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Nitrosamine impurities in pharmaceutical dosage forms: Current challenges and mitigation strategies

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Abstract

Nitrosamine impurities have been detected in various pharmaceutical products in nowadays. These impurities are classified as probable human carcinogens and can be found in a wide range of products including pharmaceuticals, industrial chemicals and food. This review paper provides a comprehensive analysis of nitrosamine impurities in Pharmaceutical dosage forms. It covers the formation and sources of nitrosamine impurities, allowable daily intake impurities limit (ng/day), the analytical methods employed for their detection. Various methods including LC-MS, GC-MS and HPLC for nitrosamine impurities, regulatory guidelines, notable incidents, case studies and the impact of nitrosamine impurities contamination on the pharmaceutical landscape and additionally, case studies of previous incidents involving nitrosamine-contaminated pharmaceutical products. Furthermore, this overall review provides outlines the current mitigation strategies, risk assessment, future directions and challenges adopted by pharmaceutical companies to ensure Drug safety and regulatory compliance in worldwide also provides a comprehensive examination of the current state of knowledge regarding nitrosamine impurities in pharmaceutical dosage forms.

Keywords: Nitrosamine Impurities; Formation and sources of Nitrosamines; Analytical Methods; Regulatory Guidelines; Mitigation Strategies

Graphical abstract

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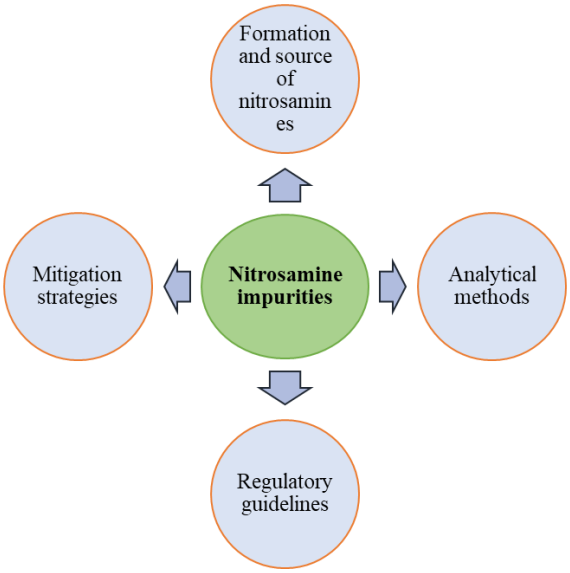


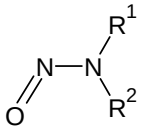
1. Introduction

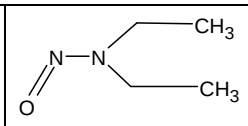
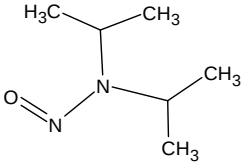
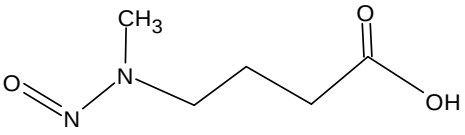
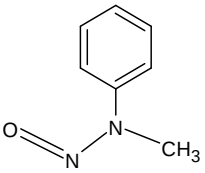
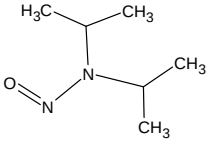
N-nitrosamines are chemical compounds with a functional N-nitroso group (>N-N=O), typically derived from secondary or tertiary amines in the presence of nitrosating agents.[1] They considered a "cohort of concern" by the (ICH) International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use M7, 2 due to their possible human carcinogenic potential. [2,3]

In the early years, nitrosamine impurities were not a major focus within the pharmaceutical industry. In recent years, the issue of nitrosamine impurities in pharmaceutical dosage forms has emerged as a matter of significant concern for the global healthcare industry. Due to their carcinogen potential the presence of nitrosamine impurities in pharmaceutical and other consumer products is a significant concern for public health and regulatory agencies. Pharmaceutical dosage forms including tablets, capsules, topical formulations and injectables, and are designed to deliver precise and safe doses of active pharmaceutical ingredients to the patients. However, the occurrence of nitrosamine impurities in these products raises questions about their safety and quality. [4] Nitrosamines can form through various mechanisms during the manufacturing process, storage or packaging and their presence may not always be immediately apparent, making detection and prevention challenging tasks for pharmaceutical manufacturers. [5] Their presence in pharmaceutical products poses potential health-related risks to patients, necessitating a thorough examination of their formation, sources, detection and mitigation strategies with advancements in the analytical methods and growing awareness of the health risks associated with nitrosamine impurities.[6]

Over the years, as analytical techniques became more sensitive and regulations more stringent, more cases of nitrosamine contamination were uncovered in various pharmaceutical products. Notable incidences include the detection of nitrosamines in angiotensin receptor blockers (ARBs), used for hypertension management and certain diabetes medications [7]. In response to these findings regulatory agencies worldwide the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have taken swift action to address the nitrosamine impurity issue. They have issued guidelines and set acceptable limits for nitrosamines in pharmaceutical dosage forms to protect public health and ensure the safety of medications. Compliance with these regulations has become a priority for pharmaceutical companies to avoid recalls and maintain consumer trust. [8, 9]

Table 1 Nitrosamines and their structure present in drug

Name of impurity	**Structure**	**Allowable daily intake (AI Limit) (ng/day)**
NDMA- N-Nitrosodimethylamine		96

NDEA- N-Nitrosodiethylamine		26.5
NDIPA- N-Nitrosodiisopropylamine		26.5
NMBA- N-Nitroso-N-methyl-4-aminobutyric acid		96
NMPA- N-Nitrosodimethylphenylamine		26.5
NDIPA- N-Nitrosodisopropylamine		26.5

In July 2018 Food and drug administration and European medical announced that carcinogenic impurities are present in N- Nitrosodimethylamine (NDMA) and N- N-Nitrosodimethylamine are generic substance present in drug product. [10, 11]

These all limits are applicable only if a drug product contains a single nitrosamine. If the nitrosamine impurities identified more than one in Table no.1 is the total amount of nitrosamine impurities 26.5 ng/day based on the maximum daily dose (MDD), then the manufacturer should contact the Agency for evaluation. For the drug products with an MDD of less than 880 mg/day a recommended limit for total nitrosamines of 0.03 ppm is not more than 26.5 ng/day is considered. For the drug products with an MDD above 880 mg/day and the limit for total nitrosamines should be adjusted and not exceed to the limit of 26.5 ng/day. [12]

1.1. Nitrosamine Contamination of Valsartan and Other Sartan Drugs

In 2018 the United States Food and Drug Administration issued a recall of certain blood pressure medications containing the active ingredient valsartan due to the detection of N-nitrosodimethylamine (NDMA) a potential carcinogenic nitrosamine. This recall affected multiple manufacturers and raised concerns globally about the safety of other sartan drugs. Furthermore, many other sartan-containing medications were also found to have nitrosamine impurities leading to further recalls and regulatory actions worldwide. [13]

1.2. Ranitidine Contamination

In 2019, concerns were raised about the presence of nitrosamine impurities, primarily NDMA and N-nitrosodiethylamine (NDEA) in ranitidine products commonly used to treat heartburn and acid reflux. Multiple pharmaceutical companies including large generics manufacturers initiated voluntary recalls of their ranitidine products globally. [14]

1.3. Controlling nitrosamine contamination in drug products is of most importance due to the following key reasons

Regulatory Compliance- Regulatory agencies worldwide have established guidelines and limits for nitrosamine impurities in pharmaceuticals. Fail to comply with regulations can lead to serious consequences, product recalls, fines

and damage to a company's reputation. Understanding the sources of nitrosamine contamination are essential to meeting regulatory requirements and maintaining market access.

Patient Safety- The primary concern is protecting health of patients who depends on the pharmaceutical medications. Nitrosamines have been classified as probable human carcinogens; means they have potential to cause cancer in humans. Small amounts of nitrosamines exposure over an extended period of time can cause serious health risks. By understanding and controlling nitrosamine contamination in pharmaceutical companies can ensure that their marketed products are safe for patients.[15]

1.4. Sources of nitrosamine impurities

Nitrosamine impurities can made from many different sources:-[16]

Raw Materials: Nitrosamines can be introduced into pharmaceutical products through the presence of nitrosamine-containing raw materials. Certain starting key materials or intermediates which is used in drug synthesis may inherently contain nitrosamine impurities which can transfer to the final drug product during production process.

Nitrite-Containing Reagents: Some manufacturing processes may involve the use of nitrite-containing reagents which can lead to the formation of nitrosamines as by-products. These reagents can react with amines or amides present in the drug formulation or manufacturing process resulting in formation of nitrosamine impurities. [17]

Interactions with Drug Components: Nitrosamines can form as a result of chemical interactions between different drug components during formulation or storage.

Environmental Contamination: External environmental factors such as air pollution or cross-contamination in the manufacturing facility can lead to the introduction of nitrosamine impurities into final product. [18]

Reactions during Storage: Some drug products, particularly those containing certain drug classes e.g. angiotensin receptor blockers - ARBs, have been found to form nitrosamines during long-term storage under specific conditions, such as exposure to light, heat or humidity. [19]

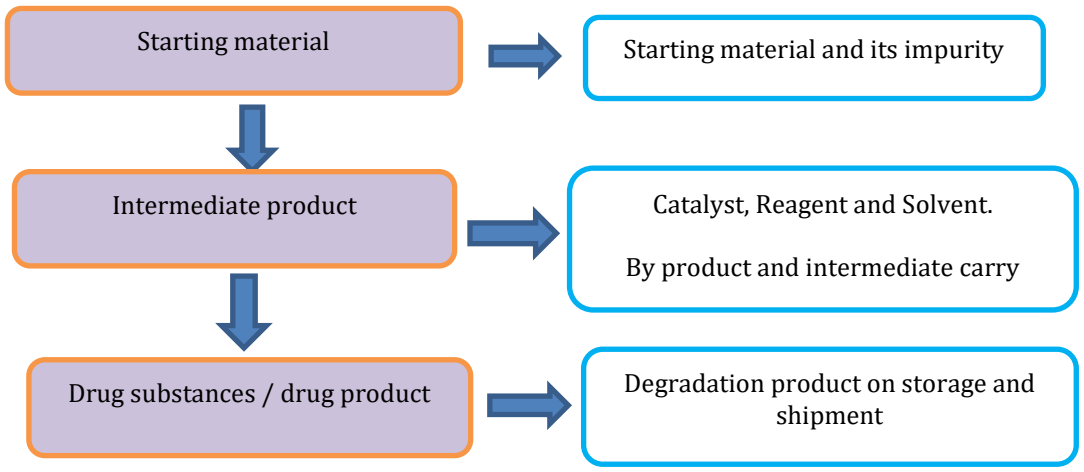


Figure 1 Possible source of possible source of nitrosamine

Impurities from Excipients: In some cases, excipients used in drug formulations may contain trace amounts of nitrosamines as impurities contributing to the overall nitrosamine content in the final product. [20]

Cross contamination: Cross contamination during the manufacturing process mainly in equipment or facilities can lead to the introduction of nitrosamine into pharmaceutical products.

Contamination in Vendor-Sourced Raw Materials Nitrosamine impurities can be introduced when vendor-source materials including starting materials and raw materials are contaminated.

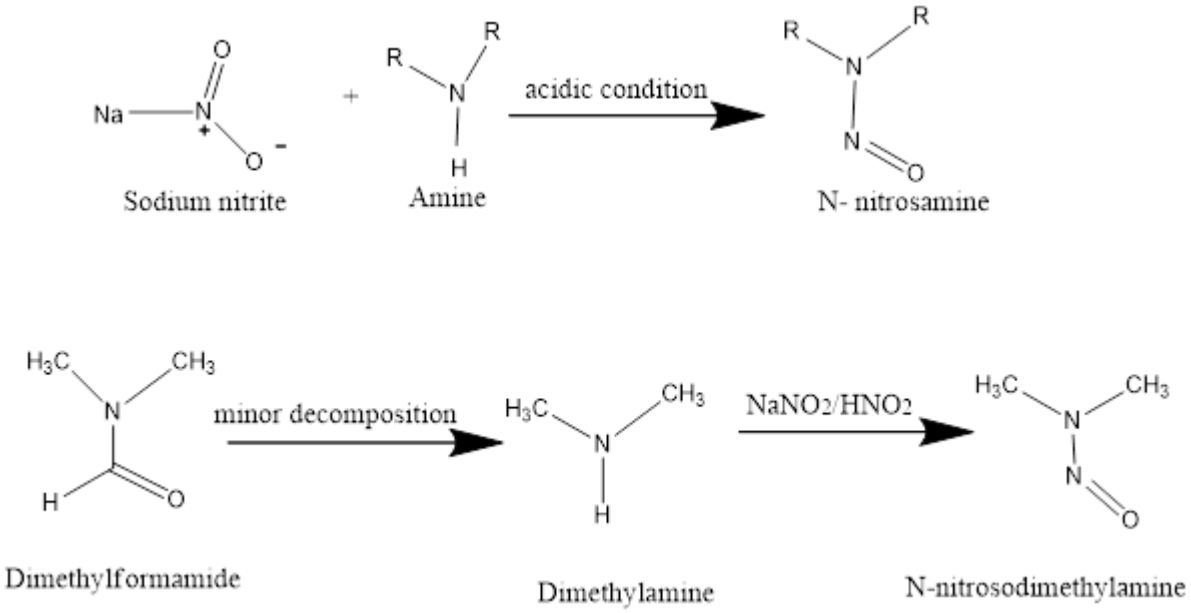


Figure 1 Formation of nitrosamine impurity [21]

The following contaminations and root cause has observed by agencies:

Nitrosamine contamination has occurred when fresh solvents were contaminated during shipment from vendors. Awareness of the supply chain of raw materials is an important factor in preventing contamination. For example, Producers of APIs may not be aware of nitrosamine contamination in raw or starting materials they have sourced from vendors; a producer whose manufacturing process is not normally susceptible to nitrosamine formation may not realize that vendor-sourced material may have had impurities introduced during production or transport.[22]

Primary, secondary, tertiary amines and quaternary ammonium salts with nitrosating agents such as Sodium nitrite are considered to be precursors for the generation of Nitrosamines impurities. The extent of Nitrosamine impurity formation depends on the type of reagents their structure and the concentration of the nitrosating agent. Secondary amines remain considered to be more reactive. [23]

Trace amount of these impurities may be formed due to decomposition of solvent or other materials used in the synthesis of drug substances. Also, by-products formed in the drug synthesis process may get be carried forward to the drug substances as Nitrosamine impurities.

Solvents may form potential NDMA and NDEA impurities such as Dimethylformamide (DMF), Dimethylacetamide (DMA) or Diethylacetamide (DEA) [24]

Detection and quantification of nitrosamine impurities in pharmaceutical products required sensitive and reliable analytical methods. For this purpose, several techniques are commonly employed:

1.5. Detection Methods

The detection of nitrosamine impurities in pharmaceutical products is crucial to ensure drug safety. Analytical methods commonly employed for nitrosamine detection contain Liquid Chromatography-Mass Spectrometry (LC-MS), Gas Chromatography-Mass Spectrometry (GC-MS), High-Performance Liquid Chromatography (HPLC) with UV or fluorescence detection and NMR Spectroscopy (Nuclear Magnetic Resonance).

LC-MS is one of the most widely used methods for nitrosamine detection and quantification. It involves separating nitrosamines using liquid chromatography and then identifying and quantifying them based on their mass-to-charge ratios using mass spectrometry. LC-MS offers more sensitivity, specificity and the ability to analyze multiple nitrosamines simultaneously.[25]

Gas Chromatography-Mass Spectrometry (GC-MS): GC-MS is one of the most important powerful method for nitrosamine analysis. GC is particularly useful for volatile nitrosamines. It involves separating and quantifying nitrosamines in a gaseous state using gas chromatography and then identifying them based on their mass spectra with mass spectrometry. [26]

High-Performance Liquid Chromatography (HPLC): HPLC with UV or fluorescence detection is employed for nitrosamine analysis in cases where MS instruments are not available or for routine testing purposes. It allows for the separation and quantification of nitrosamines based on their absorbance or fluorescence properties. [27]

NMR Spectroscopy (Nuclear Magnetic Resonance): NMR spectroscopy is a non-destructive method used for structural elucidation and confirmation of nitrosamine impurities. It helps in identifying specific functional groups and molecular structures of nitrosamines. [28]

Liquid Chromatography: Tandem Mass Spectrometry (LC-MS/MS): It is a highly sensitive and specific technique that combines liquid chromatography with multiple stages of mass spectrometry. It offers improved quantification accuracy and selectivity for trace-level analysis of nitrosamines. [29]

Table 2 Different detection used to detect impurities

Detection methods	**Impurities**
GC/MS method	N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) [30]
GC-MS/MS	NDMA and NDEA
Direct injection GC-MS method	NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA) [31]
Headspace GC-MS	NDMA, NDEA, NDIPA, and NEIPA [32]
Rapid Fire-MS/MS method	NEIPA, NDIPA, NDBA, and NMBA [33]
LC-HRMS method	NDMA in ranitidine [34]
LC-MS/MS method	NDMA in ranitidine [35]

1.5.1. Some key aspects of the regulatory landscape includes

Guidelines and Limits: Regulatory agencies like US Food and Drug Administration, Medicines and Healthcare products Regulatory Agency in the UK, European Medicines Agency and Health Canada and others have issued guidelines and limits for nitrosamine impurities in pharmaceuticals. These guidelines specify acceptable levels of specific nitrosamines in drug products to minimize health risks. [36]

Enhanced Detection Technologies: Analytical methods for nitrosamine detection and quantification are expected to improve further, becoming more sensitive, specific, and efficient. Advancements in mass spectrometry, chromatography methods and other spectroscopic techniques will enable quicker and more accurate identification of nitrosamine impurities. [37]

Manufacturers are required to conduct a risk assessment to evaluate the potential presence of nitrosamine impurities in their drug products. This assessment should consider the manufacturing process, starting materials, and potential sources of nitrosamine contamination.

1.6. Set Limits and Action Levels

Health authorities have established acceptable limits and action levels for specific nitrosamine impurities in pharmaceutical products. These limits are based on safety considerations and may vary depending on the drug's therapeutic class and intended patient population.

1.6.1. Testing Requirements

Manufacturers are expected to perform rigorous testing to detect and quantify nitrosamine impurities in their products. Analytical methods used for testing should be validated, sensitive, and specific to the nitrosamines of interest.

1.6.2. Reporting Obligations

Manufacturers are required to report any confirmed or suspected cases of nitrosamine contamination to the relevant regulatory authorities. This reporting ensures timely action and potential recalls, if necessary to protect public health.

1.6.3. Preventive Measures

Health authorities encourage pharmaceutical manufacturers to implement robust measures to prevent the formation of nitrosamines during the drug manufacturing process. This may involve optimizing reaction conditions, carefully selecting raw materials and employing good manufacturing practices (GMP) to minimize contamination risks.

1.6.4. Recalls and Safety Alerts

In case of confirmed nitrosamine contamination above the established limits, health authorities may require manufacturers to recall affected batches of pharmaceutical products to prevent patient exposure to potentially harmful impurities. Safety alerts may also be issued to inform healthcare professionals and patients about the situation. [38]

1.6.5. Post-Marketing Surveillance

Health authorities emphasize the importance of continuous post-marketing surveillance for nitrosamine impurities in pharmaceutical products. This includes routine testing of marketed drugs to ensure ongoing compliance and it is most important for pharmaceutical companies to comply with these regulatory guidelines and requirements to ensure the Quality, Efficacy and Safety of their products. [39]

1.7. Mitigation process

Improved Analytical Methods: Analytical methods with high sensitivity and specificity for nitrosamine detection. Regularly test raw materials, in-process samples and finished products to ensure compliance with regulatory limits and identify any potential sources of contamination. [40]

Optimization of process: Modifying manufacturing processes to minimize or eliminate the formation of nitrosamine impurities is a critical mitigation strategy. This may involve adjusting reaction conditions, using alternative reagents optimizing the process to minimize the potential for nitrosamine formation. [41]

Change Control and Validation: Any changes to the manufacturing process or formulation that could impact nitrosamine impurities should be subjected to rigorous change control procedures and validated to ensure the changes do not increase the risk of contamination.[42]

Enhanced Quality Control: Strengthen quality control processes throughout the supply chain to monitor and control the presence of nitrosamine impurities. Employ both internal and external audits to verify compliance with established standards.[43]

Collaboration and Knowledge Sharing: Collaborate with regulatory authorities, industry organizations, and analytical laboratories to share knowledge, best practices and data related to nitrosamine impurities. This collaborative approach will drive the development of standardized procedures and improve overall safety standards. [44]

Pharmacovigilance and Patient Communication: Strengthen pharmacovigilance efforts to monitor and assess the safety of pharmaceutical products in real-world use. In case of any potential safety concerns related to nitrosamine. [45]

1.7.1. Risk assessment [46,47]

Packaging -Thermal decomposition of Nitrocellulose to produce nitrites followed by migration to the Drug Product Biodegradation of Nitrocellulose to produce nitrites followed by migration to the Drug product

Solvent- Presence of nitrites or other nitrosating agents, Limited controls/specification limits for recycled solvents, Presence of residual tri-substituted amines that can degrade to form dialkyl amines.

Drug Substance - Use of recycled solvents which may contain nitrosamines or their precursors, Need of extra purification steps.

2. Conclusion

Nitrosamine impurities in pharmaceutical dosage forms represent a significant concern for the pharmaceutical industry and regulatory authorities in worldwide. The potential carcinogenicity and health risks associated with nitrosamines necessitate thorough understanding detection and control measures to ensure patient safety and regulatory compliance.

Through this comprehensive review, we have explored the sources of nitrosamine impurities, the analytical methods employed for their detection and quantification, the evolving regulatory landscape, and the impact of nitrosamine contamination on the pharmaceutical industry. Additionally, we have discussed the implementation of mitigation strategies to safeguard public health. The future viewpoints on nitrosamine impurities are promising with advancements in analytical technologies, increased regulatory scrutiny, and ongoing collaboration between industry stakeholders and regulatory agencies. These efforts will continue to improve drug safety, quality and efficacy further reinforcing public trust in the pharmaceutical industry.

In the face of evolving challenges continued research and innovation will play essential role in ensuring a safer and healthier future for pharmaceutical products free from the risks associated with nitrosamine impurities. Together, the industry can maintain their commitment to patient safety and the delivery of high-quality pharmaceutical industry to meet healthcare needs of worldwide peoples.

Top of Form

Mitigation strategies for nitrosamine impurities in pharmaceutical dosage forms are essential to minimize the presence of these potentially harmful compounds and ensure the safety of pharmaceutical products. The following are key mitigation strategies employed by pharmaceutical companies:

Risk Assessment and Control: Conducting a thorough risk assessment is crucial to identify potential sources of nitrosamine impurities in the drug product. This assessment should include a comprehensive evaluation of raw materials, manufacturing processes, and storage conditions. Based on the risk assessment, appropriate control measures can be implemented to prevent or reduce nitrosamine formation.

Compliance with ethical standards

Disclosure of conflict of interest

We declare no conflict of interest.

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