Symeres

Making Molecules Matter. Together.

DRUG DISCOVERY, SYNTHETIC CHEMISTRY, DRUG DEVELOPMENT, ADMESCOPE

Managing nitrosamines in the pharmaceutical industry: a comprehensive approach

KIRILL KULISH

"The danger which is least expected soonest comes to us."
Voltaire

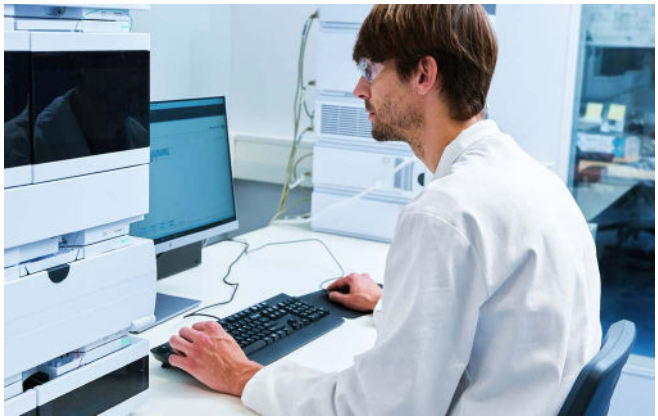
At Symeres, we care about patient safety, as our services are aimed at healing people and restoring their quality of life. To achieve this, we focus not only on providing best-in-class new drug R&D services, but also on controlling toxic impurities, such as nitrosamine in the drug substance and/or formulated product. A comprehensive overview of nitrosamine risk assessment, including potential formation, scavenging, and analysis, is described here.

Introduction

Nitrosamines are a class of chemical compounds characterized by the presence of the nitroso functional group (–NO) bonded to an amine group. They are known to be potent carcinogens and can pose serious health risks to humans.[1] Nitrosamines have attracted significant attention in the pharmaceutical industry due to their potential presence as impurities in drug products.[2] Even at trace levels, nitrosamines can be harmful to the body.[1] The presence of nitrosamines in pharmaceuticals can lead to product recalls, regulatory actions, and loss of consumer trust. Therefore, it is essential for manufacturers to implement robust quality-control measures and adhere to regulatory guidelines to prevent and manage nitrosamine contamination in pharmaceuticals.

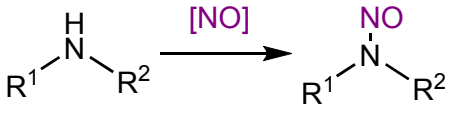
Nitrosamines formation: types of reactions

Nitrosamines can form through various chemical reactions involving amines and nitrosating agents, which can include nitrous acid, nitrites, and other nitrogen oxides.[3] These reactions often occur under specific conditions such as acidic or basic environments, high temperatures, and the presence of certain catalysts.[2]



Several pharmaceutical reactions are known to potentially facilitate nitrosamine formation, including:

- Nitrosation of secondary amines or amidine groups in drug substances or formulated products. Generally, primary amines have a lower risk factor due to their decomposition into safer compounds via diazotization, and tertiary amines require dealkylation, induced, for example, by NO_x to form a secondary amine precursor suitable for stable nitrosamine formation.
- Interaction between amines and nitrosating agents during synthesis or formulation processes.
- Decomposition or degradation of certain drug substances under specific conditions, leading to nitrosamine formation as a byproduct.
- Nitrosamines can grow and accumulate during storage.



[NO] = nitrites, nitro/nitrosoalkyls, etc.

Conditions = pH, heat, catalyst (e.g. formaldehyde), water, etc.

In practice, the analysis of nitrosamines is always challenging due to selectivity and sensitivity requirements, as well as the need for nitrosamine standards for quantitative analysis. Symeres has consolidated experience of making these nitrosoamine impurities/standards. For further reading, please see www.symeres.com/impurity-synthesis/.

Case Studies: High-Profile Nitrosamine Contamination Incidents

Several high-profile incidents of nitrosamine contamination in pharmaceuticals have occurred in recent years, prompting regulatory scrutiny and product recalls. Notable examples include:

- The discovery of N-nitrosodimethylamine (NDMA) contamination in valsartan and other angiotensin II receptor blockers (ARBs), leading to widespread recalls and investigations by regulatory authorities worldwide.[4]
- Identification of NDMA and N-nitrosodiethylamine (NDEA) in ranitidine products (commonly known as Zantac), resulting in market withdrawals and investigations into the root causes of contamination.[5]
- Detection of nitrosamine impurities in certain metformin formulations, leading to recalls and regulatory assessments to ensure the safety of diabetes medications.[1,2]

At Symeres, we understand the high importance of proactive monitoring, risk assessment, and adherence to quality-control standards throughout the pharmaceutical manufacturing process to prevent and mitigate nitrosamine contamination incidents. Therefore, whenever we notice the potential formation of nitrosamines, we notify our clients to address this issue before processes are locked in or analytical methods are fixed for production.

Analytical methods for detection of nitrosamines

Regulatory agencies such as the FDA, EMA, and others have issued guidelines requiring pharmaceutical manufacturers to implement robust testing protocols for the detection and quantification of nitrosamine impurities in drug products. These guidelines outline acceptable limits for nitrosamine levels and specify the use of validated analytical methods for detection and quantification.

Our comprehensive analytical techniques allow us to analyze nitrosamine contents to parts per million (ppm) and even parts per billion (ppb) levels. We carry out complete method development by identifying a suitable detection method, prevalidating method parameters, validating the method, and testing the compound of interest for the presence of the respective nitrosamines. The most frequently used technique is LC-MS due to its sensitivity, selectivity, and ability to separate complex mixtures. Symeres employs triple quadrupole LC-MS instruments to ensure high precision in measuring toxic impurities such as nitrosamines. In addition, all samples should be stored under mild conditions away from light and air to avoid further degradation of the samples.

Best practices to quench and purge nitrosamines

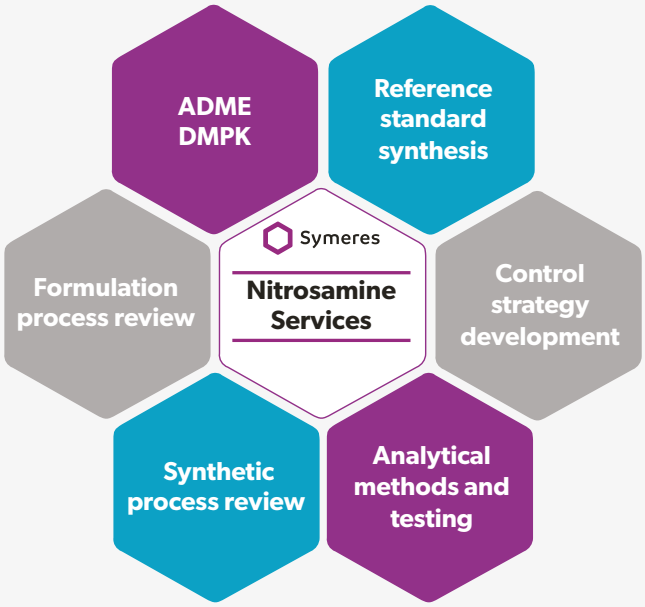
First, we start by evaluating the synthesis route before implementing the synthesis process. Designing robust synthetic routes involves selecting reaction conditions and reagents that minimize the potential for nitrosamine formation. Our chemists prioritize synthetic pathways that avoid the use of nitrosating agents or employ mild conditions that reduce the likelihood of unintended nitrosation reactions. Optimization efforts may include controlling reaction parameters such as temperature, pH, and reaction time to prevent conditions favorable for nitrosamine formation.

Quenching strategies involve methods aimed at neutralizing or eliminating nitrosamines to prevent their formation or reduce their concentration in pharmaceutical products. For example, the addition of reducing agents like sodium sulfite or sodium ascorbate can effectively quench nitrosamines by reducing the nitroso group. Adsorbents such as activated charcoal or silica gel can be employed to adsorb nitrosamines from process streams or pharmaceutical formulations. Adsorption helps to physically remove nitrosamines from the solution, reducing their concentration to acceptable levels.

ADME and DMPK studies

Understanding the fate of nitrosamines within biological/physiological systems is essential for assessing their safety. In ADME and DMPK studies, it is crucial to employ sophisticated analytical techniques to ensure their sensitive detection and quantification in complex biological matrices.

If a drug candidate, or its metabolites, contains structural elements prone to nitrosamine formation, such as secondary amines, researchers might detect nitrosamine impurities during these early stages of drug development. If nitrosamines are formed as degradation products under specific storage conditions (e.g., exposure to light, heat, or acidic pH), these impurities might be identified and quantified during stability testing conducted as part of ADME studies.



Symeres nitrosamine services

Symeres is committed to delivering the highest-quality science and our approach to nitrosamines is no exception. Working closely with our clients, we provide a comprehensive offering towards understanding and control of nitrosamines, including:

- Development of a stage-appropriate risk assessment, including evaluation of the synthetic process (solvents, reagents, processing aids, impurities, etc.) and the drug product process (excipients, degradants, etc.) for possible sources of nitrosating agents or nitrosamine substrates.
- Synthesis of nitrosamine reference standards.
- Development of analytical methods for the quantitation of nitrosamines in drug substances and drug products.
- Analysis of drug substance and product samples.

Collaboration with us gives you comprehensive support from our analytical/ADME, synthetic, discovery, and development teams to deliver safe materials with high quality standards.

[1] *Org. Process Res. Dev.* **2023**, *27, 1719–1735*
[2] *Org. Process Res. Dev.* **2023**, *27, 2123–2133*
[3] *Org. Process Res. Dev.* **2023**, *27, 1736–1750*
[4] European Medicines Agency (EMA). Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group, 2021.
[5] FDA Requests Removal of All Ranitidine Products (Zantac) from the Market. U.S. Food and Drug Administration, April 1, 2020.

For further inquiries or collaboration opportunities,
please contact us via: science@symeres.com
www.symeres.com

Symeres