; Mahapatra, S. A MultiAnalyte LC-MS/MS Method for Determination and Quantification of Six Nitrosamine Impurities in Sartans like Azilsartan, Valsartan, Telmisartan, Olmesartan, Losartan and Irbesartan. J. Chromatogr Sci, 2022. DOI: 10.1093/chromsci/bmac059.
41. Bodiwala, K. B.; Panchal, B. G.; Savale, S. S.; Dave, J. B.; Sureja, D. K.; Dhameliya, T. M.; Chhabria, M. T. Simultaneous Estimation of Six Nitrosamine Impuritiesin Valsartan Using LiquidChromatographic Method. J. AOAC Int, 2022; 105. DOI: 10.1093/jaoacint/qsab100.
42. asada, S.; Tsuji, G.; Arai, R.; Uchiyama, N.; Demizu, Y.; Tsutsumi, T.; Abe, Y.; Akiyama, H.; Hakamatsuka, T.; Izutsu, K. ichi; Goda, Y.; Okuda, H. Rapid and Efficient High-Performance Liquid Chromatography Analysis of N-Nitrosodimethylamine Impurity in Valsartan Drug Substance and Its Products. Sci. Rep, 2019; 9(1), DOI: 10.1038/s41598-019-48344-5.
43. Guo, L.; Long, Z.; Leng, X.; Turner, J. Rapid Analysis of Genotoxic Nitrosamines by HPLC-MS/MS. Phenomenex, 2019; 1−4.
44. Patil, S.; Chadar, R.; Prasad, A.; Koppula, P.; Koppula, S. Quantification and Validation of a HPLC-UV Method for Simultaneous Analysis of Nitrosoamine Impurities (NDMA, NDEA and NDIPA) in Losartan. Journal of Pharmaceutical Research, 2021; 20(4): 43−49.
45. Abd El-Hay, S. S.; Elhenawee, M.; Maged, K.; Ibrahim, A. E. Cost-Effective, Green HPLC Determination of Losartan, Valsartan and Their Nitrosodiethylamine Impurity: Application to Pharmaceutical Dosage Forms. R. Soc. Open Sci, 2022. DOI: 10.1098/rsos.220250.
46. LC-HRMS Based Analytical Platform to Determine Nitrosamines in Pharmaceuticals: Modern Analytical Techniques Meet Regulatory Needs | FDA. https://www.fda.gov/science-research/fda-science-forum/lchrms-based-analytical-platform-determine-nitrosaminespharmaceuticals-modern-analytical (accessed 2024-01-19)
47. González, R.; Torrado, G.; Arribas, J. M.; Peña, M. A. Development of an Analytical Method for the Determination and Quantification of N-Nitrosodimethylamine in Olmesartan by HPLCMS/MS. Microchemical Journal, 2022; 179: 107402.
48. Chidella, K. S.; Dasari, V. B.; Anireddy, J.; Chidella, K. S.; Dasari, V. B.; Anireddy, J. Ultra-Sensitive LC-MS/MS Method for the Trace Level Quantification of Six Potential Genotoxic Nitrosamine Impurities in Telmisartan. Am. J. Analyt Chem, 2021; 12(6): 227−240.
49. Hao, G.; Hu, R.; Wang, X.; Gao, P.; Wang, L.; Jiang, M.; Xin, L.; Tan, G.; Zhao, Y.; Sun, F.; Chu, D.; Lv, J.; You, J.; Huang, F.; Song, X. N-Nitrosodimethylamine Formation in Metformin Hydrochloride Sustained-Release Tablets: Effects of Metformin and Hypromellose Used in Drug Product Formulation. J. Pharm. Biomed Anal, 2023; 222: 115066.
50. Chander Mani, A.; Srinivas Chidella, K.; Banerjee, S.; Vyas, S. Simultaneous Determination of Eight Nitrosamine Impurities in Metformin Extended-Release Tablets Using the Agilent 6470 Triple Quadrupole LC/MS. Application Note: Pharmaceutical Small Molecules; Agilent Trusted Answers, 2020.
51. himadzu. Liquid Chromatography Mass Spectrometry Got DMF? Chromatographic Separation and Identification of NDMA and DMF Using LCMS-9030, Shimadzu. https://www.ssi.shimadzu.com/ sites/ssi.shimadzu.com/files/pim/pim_document_file /ssi/ applications/application_note/23949/01%20-

%202_LCMS9030%20determination%20of%20DMF%20and%20NDMA%20 ver%202.pdf, 2020.
52. Shimadzu. Simultaneous Analysis of Nitrosamines Impurities in Metformin Drug Substance and Drug Product Using Shimadzu LCMS8050 Triple Mass Spectrometer, Shimadzu. https://www.ssi.shimadzu.com/sites/ssi.shimadzu.com/files/pim/pim_document_file/ssi/applications/application_note/23950/LCMS-8050-analysis-ofnitrosamines.pdf, 2020.
53. Wu, Q.; Kvitko, E.; Zenzola, N.; Kucera, K.; Light, D. Y. A Broadly Accessible Liquid Chromatography Method for Quantification of Six Nitrosamine Compounds and N,N-Dimethylformamide in Metformin Drug Products Using High Resolution Mass Spectrometry. ChemRxiv, 2020, DOI: 10.26434/CHEMRXIV.13202849.V1
54. LC-HRMS Based Analytical Platform to Determine Nitrosamines in Pharmaceuticals: Modern Analytical Techniques Meet Regulatory Needs | FDA. https://www.fda.gov/science-research/fda-science-forum/lchrms-based-analytical-platform-determine-nitrosaminespharmaceuticals-modern-analytical (accessed 2024-01-19).
55. FDA. Liquid Chromatography-Electrospray Ionization-High Resolution Mass Spectrometry (LC-ESI-HRMS) Method for the Determination of Nitrosamine Impurities in Metformin Drug Substance and Drug Product. https://www.fda.gov/media/134914/ download, 2020.
56. Authors Chander Mani, B.; Banerjee, S. Determination of NDMA Impurity in Ranitidine Using the Agilent 6470 Triple Quadrupole LC/MS Detection of Regulated Genotoxic Impurity from the Drug Manufacturing Process. Application Note: Pharma & Biopharma; Agilent Trusted Answers, 2020. Chemical Research in Toxicology pubs.acs.org/crt Review https://d
57. Trudeau Lame, M.; Hatch, L. High Sensitivity Quantitation of Nitrosamine Genotoxic Impurities: LC-MS Analysis of Ranitidine Drug Product Using the Waters ACQUITYTM UPLCTM I-Class/XevoTM TQ-XS Tandem Quadrupole Mass Spectrometer, Waters Corporation. https://www.semanticscholar.org/paper/High-SensitivityQuantitation-of-Nitrosamine-LC-MS-Lame-Hatch/d73dd93bad4c10b30730aeaa7e88e71cdbc42bf9, 2019, 2022; 50: 100150. (227)
58. 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, 2021; 20(4): 255−264.
59. Tsanaktsidou, E.; Kanata, L.; Almpani, S.; Zacharis, C. K.; Markopoulou, C. K. 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; 9(11): 347.
60. Boczar, D.; Wyszomirska, E.; Zabrzewska, B.; Chyła, A.; Michalska, K. Development and Validation of a Method for the SemiQuantitative Determination of n-Nitrosamines in Active Pharmaceutical Ingredient Enalapril Maleate by Means of Derivatisation and Detection by HPLC with Fluorimetric Detector. Applied Sciences (Switzerland), 2021; 11(16): 7590.
61. LC-HRMS Based Analytical Platform to Determine Nitrosamines in Pharmaceuticals: Modern Analytical Techniques Meet Regulatory Needs | FDA. https://www.fda.gov/science-research/fda-science-forum/lchrms-based-analytical-platform-determine-nitrosaminespharmaceuticals-modern-analytical (accessed 2024-01-19).
62. Partani, P.; Choudhary, S.; Bharataiya, P.; Gunta, U.; Kumar Ponnamaneni, R.; Pillai, M.; Baghla, R.; Nandita, E. Sensitive and Reproducible Quantification of N-Nitroso Propranolol in a Propranolol Drug Substance and Product Featuring a Workflow for Quantifying NNitroso Propranolol Using the QTRAP 6500+ System. Kinetex Technical Notes, 2023.
63. Xie, Y.; Zhang, L.; Hou, W.; Cheng, Y.; Luo, F.; Liu, Z.; Zhang, Z. Pharmaceutical Biotechnology A Novel Method for Monitoring NNitrosamines Impurities Using NH 2-MIL-101(Fe) Mediated Dispersive Micro-Solid Phase Extraction Coupled with LC-MS/MS in Biopharmaceuticals. J. Pharm. Sci, 2023; 112: 2783−2789.
64. Hussain S, Gosar A, Shaikh T. Impurity profiling in pharmaceuticals: a review. World Journal of Pharmaceutical Research, 2018; 5, 7(9): 305-20.
65. 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. IP VOL I
66. Indian Pharmacopoeia, The Indian Pharmacopoeia Commission (ninth edition),Volume I, Page no. 1210, Ministry of Health & Family Welfare, Government of India, 2022.
67. Bayne AC, Misic Z, Stemmler RT, Wittner M, Frerichs M, Bird JK, Besheer A. N-nitrosamine mitigation with nitrite scavengers in oral pharmaceutical drug products. Journal of Pharmaceutical Sciences, 2023; 1, 112(7): 1794-800.
68. Pan C, Liu F, Motto M. Identification of pharmaceutical impurities in formulated dosage forms. Journal of pharmaceutical sciences, 2011; 1, 100(4): 1228-59.
69. Boetzel R, Schlingemann J, Hickert S, Korn C, Kocks G, Luck B, Blom G, Harrison M, Francois M, Allain L, Wu Y. A nitrite excipient database: a useful tool to support N-nitrosamine risk

assessments for drug products. Journal of Pharmaceutical Sciences, 2023; 1, 112(6): 1615-24.
70. Wu Y, Levons J, Narang AS, Raghavan K, Rao VM. Reactive impurities in excipients: profiling, identification and mitigation of drug–excipient incompatibility. Aaps Pharmscitech, 2011; 12: 1248-63.
71. Hoydonckx HE, Van Rhijn WM, Van Rhijn W, De Vos DE, Jacobs PA. Furfural and derivatives. Ullmann's encyclopedia of industrial chemistry, 2000; 15.
72. Nasr NE, Metwaly MG, Ahmed EO, Fares AR, ElMeshad AN. Investigating the root cause of N-nitrosodimethylamine formation in metformin pharmaceutical products. Expert opinion on drug safety, 2021; 3, 20(7): 855-62.