JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

A Review on Nitrosamine Impurities in Pharmaceutical Products

Nagalaxmi Pinnamraju*[1], Hemadurga S[2], Dhanya Sri P[2]

[1] *Assistant Professor, Department of Pharmaceutics, Koringa College of Pharmacy, Korangi, Tallarevu, Andhra Pradesh, India*
[2] *UG Scholar, Department of Pharmaceutics, Koringa College of Pharmacy, Korangi, Tallarevu, Andhra Pradesh, India*

Publication history: Received on 1st July 2025; Revised on 8th Aug 2025; Accepted on 17th August 2025

Article DOI: 10.69613/qn1fmm61

Abstract: Nitrosamine impurities in pharmaceutical products could be a critical quality concern since their initial detection in sartan-based medications in 2018. These genotoxic compounds can form during drug synthesis, manufacturing, storage, or degradation through various pathways involving secondary or tertiary amines and nitrosating agents. The acceptable daily intake limit of 26.5 nanograms established by regulatory authorities reflects the serious carcinogenic potential of these compounds. Multiple analytical techniques including LC-MS/MS, GC-MS, and HPLC have been developed and validated for detecting trace levels of nitrosamines such as N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) in pharmaceutical products. Root cause investigations have identified several factors contributing to nitrosamine formation, including contaminated raw materials, degradation of solvents like DMF, cross-contamination during manufacturing, and API instability. Prevention strategies focus on controlling nitrosating conditions, using nitrite scavengers like ascorbic acid and α-tocopherol, and implementing robust analytical testing protocols. Recent cases involving valsartan, ranitidine, and metformin have led to significant regulatory oversight and development of control frameworks. The knowledge of formation mechanisms combined with sensitive analytical methods and preventive measures continues to evolve to ensure patient safety through elimination of these harmful impurities from pharmaceutical products.

Keywords: Nitrosamine impurities; Genotoxic impurities; Pharmaceutical analysis; Drug safety; Formation mechanisms

1. Introduction

Nitrosamines are a class of genotoxic compounds formed through the interaction of secondary or tertiary amines with nitrosating agents. Their discovery in pharmaceutical products has raised significant concerns due to their established carcinogenic potential [1]. The initial identification of nitrosamine impurities in pharmaceutical products occurred in 1874 when Otto N. Witt discovered them as condensation products during experiments with nitrous acid and amines [2]. However, their significance in pharmaceutical quality remained largely unexplored until 2018, when N-nitrosodimethylamine (NDMA) was detected in valsartan products [3]. Nitrosamines can form through multiple pathways during pharmaceutical manufacturing and storage. The primary formation mechanism involves the reaction between secondary or tertiary amines and nitrosating agents under specific conditions, particularly in acidic environments [4]. The presence of these impurities can result from contaminated raw materials, degradation of solvents, cross-contamination during manufacturing, or API instability [5].

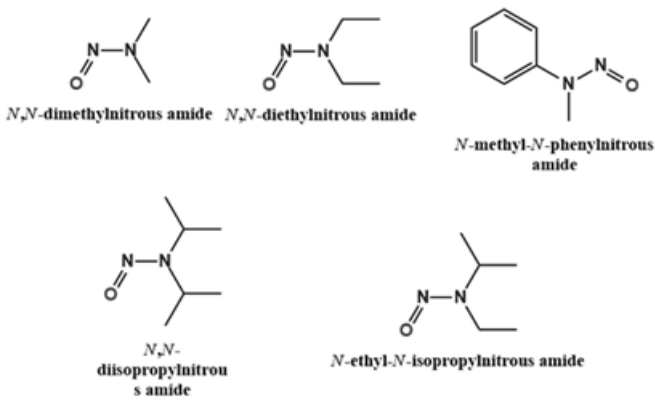

Figure 1. Structures of Nitrosamine Impurities

* Corresponding author: Nagalaxmi Pinnamraju

2. Chemical Nature and Formation of Nitrosamines

2.1. Structure and Properties

Nitrosamines contain the characteristic N-N=O functional group, where one nitrogen atom carries two organic substituents [10]. Their physical properties vary depending on the alkyl or aryl substituents, but most pharmaceutical nitrosamine impurities are small, relatively polar molecules with good solubility in both aqueous and organic media [11]. Common pharmaceutical nitrosamine impurities include:

- N-Nitrosodimethylamine (NDMA)
- N-Nitrosodiethylamine (NDEA)
- N-Nitrosodiisopropylamine (NDIPA)
- N-Nitrosoethylisopropylamine (NEIPA)
- N-Nitroso-di-n-butylamine (NDBA)
- N-Nitrosomethylethylamine (NMEA)
- N-Nitroso-di-n-propylamine (NDPA)
- N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)

Table 1. Common Pharmaceutical Nitrosamines and Their Physical Properties

Nitrosamine	Molecular Weight	Log P	Boiling Point (°C)	Solubility in Water
NDMA	74.08	-0.57	154	Miscible
NDEA	102.14	0.48	177	106 g/L
NDIPA	130.19	1.36	206	13.5 g/L
NEIPA	116.16	0.94	192	28.7 g/L
NDBA	158.24	2.63	236	1.27 g/L
NMEA	88.11	-0.18	163	300 g/L

2.2. Formation Mechanisms

2.2.1. Primary Formation Pathways

The formation of nitrosamines in pharmaceutical products occurs through several established mechanisms. The most common pathway involves the reaction between secondary amines and nitrous acid, generated in situ from nitrites under acidic conditions [12]. This reaction proceeds through the formation of a nitrosonium ion (NO^+), which then attacks the amine nitrogen [13].

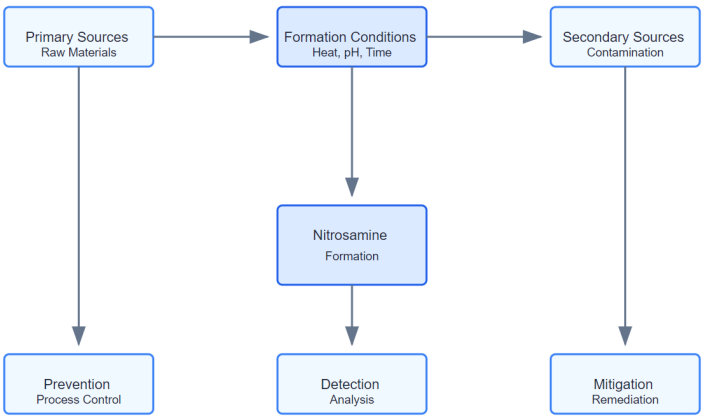

Figure 2. Pathways for Formation of Nitrosamine Impurities

2.2.2. Secondary Formation Routes

Alternative formation pathways include:

- Degradation of tertiary amines followed by nitrosation
- Reaction of primary amines with nitrites leading to diazonium intermediates

- Decomposition of N-nitrosamino acids
- Nitrosation by nitrogen oxides in air [14]

2.2.3. Environmental and Process Factors

Temperature, pH, and the presence of catalysts significantly influence nitrosamine formation kinetics in pharmaceutical processes. Acidic conditions particularly facilitate nitrosation reactions by promoting the formation of nitrous acid from nitrite ions. The reaction rate increases substantially at pH values below 4, while becoming negligible in alkaline conditions [15]. Metal ions, especially copper and iron, can catalyze these reactions by stabilizing reaction intermediates and lowering activation energy barriers [16].

2.2.4. Solvent-Mediated Formation

The choice of solvents in pharmaceutical manufacturing processes plays a crucial role in nitrosamine formation. N,N-dimethylformamide (DMF), commonly used as a polar aprotic solvent, can decompose under thermal stress or basic conditions to generate dimethylamine. This decomposition product readily undergoes nitrosation when exposed to nitrosating agents, leading to NDMA formation [17]. Similar mechanisms occur with other amide solvents such as N,N-dimethylacetamide and N-methylpyrrolidone [18].

3. Sources of Nitrosamine Contamination

3.1. Contamination of Raw Materials

Raw material quality directly impacts nitrosamine formation in pharmaceutical products. Sodium azide, commonly used in tetrazole ring formation, often contains sodium nitrite as an impurity. This contamination stems from the manufacturing process of sodium azide itself, where sodium nitrite serves as a starting material [19]. The presence of nitrite in combination with amine-containing compounds creates conditions favorable for nitrosamine formation during API synthesis [20].

3.2. Manufacturing Process Variables

3.2.1. Equipment-Related Factors

Manufacturing equipment design and maintenance significantly influence nitrosamine contamination. Cross-contamination can occur when equipment is used for multiple products without adequate cleaning validation. Stainless steel surfaces may catalyze nitrosation reactions, particularly in the presence of residual nitrites and amines [21]. The accumulation of reaction intermediates in hard-to-clean areas of equipment presents additional risks for nitrosamine formation during subsequent manufacturing campaigns [22].

3.2.2. Process Parameters

Critical process parameters such as reaction temperature, pressure, and mixing conditions affect nitrosamine formation. Extended heating periods, particularly during drying operations, can accelerate the degradation of amine-containing compounds and promote nitrosamine formation. Inadequate mixing during pH adjustments may create localized acidic regions favorable for nitrosation reactions [23].

3.3. Storage and Degradation Pathways

3.3.1. Stability Considerations

The stability of pharmaceutical products during storage presents another avenue for nitrosamine formation. Environmental factors such as temperature, humidity, and light exposure can trigger degradation reactions leading to nitrosamine formation. For instance, ranitidine demonstrates particular susceptibility to NDMA formation during storage, especially under elevated temperature conditions [24]. The presence of nitrite-containing packaging materials or atmospheric nitrogen oxides may contribute to nitrosamine formation during long-term storage [25].

3.3.2. Degradation Mechanisms

API degradation often involves complex reaction networks that can generate nitrosamine precursors. In the case of metformin, the degradation of the biguanide structure can release methylamine, which subsequently undergoes nitrosation. Similar degradation pathways exist for other amine-containing drugs, where the breakdown of the parent molecule creates conditions favorable for nitrosamine formation [26].

4. Analytical Methods for Nitrosamine Detection

4.1. Chromatographic Techniques

4.1.1. High-Performance Liquid Chromatography (HPLC)

HPLC methodology has evolved significantly for nitrosamine analysis in pharmaceutical products. The selection of stationary phases plays a crucial role in achieving adequate separation and sensitivity. C18 columns modified with polar embedded groups demonstrate superior selectivity for nitrosamine separation, while phenyl-hexyl columns offer complementary selectivity through π-π interactions [27]. Mobile phase optimization typically involves acetonitrile-water or methanol-water systems, with careful consideration of pH control to maintain consistent retention times and peak shapes [28].

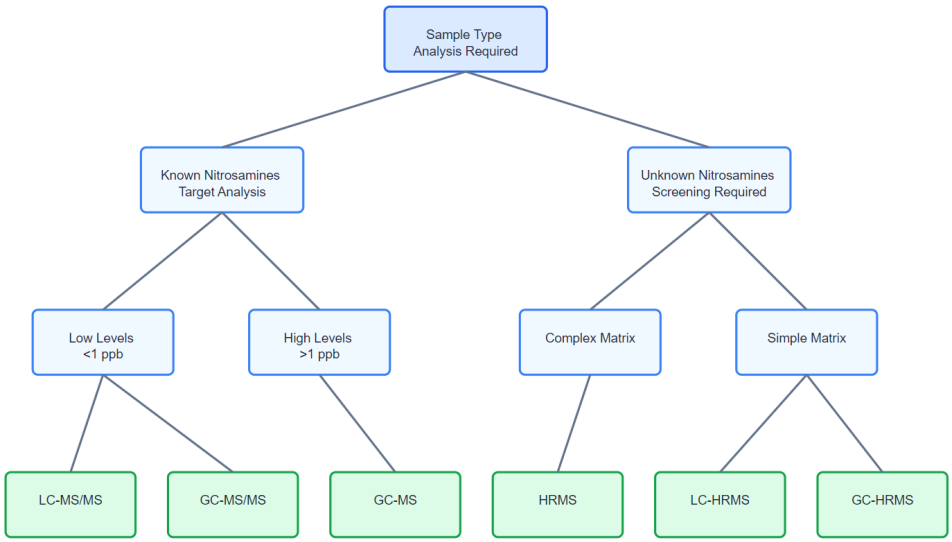

Figure 3. Analytical Method Selection for Determination of Nitrosamines

4.1.2. Gas Chromatography

Gas chromatography offers distinct advantages for volatile nitrosamine analysis. The development of specialized injection techniques, particularly headspace sampling, has improved detection limits and reduced matrix interference. Temperature-programmed injection helps minimize thermal degradation while maintaining chromatographic efficiency. Modern GC columns with low-bleed stationary phases and optimized film thickness provide excellent resolution of structurally similar nitrosamines [29].

4.2. Detection of Mass Spectrometry

4.2.1. LC-MS/MS Applications

Triple quadrupole mass spectrometry coupled with liquid chromatography enables highly selective and sensitive nitrosamine detection. Multiple reaction monitoring (MRM) transitions specific to each nitrosamine allow quantification at sub-ppb levels. Electrospray ionization in positive mode generates characteristic molecular ions, while collision-induced dissociation produces diagnostic product ions. The optimization of ion source parameters and collision energies significantly impacts method sensitivity [30].

Table 2. LC-MS/MS Method Parameters for Determination of Nitrosamine

Compound	Precursor Ion (m/z)	Product Ion (m/z)	Collision Energy (eV)	RT (min)
NDMA	75.1	43.2, 58.1	15, 10	2.8
NDEA	103.1	75.1, 47.2	12, 15	3.5
NDIPA	131.1	89.1, 43.2	12, 15	4.2
NMBA	147.1	117.1, 44.1	10, 15	3.0
NDBA	159.1	103.1, 41.2	15, 20	5.8

4.2.2. GC-MS Methodology

GC-MS methods employ both electron ionization and chemical ionization techniques. Electron ionization provides rich fragmentation patterns useful for structural confirmation, while chemical ionization offers enhanced sensitivity for molecular ion detection. The application of selected ion monitoring (SIM) mode allows detection limits comparable to LC-MS/MS methods. Modern time-of-flight and triple quadrupole GC-MS systems provide additional selectivity through accurate mass measurement and MS/MS capabilities [31].

4.3. Sample Preparation Techniques

4.3.1. Extraction Techniques

Sample preparation methodology significantly influences analytical method performance. Liquid-liquid extraction using dichloromethane or ethyl acetate provides efficient nitrosamine isolation from aqueous matrices. Solid-phase extraction utilizing mixed-mode sorbents combines reversed-phase and ion-exchange mechanisms to achieve selective enrichment. The incorporation of isotope-labeled internal standards early in the sample preparation process compensates for extraction variability [32].

4.3.2. Management of Matrix Effects

Matrix effects present significant challenges in nitrosamine analysis. The development of matrix-matched calibration standards helps ensure accurate quantification. Standard addition techniques prove valuable for complex pharmaceutical formulations where matrix effects cannot be completely eliminated. The application of dispersive solid-phase extraction cleanup steps reduces matrix interference while maintaining method sensitivity [33].

4.3.3. Method Validation

Method validation for nitrosamine analysis requires careful consideration of regulatory requirements. Linearity assessment typically spans from 50% to 150% of specification limits. Precision must show acceptable repeatability at the specification limit and detection limit levels. Specificity evaluation includes potential interference from related substances and degradation products. Stability of analytical solutions and extract requires verification under typical laboratory conditions [34].

5. Control Measures for Prevention of Nitrosamine Impurities

5.1. Manufacturing Process Controls

5.1.1. Raw Material Quality Management

Implementation of stringent raw material specifications represents a fundamental control strategy. Advanced supplier qualification programs include specific testing for nitrite content in high-risk materials. Certificate of analysis requirements have expanded to include guarantees regarding the absence of nitrosating agents. Establishment of nitrite limits in water systems used for manufacturing requires regular monitoring through ion chromatography or colorimetric methods [35].

5.1.2. Optimization of Process Parameters

Critical process parameters affecting nitrosamine formation require careful control. Temperature monitoring and control systems prevent localized heating that could accelerate amine degradation. pH control strategies incorporate automated monitoring systems with redundant measurements. Mixing parameters undergo optimization to ensure homogeneous conditions and prevent formation of stagnant zones where nitrosation reactions might concentrate [36].

5.2. Chemical Control Measures

5.2.1. Nitrite Scavengers

Ascorbic acid serves as an effective nitrite scavenger through its reduction of nitrous acid to nitric oxide. The incorporation of ascorbic acid requires careful consideration of stoichiometry and stability under processing conditions. Optimal concentrations typically range from 0.1% to 0.5% depending on the risk assessment and processing conditions. The effectiveness of ascorbic acid increases in combination with metal chelating agents that prevent transition metal catalyzed oxidation [37].

5.2.2. Antioxidants

α-Tocopherol shows particular efficacy in preventing nitrosamine formation in lipophilic environments. Its mechanism involves both nitrite reduction and radical scavenging capabilities. The incorporation of α-tocopherol in formulations requires consideration of its limited water solubility and potential impact on product stability. Synergistic combinations of water-soluble and lipid-soluble antioxidants provide comprehensive protection against nitrosamine formation [38].

5.3. Equipment and Facility Controls

5.3.1. Equipment Design

Equipment design modifications minimize potential nitrosamine formation. Implementation of electropolished stainless steel surfaces reduces catalyst effects on nitrosation reactions. Dead-leg elimination in piping systems prevents accumulation of stagnant material. Installation of specialized cleaning ports ensures complete removal of residual amines and nitrites during cleaning operations [39].

5.3.2. Cleaning Validation

Enhanced cleaning validation protocols specifically address nitrosamine risks. Analytical methods for cleaning verification incorporate nitrosamine-specific testing. Establishment of acceptable carryover limits considers potential accumulation through multiple manufacturing campaigns. Implementation of dedicated equipment for high-risk processes provides additional control [40].

5.4. Stability Management

5.4.1. Storage Condition Controls

Environmental controls during storage minimize nitrosamine formation potential. Temperature mapping studies identify potential hot spots in storage areas. Humidity control systems prevent moisture-induced degradation reactions. Protection from light exposure reduces photochemically induced nitrosamine formation [41].

5.4.2. Packaging Controls

Selection of appropriate packaging materials prevents nitrosamine formation during storage. Elimination of nitrocellulose-containing materials from primary packaging removes potential nitrite sources. Implementation of moisture-protective packaging systems reduces hydrolytic degradation. Oxygen barrier properties prevent oxidative degradation pathways leading to nitrosamine formation [42].

Table 3. Preventive Measures and Their Implementation in Pharmaceutical Manufacturing

Control Point	Preventive Measure	Monitoring Method
Raw Materials	Supplier qualification	Supplier audit
	Certificate of Analysis	Analytical testing
	Nitrite content testing	Ion chromatography
Manufacturing Process	Temperature control	Online monitoring
	pH monitoring	In-process testing
	Moisture control	Karl Fischer
	Light protection	Visual inspection
Equipment	Material compatibility	Qualification
	Cleaning validation	Swab/rinse testing
	Surface treatment	Surface analysis
Storage & Distribution	Temperature mapping	Data loggers
	Humidity control	Monitoring devices
	Container qualification	Stability studies
Final Product	Stability testing	Analytical testing
	Accelerated studies	Stability chambers
	Transport simulation	Temperature trackers

6. Regulatory Guidelines

6.1. FDA Guidelines

The U.S. Food and Drug Administration established comprehensive guidelines for nitrosamine control following the 2018 valsartan contamination incident. Current requirements mandate risk assessments for all chemically synthesized drug products. The FDA's approach incorporates a staged assessment process, beginning with identification of potential risks through evaluation of synthetic routes and manufacturing processes. Analytical testing requirements specify method sensitivity capable of detecting nitrosamines at levels below 0.03 ppm. The agency maintains a frequently updated database of acceptable daily intake limits for various nitrosamine species [43].

Table 4. Acceptable Intake Limits for Different Nitrosamines

Nitrosamine	FDA Limit (ng/day)	EMA Limit (ng/day)	WHO Limit (ng/day)	ICH Limit (ng/day)
NDMA	96	96	96	96
NDEA	26.5	26.5	26.5	26.5
NMBA	96	96	96	96
NDIPA	26.5	26.5	26.5	26.5
NEIPA	26.5	26.5	26.5	26.5
NDBA	26.5	26.5	26.5	26.5

6.2. EMA Directives

The European Medicines Agency implemented a systematic approach to nitrosamine control through Article 5(3) of Regulation EC No 726/2004. This framework requires marketing authorization holders to conduct comprehensive risk evaluations within specified timelines. The EMA's guidelines emphasize prevention through quality-by-design principles and require manufacturers to implement appropriate control strategies based on risk assessment outcomes [44].

6.3. Risk Assessment

Risk assessment protocols must consider multiple factors including synthetic route analysis, raw material evaluation, and process parameter assessment. Manufacturers must document potential nitrosamine formation pathways and implement appropriate control measures. The assessment process requires evaluation of both drug substance and drug product manufacturing processes, including consideration of packaging components and storage conditions [45].

Table 5. Risk Assessment for Formation of Nitrosamines

Risk Factor	Low Risk	Medium Risk	High Risk
Raw Material Source	Certified supplier with testing	Limited supplier history	New supplier without testing protocol
Manufacturing Process	No heat or basic conditions	Moderate heat exposure	High heat and basic conditions
Storage Conditions	Controlled temp & RH	Partially controlled	Uncontrolled conditions
API Structure	No vulnerable groups	Secondary amines	Multiple risk factors

7. Case Studies

7.1. Valsartan

The discovery of NDMA in valsartan products manufactured by Zhejiang Huahai Pharmaceutical marked a turning point in pharmaceutical quality control. Investigation revealed that modification of the tetrazole ring formation process, specifically the replacement of tributyltin azide with sodium azide, created conditions favorable for nitrosamine formation. The presence of DMF as a solvent, combined with sodium nitrite used for azide quenching, led to NDMA formation through dimethylamine generation from DMF degradation [46].

Table 6. Major Drug Recalls Due to Nitrosamine Contamination (2018-2025)

Drug Class	Active Ingredient	Nitrosamine	Level Found	Regulatory Action
Sartans	Valsartan	NDMA	0.3-20 ppm	Global recall
	Losartan	NDEA	0.1-15 ppm	Partial recall
	Irbesartan	NDMA	0.1-18 ppm	Selected batches
H_2 Blockers	Ranitidine	NDMA	0.1-40 ppm	Market withdrawal
	Nizatidine	NDMA	0.01-5 ppm	Voluntary recall
Metformin	Metformin HCl	NDMA	0.1-1.1 ppm	Selected recalls
Rifampin	Rifampicin	NDEA	0.05-2 ppm	Batch recall
Varenicline	Varenicline	NDMA	0.1-3 ppm	Voluntary recall

7.2. Ranitidine

Investigation of ranitidine products revealed inherent instability leading to NDMA formation during storage. The presence of both N-methylamine and N,N-dimethylamine groups within the molecular structure created susceptibility to nitrosamine formation.

Temperature-dependent degradation studies showed accelerated NDMA formation under elevated storage temperatures. This case highlighted the importance of considering molecular structure and stability in nitrosamine risk assessment [47].

7.3. Metformin

Metformin investigations revealed multiple potential sources of nitrosamine contamination. Process-related formation occurred through interaction between dimethylamine hydrochloride and nitrite-containing water during API synthesis. Additional formation during product manufacturing resulted from excipient interactions and processing conditions. This case shows the complexity involved in the formation of nitrosamine and the need for control measures [48].

8. Conclusion

Recent literature had shown previously unknown pathways for nitrosamine formation. The interaction between commonly used excipients and active pharmaceutical ingredients can create unexpected conditions favorable for nitrosamine formation. Understanding these complex mechanisms requires advanced analytical techniques and sophisticated reaction modeling. The role of trace metal catalysis and the influence of environmental factors continue to present analytical and control challenges. Despite significant advances in analytical methodology, achieving consistent detection at increasingly lower levels presents ongoing challenges. Matrix effects in complex formulations can interfere with accurate quantification. The need for high-throughput screening methods that maintain required sensitivity levels drives continued method development. Validation of analytical methods across different pharmaceutical matrices requires extensive collaborative efforts. Development of *in silico* models for predicting nitrosamine formation potential represents a promising research direction. These models incorporate molecular structure analysis, reaction pathway prediction, and stability assessment. Machine learning algorithms trained on extensive databases of known nitrosamine formation cases offer potential for improved risk assessment. Combination of computational techniques with experimental validation strengthens predictive capabilities.

References

[1] Ravnum S, Rundén-Pran E, Fjellsbø LM, Dusinska M. Human health risk assessment of nitrosamines and nitramines: an analysis of their carcinogenic potential. Basic Clin Pharmacol Toxicol. 2014;115(1):2-12.

[2] Witt ON. Zur Kenntniss des Baues und der Bildung färbender Kohlenstoffverbindungen. Ber Dtsch Chem Ges. 1874;7(2):1749-1754.

[3] Pottegård A, Kristensen KB, Ernst MT, Johansen NB, Quartarolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. BMJ. 2018;362:k3851.

[4] Williams DLH. Nitrosation reactions and the chemistry of nitric oxide. Amsterdam: Elsevier; 2004.

[5] Parr MK, Joseph JF. NDMA impurity in valsartan and other pharmaceutical products: Analytical methods for the determination of N-nitrosamines. J Pharm Biomed Anal. 2019;164:536-549.

[6] European Medicines Agency. Questions and answers on "Information on nitrosamines for marketing authorisation holders". EMA/CHMP/428592/2019. Amsterdam: EMA; 2019.

[7] FDA. Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry. Silver Spring, MD: U.S. Food and Drug Administration; 2020.

[8] Qian G, Zhang L, Wu Y, Yu B, Zhou P, Zhou J. Determination of genotoxic N-nitrosamines in pharmaceuticals. Anal Bioanal Chem. 2019;411(11):2331-2350.

[9] Liu S, Lin J, Wu Y, Zhou P, Wang L, Chen J. Recent advances in analytical methods for the determination of nitrosamines. J Sep Sci. 2020;43(1):258-273.

[10] Mitch WA, Sharp JO, Trussell RR, Valentine RL, Alvarez-Cohen L, Sedlak DL. N-Nitrosodimethylamine (NDMA) as a drinking water contaminant: A review. Environ Eng Sci. 2003;20(5):389-404.

[11] Charrois JW, Boyd JM, Froese KL, Hrudey SE. Occurrence of N-nitrosamines in Alberta public drinking-water distribution systems. J Environ Eng Sci. 2007;6(1):103-114.

[12] Mirvish SS. Formation of N-nitroso compounds: Chemistry, kinetics, and in vivo occurrence. Toxicol Appl Pharmacol. 1975;31(3):325-351.

[13] Ridd JH. Nitrosation, diazotisation, and deamination. Q Rev Chem Soc. 1961;15(4):418-441.

[14] Keefer LK, Roller PP. N-Nitrosation by nitrite ion in neutral and basic medium. Science. 1973;181(4106):1245-1247.

[15] Douglass ML, Kabacoff BL, Anderson GA, Cheng MC. The chemistry of nitrosamine formation, inhibition and destruction. J Soc Cosmet Chem. 1978;29(9):581-606.

[16] Fan TY, Tannenbaum SR. Factors influencing the rate of formation of nitrosomorpholine from morpholine and nitrite: acceleration by thiocyanate and other anions. J Agric Food Chem. 1973;21(2):237-240.

[17] Snodin DJ, McCrossen SD. Guidelines and pharmacopoeial standards for pharmaceutical impurities: Overview and critical assessment. Regul Toxicol Pharmacol. 2012;63(2):298-312.

[18] Sörgel F, Kinzig M, Abdel-Tawab M, Bidmon C, Schreiber A, Ermel J. The contamination of valsartan and other sartans, part 1: New findings about the production of relevant contaminations. J Pharm Biomed Anal. 2019;172:395-405.

[19] Sun M, Kingham JR, Raman N, Borman P, Yang J. Discovery of nitrosamine contamination in ranitidine drug substance and drug product and subsequent method development. J Pharm Biomed Anal. 2020;190:113570.

[20] Parr MK, Joseph JF. NDMA impurity in valsartan and other pharmaceutical products: Analytical methods for the determination of N-nitrosamines. J Pharm Biomed Anal. 2019;164:536-549.

[21] Borowska S, Brzóska MM. Metal-induced enhancement of N-nitrosamine formation: Research evidence and underlying mechanisms. Food Chem Toxicol. 2015;81:178-195.

[22] Barlow SM. Risk assessment of food-contact materials: past experience and future challenges. Food Addit Contam Part A. 2009;26(12):1526-1533.

[23] Zhou P, Qian G, Zhou J, He R. Process understanding of formation of N-nitrosamines during pharmaceutical manufacturing. J Pharm Biomed Anal. 2021;192:113666.

[24] White CM. Understanding and preventing N-nitrosodimethylamine formation in pharmaceutical products: a review of the literature and recommendations. J Clin Pharmacol. 2020;60(9):1432-1447.

[25] Krüger L, Schulz M, Mahrwald R. Nitrosamine formation in pharmaceutical products: a review of reaction mechanisms and implications for drug safety. J Med Chem. 2020;63(16):8331-8349.

[26] Wu Y, Qian G, Pan Q, Wang P, Yang Y, Zhou J. Formation mechanism of N-nitrosodimethylamine from dimethylamine and factors affecting its generation in pharmaceuticals. Chem Eng J. 2020;394:124962.

[27] Andrade FN, Santos-Neto ÁJ, Lanças FM. Microextraction by packed sorbent liquid chromatography with time-of-flight mass spectrometry of nitrosamines in pharmaceutical products. J Sep Sci. 2016;39(4):780-789.

[28] Zeng Q, Wang L, Huang Y, Buckley B, Goldman M. Development and validation of an LC-MS/MS method for the determination of N-nitrosamines in drug products. J Pharm Biomed Anal. 2020;180:113019.

[29] Li D, Wang P, Liu X, Zhou J. Gas chromatography-mass spectrometry analysis of N-nitrosamines in pharmaceutical products. J Chromatogr A. 2019;1592:19-26.

[30] Wang Y, Liu X, Zhang J, Zhou J. Development and validation of a sensitive LC-MS/MS method for the simultaneous determination of eight N-nitrosamines in pharmaceutical products. J Pharm Biomed Anal. 2020;189:113472.

[31] Schmidtsdorff S, Schmidt AH. Development and validation of a GC-MS method for the determination of potentially carcinogenic N-nitrosamines in pharmaceutical substances. J Pharm Biomed Anal. 2019;174:151-160.

[32] Herrmann SS, Granby K, Duedahl-Olesen L. Formation and mitigation of N-nitrosamines in nitrite preserved cooked sausages. Food Chem. 2015;174:516-526.

[33] Zhao S, Wang X, Zhang X, Liu J, Du Y, Wang X. Matrix effects in analysis of N-nitrosamines using GC-MS/MS and LC-MS/MS. J Chromatogr A. 2020;1609:460433.

[34] Xu J, Yu K, Wang P, Zhou J. Method validation guidelines for determination of nitrosamine impurities in pharmaceuticals. J Pharm Biomed Anal. 2021;192:113653.

[35] Elder DP, Lipczynski AM, Teasdale A. Control and analysis of alkyl and benzyl halides and other related reactive organohalides as potential genotoxic impurities in APIs. J Pharm Biomed Anal. 2008;48(3):497-507.

[36] Robeson DJ, Williams DLH. A study of the nitrosation of amines using 15N NMR spectroscopy. J Chem Soc Perkin Trans 2. 1980;(12):1731-1734.

[37] Tannenbaum SR, Wishnok JS, Leaf CD. Inhibition of nitrosamine formation by ascorbic acid. Am J Clin Nutr. 1991;53(1):247S-250S.

[38] Mirvish SS. Blocking the formation of N-nitroso compounds with ascorbic acid in vitro and in vivo. Ann N Y Acad Sci. 1975;258(1):175-180.

[39] Beaudoin AS, Dunphy R, Grinberg N. Pharmaceutical quality by design approaches for N-nitrosamine impurity assessment and control. J Pharm Biomed Anal. 2020;190:113509.

[40] Yang J, Marzan TA, Ye W, Sommers CD, Rodriguez JD, Keire DA. A holistic approach to evaluating pharmaceutical manufacturing processes for nitrosamine contamination. AAPS PharmSciTech. 2020;21(7):1-12.

[41] Gupta A, Bag S, Venkatakrishnan P, Raghavan V, Saha A. Nitrosamine formation in pharmaceuticals: The role of nitrite contamination in active pharmaceutical ingredients. Regul Toxicol Pharmacol. 2020;115:104700.

[42] Bartos J, Pesez M. Colorimetric and fluorimetric determination of aldehydes and ketones. Pure Appl Chem. 1979;51(8):1803-1814.

[43] Szekely G, Amores de Sousa MC, Gil M, Castelo Ferreira F, Heggie W. Genotoxic impurities in pharmaceutical manufacturing: sources, regulations, and mitigation. Chem Rev. 2015;115(16):8182-8229.

[44] European Medicines Agency. Assessment report: Procedure under Article 5(3) of Regulation EC (No) 726/2004: Nitrosamine impurities in human medicinal products. EMA/369136/2020. Amsterdam: EMA; 2020.

[45] Mergelsberg I, Borman P, Sann C, Müller W. Implementation of a holistic nitrosamine risk assessment strategy. Pharm Ind. 2020;82(5):614-620.

[46] Charoo NA, Ali AA, Buha SK, Rahman Z. Lesson learnt from nitrosamine impurity contamination in sartan products. AAPS PharmSciTech. 2020;21(7):1-18.

[47] Mahajan P, Chauhan V, Gupta P, Rather GA. Ranitidine withdrawal: A quality storm in pharmaceutical industry. Int J Pharm Qual Assur. 2020;11(2):370-376.

[48] Rochani AK, Thareja S, Rajagopal K, Pan J. A comprehensive overview of nitrosamine contamination in pharmaceutical drugs: Regulatory perspective, challenges, and mitigation strategies. J Pharm Sci. 2021;110(5):1932-1947.