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Review Article

Strategies For Mitigating N-Nitrosamine Impurities In Drug Products: A Comprehensive Review

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ABSTRACT

The presence of nitrosamine impurities has been detected recently in several drug substances and drug products. N-nitroso compound are the among the structural groups having high potency mutagenic carcinogens in several animal species, and some are classified human carcinogens in ICH M7(R1). There are various potential source of nitrosamine impurities formation in drug product. The control of potentially mutagenic impurities in Pharmaceutical Product is key of importance in assessing carcinogenic risk to humans. Nitrosamine impurities can be avoided by change in manufacturing process or precautions in drug substance or drug products manufacturing. Recent studies have highlighted the importance of understanding and mitigating N-nitrosamine impurity (NDSRIs- Nitrosamine drug substance-related impurities) formed during drug product formulation. FDA has identified seven nitrosamine impurities that could be present in drug products. This comprehensive review aims to provide an in-depth analysis of strategies for mitigating NDSRIs in drug products, with a particular focus on the role of nitrite scavengers and control of nitrite concentration. Detailed studies provide guidance for the control of nitrosamine impurities in order to ensure that the potential presence of nitrosamines in drug substances & drug products is identified, assessed and controlled.

INTRODUCTION

N-nitrosamines are a type of organic compounds that have withdraw significant attention due to their potential carcinogenic properties. These compounds can form in various environmental and industrial processes, including tobacco smoke, food preservation, and pharmaceutical manufacturing. In the pharmaceutical industry, N-nitrosamine impurities in drug products have emerged as a critical concern, prompting regulatory agencies worldwide to issue guidelines and directives for their control and mitigation. While the focus initially was on N-nitrosamines originating from drug substance manufacturing

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processes, recent investigations have shed light on the formation of NDSRIs during drug product formulation. This review aims to provide a comprehensive overview of strategies for mitigating NDSRIs in drug products, with a particular emphasis on the role of nitrite scavengers and control of nitrite concentration

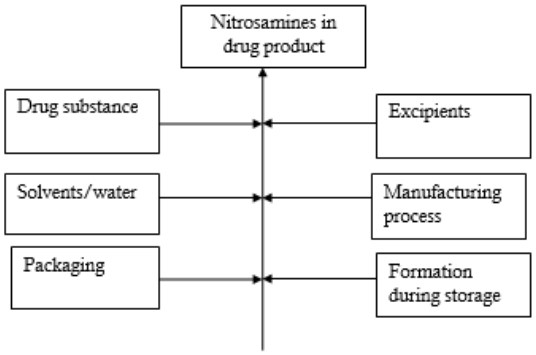
Risk Factors For N-Nitrosamine Formation

In the most common pathway to formation of N-nitrosamines, three factors are required

1. Presence of a nitrosatable amine.
2. Presence of a nitrosating agent.
3. Conditions conducive to N-nitrosamine formation.

Removing one of these factors is sufficient to mitigate the risk of N-nitrosamine formation.

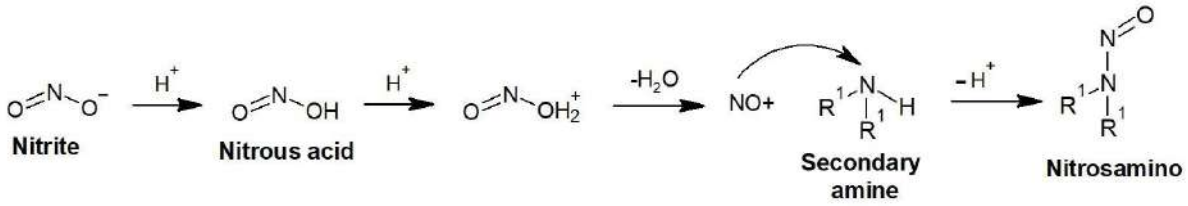
Source of nitrosamine impurities in drug product



a Primary/predominante source of potential nitrosamine
b Secondary source of potential nitrosamine
c Formed by a mechanism other than degradation of drug substance

Mechanisms of Nitrosamine drug substance-related impurities (NDSRI) Formation:

Understanding the mechanisms underlying the formation of NDSRIs is crucial for developing effective mitigation strategies. NDSRIs primarily form through the reaction of nitrite with vulnerable secondary amines present in drug formulations. Nitrosamines are formed by reaction of secondary or tertiary amines with a nitrosating agent.



Formation of Nitrosamine

Factors influencing NDSRI formation include the reactivity of the amine, the concentration of nitrite, and the formulation conditions. Reactive nitrogen species, such as nitrous acid and nitrosating agents, play key roles in mediating these reactions. The mechanisms of NDSRI formation vary depending on the chemical properties of the interacting molecules and the environmental conditions. Detailed mechanistic studies have provided valuable insights into the kinetics and pathways of NDSRI formation, enabling the development of targeted mitigation strategies. FDA has identified seven nitrosamine impurities that theoretically could be present in drug products with acceptable intake (AI) limits:

Nitrosamine	AI Limit (ng/day)
NDMA (N-Nitrosodimethylamine)	96
NDEA (N-nitrosodiethylamine)	26.5
NMPA (N-Nitrosomethylphenylamine)	26.5
NDIPA (N-nitrosodiisopropylamine)	26.5
NIPEA (N-nitrosoisopropylethylamine)	26.5
NDBA (N-nitrosodibutylamine)	-
NMBA (N-Nitroso-N-methyl-4-aminobytric acid)	96

Based on literature reports, two main categories of additives can be identified to facilitate the control of (complex) N-nitrosamines in drug products:

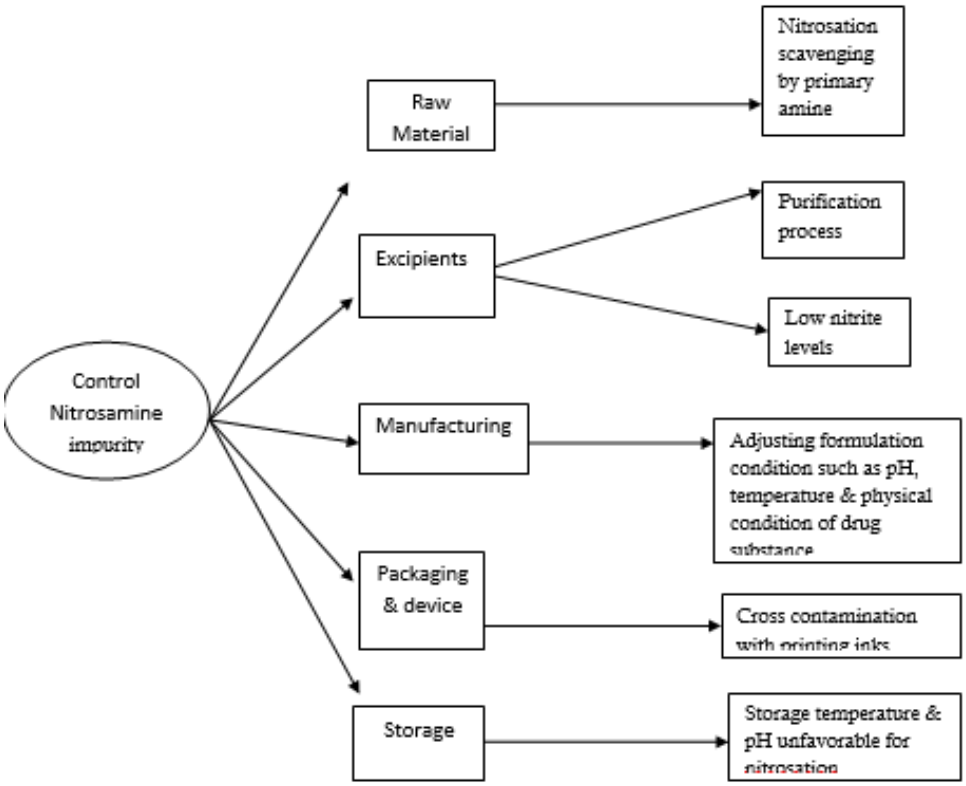
1. nitrite scavengers (antioxidants, amino acids, etc.) and
2. pH modulators (inorganic bases).

Role of Nitrite Scavengers:

Nitrite scavengers are compounds that react with nitrite or nitrite-derived species to prevent NDSRI formation. These scavengers can be classified into various categories based on their chemical properties and mechanisms of action. Antioxidants, primary amines, and amino acids are among the most commonly used nitrite scavengers in pharmaceutical formulations. Examples of effective scavengers include ascorbic acid, propyl gallate, p-aminobenzoic acid (PABA), and various amino acids. Studies have demonstrated the efficacy of these scavengers in reducing NDSRI formation both in solution and solid-phase formulations. The choice of scavenger depends on factors such as the reactivity of the nitrite species, the compatibility with other formulation components, and the desired pharmacological properties of the drug product.

Control of Nitrite Concentration:

Controlling the concentration of nitrite in pharmaceutical formulations is essential for mitigating NDSRI formation. Nitrite can originate from various sources, including raw materials, excipients, and manufacturing processes. Strategies for reducing nitrite content in formulations include selecting excipient sources with lower nitrite levels, implementing purification processes, or replacing excipients with lower nitrite content alternatives. Adjusting formulation conditions, such as pH, temperature, and physical properties of the drug substance, can also help mitigate NDSRI formation. Regulatory agencies worldwide have issued guidelines and directives for controlling nitrite levels in drug products, emphasizing the importance of rigorous quality control measures throughout the manufacturing process.



Nitrosamine risk assessments

Challenges and Limitations:

Despite significant progress in understanding and mitigating NDSRI formation, several challenges and limitations remain. Variability in scavenger efficacy, formulation complexity, and regulatory requirements pose significant challenges for implementation. The compatibility of scavengers with other formulation components, stability concerns, and potential toxicity issues require careful consideration during formulation development. Additionally, the heterogeneity of nitrite sources and the complexity of formulation processes make it challenging to implement uniform mitigation strategies across different drug products. Further research is needed to address these challenges and develop more robust and versatile mitigation approaches.

Future Directions and Recommendations

Future research efforts should focus on addressing the remaining challenges and limitations in NDSRI mitigation. Collaborative initiatives involving regulatory agencies, pharmaceutical manufacturers, academic researchers, and other stakeholders are essential for advancing knowledge in this area. Mechanistic studies elucidating the pathways of NDSRI formation, the efficacy of nitrite scavengers, and the impact of formulation conditions on NDSRI formation are needed to inform the development of targeted mitigation strategies. Improved analytical methods for detecting and quantifying NDSRIs in drug products are also crucial for ensuring compliance with regulatory requirements. Furthermore, education and training programs for pharmaceutical scientists and regulatory professionals can help raise awareness of NDSRI-related risks and facilitate the implementation of mitigation measures.

CONCLUSION:

NDSRI formation in drug products poses a significant challenge for the pharmaceutical industry, requiring comprehensive strategies for

mitigation. Nitrite scavengers and control of nitrite concentration during formulation have emerged as key approaches for reducing NDSRI formation. While progress has been made in understanding and implementing these strategies, further research and collaboration are needed to address remaining challenges and ensure the safety of drug products for patients. Regulatory agencies, pharmaceutical manufacturers, and other stakeholders must work together to advance knowledge in this area and develop effective mitigation approaches.

ABBREVIATIONS:

FDA: Food and Drug Administration

ICH: International Council for Harmonisation

NDSRIs- Nitrosamine drug substance-related impurities

PBPA –P-Aminobenzoic acid

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