SynZeal®
Quality Assured

NITROSOAMINE PRODUCTS

- Nitroso Products

Introduction

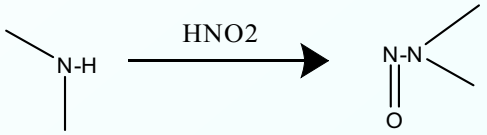
Nitrosamine compound are potent genotoxic compounds in several animal species and some are classified as probable human carcinogen by international Agency for Research on Cancer [1]. There has been recent unexpected findings of nitrosamine impurities in several drugs such as angiotensin II receptor blockers, ranitidine, nizatidine and metformin. The discovery of nitrosamines in some types of drug products led FDA and other international regulators such as European Medicines Agency (EMA), European Directorate for the Quality of Medicines and Healthcare (EDQM), Health Canada (HC), Therapeutic Goods Administration (TGA, Australia), Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency (PMDA/MHLW, Japan), Health Sciences Authority, Singapore (HSA, Singapore), and Swissmedic (Switzerland) to conduct a detailed analysis of these impurities in affected APIs and drug products. However, nitroso impurities have been detected in a few drug products and they had been recalled from the market, but there are probabilities of nitroso impurities present in drug substances as well.

FDA has been investigating the presence of nitrosamine impurities in certain drug products. Since 2018, several drug products including ARBs, ranitidine, nizatidine, and metformin have been found to contain unacceptable levels of nitrosamines. In June 2018, FDA was informed of the presence of an impurity identified as N-nitrosodimethylamine (NDMA) in the ARB valsartan. The drug product manufacturers, voluntarily recalled the affected batches of these drug products, which led to a drug shortage in some of the affected products.

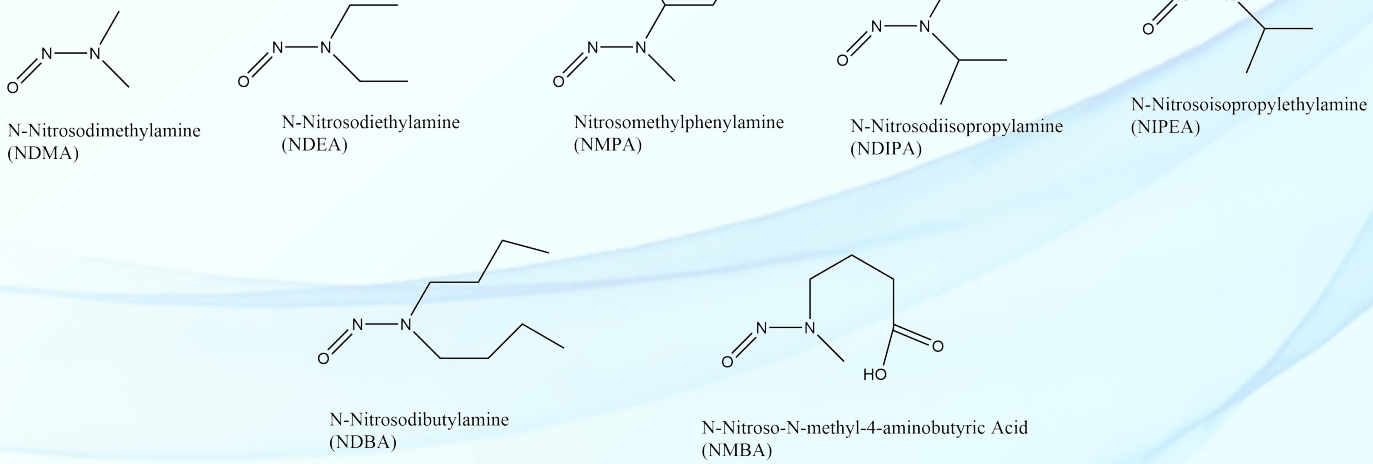
Classification and description

The term *nitrosamine* describes a class of compounds having the chemical structure of a nitroso group bonded to an amine (R1N(-R2)-N=O), The compounds can form by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions), also, There is a greater risk of nitrosamine formation if nitrous acid is used to quench residual azide (a reagent commonly used in tetrazole ring formation or introduction of azide functional group into a molecule) in the presence of precursor amines. FDA has identified seven nitrosamine impurities that

theoretically could be present in drug products: NDMA, N-nitrosodiethylamine (NDEA), N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), N-nitrosoisopropylethyl amine (NIPEA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA), and N-nitrosomethylphenylamine (NMPA). Five of them (NDMA, NDEA, NMBA, NIPEA, and NMPA) have actually been detected in drug substances or drug products.



The figure below depicts the potential Nitrosoamine impurities in API and drug products.



These are referred to as "cohort of concern" compounds in the ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* (March 2018).[2] The guidance recommends control of any known mutagenic carcinogen, such as nitroso-compounds, at or below a level such that there would be a negligible human cancer risk associated with the exposure to potentially mutagenic impurities. FDA has set an acceptable limit to the presence of N-nitroso impurities in the drug substances and drug products.

Nitroso at SynZeal

The qualitative and quantitative determination of these impurities requires certain set of standards, which are being synthesized and characterized at each stage for its authenticity. Even though the formation of n-Nitroso in drug substances and drug products forms easily, its synthesis at laboratory scale is quite critical since nitroso impurities exists in isomeric form and identification of the major isomer is enigmatic. Various analytical experiments are tend to determine the desired nitroso compound. NMR and elemental analysis are major analytical tool for the identification; HPLC and mass analysis are other additional tools.

https://monographs.iarc.fr/list-of-classifications
https://www.fda.gov/media/85885/download
https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current

#	Product Details	Structure	CAS No.	CAT No.
1	**2,Amino,5,nitroso,4,6,pyrimidinediol** **Mol.F.:** C4H4N4O3**, Mol.Wt.:** 156.1 **Inventory Status:** Under Synthesis		55482-22-9	SZ-A049019
2	**Abacavir Nitroso Impurity** **Mol.F.:** C14H17N7O2**, Mol.Wt.:** 315.3 **Inventory Status:** Custom Synthesis		NA	SZ-A049020
3	**Abacavir Nitroso Impurity 1** **Mol.F.:** C8H9N7O**, Mol.Wt.:** 219.2 **Inventory Status:** Custom Synthesis		NA	SZ-A049028
4	**Abacavir Nitroso Impurity 2** **Mol.F.:** C8H9N7O**, Mol.Wt.:** 219.2 **Inventory Status:** Custom Synthesis		NA	SZ-A049029

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