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Formation of nitrosamine impurities: Discussion and advanced method development and validation using LC-MS/MS for their detection

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Abstract

Nitrosamine impurities, known for their genotoxic and carcinogenic potential, have emerged as critical concerns in pharmaceutical manufacturing. Their presence in various drug substances and products has led to stringent regulatory actions globally. This report explores the formation mechanisms of nitrosamine impurities, including the subset of nitrosamine drug substance-related impurities (NDSRIs), which arise from API-specific interactions. Advanced analytical techniques such as LC-MS/MS, GC-MS/MS, and HRMS are reviewed for their efficacy in detecting and quantifying these impurities. The report also emphasizes regulatory frameworks and discusses comprehensive risk assessment strategies. By combining robust analytical methodologies and harmonized guidelines, the industry can ensure the safety and efficacy of pharmaceutical products.

Keywords: Nitrosamine impurities; NDSRIs; LC-MS/MS; GC-MS/MS; Method validation; Regulatory compliance; Pharmaceutical safety

1. Introduction

Nitrosamine impurities are a group of compounds that have garnered significant attention due to their carcinogenicity and potential to cause DNA damage. These impurities can form during manufacturing, storage, or due to interactions with excipients, solvents, and environmental factors. Nitrosamine drug substance-related impurities (NDSRIs), a subset of nitrosamines, are specifically linked to the structure and reactivity of active pharmaceutical ingredients (APIs). Discovered in several widely used medications, including sartans, ranitidine, and metformin, these impurities have prompted a global regulatory response. The detection and quantification of nitrosamines at trace levels are vital to ensuring patient safety and maintaining pharmaceutical product integrity.

The challenges in addressing nitrosamine impurities include:

- Their trace-level occurrence.
- Matrix complexity in pharmaceutical formulations.
- The need for ultra-sensitive and specific detection methods.

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2. Mechanisms of Nitrosamine Formation

Nitrosamines can form via several pathways:

2.1. Chemical Reactions

- Interaction between secondary or tertiary amines and nitrosating agents like nitrites.
- Degradation of APIs or excipients under acidic or oxidative conditions.

2.2. Environmental Factors

- High temperatures and humidity during storage.
- Contaminated packaging materials that introduce nitrosating agents.

2.3. Drug-Specific Pathways (NDSRIs)

- Formation linked to the structural features of APIs, such as amines and nitroso groups.
- Examples include nitrosamine formation in sartans with tetrazole rings or other APIs with reactive functional groups.

3. Analytical Techniques for Nitrosamine Detection

3.1. Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

LC-MS/MS is the gold standard for nitrosamine impurity analysis due to its sensitivity and specificity:

Advantages

- Detects impurities at levels as low as nanograms per liter.
- Provides simultaneous quantification of multiple nitrosamines.
- Versatile for a wide range of drug matrices.

3.2. Gas Chromatography-Tandem Mass Spectrometry (GC-MS/MS)

GC-MS/MS is ideal for analyzing volatile nitrosamines:

Advantages

- High precision for low molecular weight and volatile nitrosamines.

Limitations

- Requires derivatization for non-volatile impurities, reducing efficiency for broader applications.

3.3. High-Resolution Mass Spectrometry (HRMS)

- HRMS is highly suitable for identifying unknown nitrosamines and NDSRIs:

Advantages

- Offers high mass accuracy, enabling structural elucidation.
- Useful in early impurity profiling.

Limitations

- Requires advanced instrumentation and expertise.

3.4. Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR provides structural insights, making it a complementary tool:

Advantages

- Confirms structural details of nitrosamines.

Limitations

- Lower sensitivity compared to MS techniques.

4. Analytical Challenges with NDSRIs

NDSRIs present unique challenges due to their API-specific nature:

4.1. Trace-Level Quantification

- The need for detection limits aligned with regulatory acceptable intake levels.

4.2. Matrix Interference

- Co-existence with APIs and excipients complicates the analysis.

4.3. Lack of Standards

- Difficulty in obtaining impurity standards for method validation.

5. Regulatory Frameworks and Guidelines

Regulatory agencies globally have issued guidelines to manage nitrosamine risks:

5.1. FDA Recommendations

- Define acceptable intake limits for NDSRIs.
- Encourage proactive risk assessments and analytical validations.

5.2. ICH Guidelines (Q2, Q14, M7)

- Offer comprehensive frameworks for method development, validation, and impurity control.

5.3. EMA and Other Regional Authorities

- Emphasize harmonized approaches to impurity risk management, including NDSRIs.

5.4. Key Aspects

- Analytical methods must achieve sensitivity and specificity at regulatory limits.
- Risk assessment strategies should identify all possible nitrosamine formation pathways.

6. Risk Mitigation Strategies

Manufacturers must adopt a multi-faceted approach to minimize nitrosamine risks:

6.1. Process Optimization

Reduce nitrosating agents and optimize reaction conditions.

6.2. Excipient and Packaging Control

Ensure excipients and packaging are free from nitrosating agents or precursors.

6.3. Analytical Vigilance

Employ advanced analytical tools to detect and monitor nitrosamine impurities.

7. Conclusion

The detection and management of nitrosamine impurities, including NDSRIs, are critical to ensuring pharmaceutical safety. LC-MS/MS has emerged as the leading analytical technique due to its sensitivity and versatility. Complementary methods like GC-MS/MS and HRMS also play significant roles in specific applications. Regulatory frameworks provide a robust foundation for managing nitrosamine risks, and ongoing innovations in analytical technology and risk assessment are expected to further enhance impurity control strategies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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