BRIGHTLABS
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Specialist in Nitrosamine Testing

Expert in NDSRI's Analysis

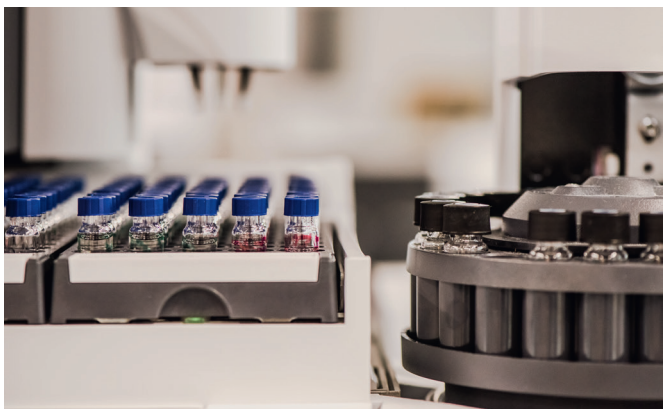
Introduction
Brightlabs is the laboratory for all your analytical questions. Located in the south of The Netherlands, close to the German and Belgium border, it is our mission to support our customers in their pharmaceutical development projects as well as pharmaceutical QC testing.

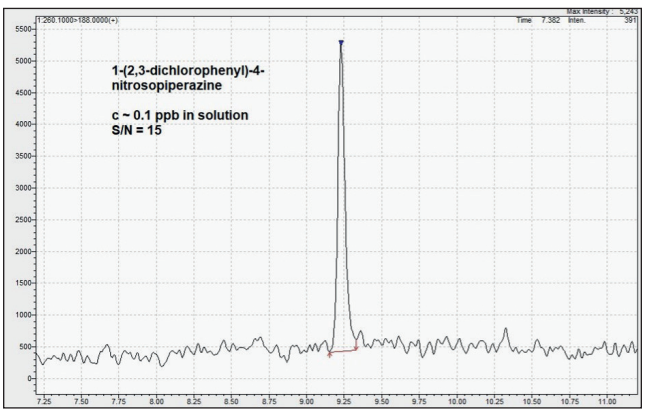
In response to the presence of nitrosamine impurities (N-nitrosamines) in a class of medication used to control high blood pressure, known as 'sartans', regulatory actions were instituted by the European Medical Agency (EMA) and the US Food and Drug Administration (US FDA).
Currently the EMA and FDA have a described approach for the risk assessment of N-nitrosamine impurities (including nitrosamine drug substance-related impurities [NDSRIs], and the requirements including the required limits related to these nitrosamine impurities for all drug products registered.

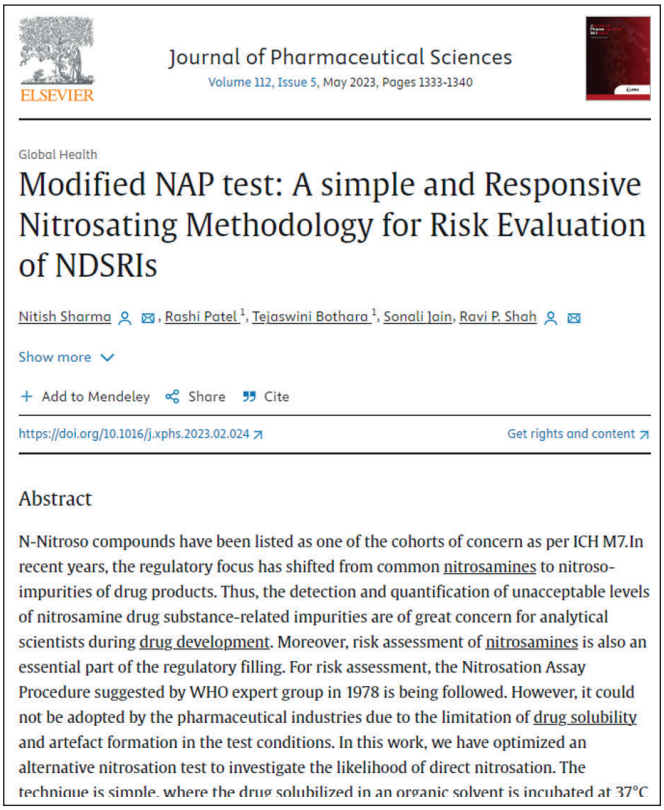
Therefore Brightlabs has developed and validated multiple methods (GC-MS/MS & LC-MS/MS) to determine low level concentrations of Nitrosamines and NDSRIs in Drug Products and API's.

API specific Nitrosamines (NDSRIs)
Next to the general known nitrosamines (i.e. NDMA, NDEA, NMBA, etc) , more and more API specific nitrosamines are being identified. Recently, there has been several withdrawals of generic medication caused by nitrosamine drug substance-related impurities (NDSRIs).
Within Brightlabs we have already developed dozen dedicated methods for the determination of these NDSRIs. For some of these NDSRIs reference standards are commercially available, however not all are. For this we work with partners to synthesize these reference materials for quick access.

For these NDSRIs usually a dedicated method needs to be developed. Using our LC-MS/MS systems generally low-level detection limits can be achieved, as shown for DCNP below. In this example normal HESI ionisation and LC-MS/MS analysis proved to be the better choice, but also APCI ionisation can help in achieving these low level detection limits. After sample preparation a LOQ of 2 ppb in drug product has been shown achievable.







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Global Health

Modified NAP test: A simple and Responsive Nitrosating Methodology for Risk Evaluation of NDSRIs

Nitish Sharma, Rashi Patel [1], Tejaswini Bothara [1], Sonali Jain, Ravi P. Shah

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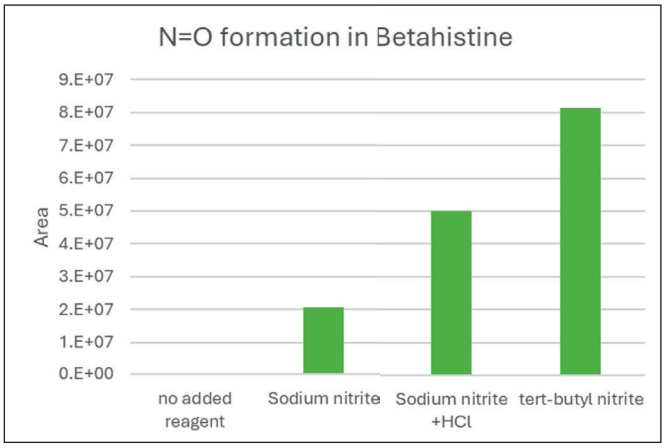
Abstract

N-Nitroso compounds have been listed as one of the cohorts of concern as per ICH M7.In recent years, the regulatory focus has shifted from common nitrosamines to nitroso-impurities of drug products. Thus, the detection and quantification of unacceptable levels of nitrosamine drug substance-related impurities are of great concern for analytical scientists during drug development. Moreover, risk assessment of nitrosamines is also an essential part of the regulatory filling. For risk assessment, the Nitrosation Assay Procedure suggested by WHO expert group in 1978 is being followed. However, it could not be adopted by the pharmaceutical industries due to the limitation of drug solubility and artefact formation in the test conditions. In this work, we have optimized an alternative nitrosation test to investigate the likelihood of direct nitrosation. The technique is simple, where the drug solubilized in an organic solvent is incubated at 37°C



Often the question arise if a certain NDSRI can be formed, either in the API itself or in the final drug product. Secondly in the formulation in combination with specific nitrogen scavengers. Therefore, it can be of added value to know if these NDSRI's can be formed under "worst case" conditions and in which level, as part of a risk assessment or in development of a new formulation.

Modified NAP test

Brightlabs is often requested to develop a method to check whether a NDSRIs are actually formed as part of a risk assessment. Therefore, Brightlabs has developed a stress-test (modified NAP test) based on the article from N. Sharma and all *(DOI:HTTPs://doi.org/10.1016/j.xphs.2023.02.024)*. Using this NAP methodology we can distinguish how vulnerable your product will be to specific nitrosamine formation. After this assessment, we are able to continue giving analytical support if shown that your product is likely to form nitrosamines.

The method which has been developed as an in-house stress testing method is tailored for active pharmaceutical ingredients (APIs) and drug products (DP) with a potential risk of forming nitrosamines. For this a comprehensive method is being used, applying two distinct nitrite sources to account for the variable reactions of different APIs. The organic source used is TBN, while the inorganic one is $NaNO_2$. In the next step, Liquid Chromatography-Triple Quadrupole Mass Spectrometry (LC-TQ-MS) is employed to ascertain whether specific or nonspecific nitrosamines are produced post-stress. This meticulous approach ensures a robust assessment of nitrosamine formation, contributing to the safety and efficacy of pharmaceutical products.

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