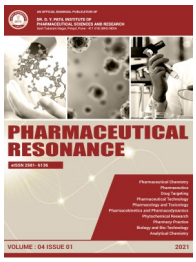
REVIEW ARTICLE

A REVIEW ON NITROSAMINE IMPURITIES PRESENT IN DRUGS



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ABSTRACT :

Nitrosamines more than one nitrosamine impurity is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day (the acceptable intake for the most potent nitrosamines) based on the maximum daily dose (MDD), the FDA requests that the manufacturer contact the agency for evaluation. A Review on Nitrosamine Impurity Present in Drugs.The control of potentially mutagenic impurities in Pharmaceutical Product is key of importance in assessing carcinogenic risk to humans. The recent discovery of Nitrosamine impurities in several marketed pharmaceutical has increased interest in their mutagenic and carcinogenic potential. The chemical class considered part of a 'cohort of concern 'indicating the standard control protocol such use of threshold of toxicological concerned (TTC) cannot be applied. Drug like Spartans, ranitidine, nizatidine. These impurities formed in drug products due to solvent, catalyst, raw materials are used manufacturing process. The various regulatory has published the press release or notice regarding control of this impurities within interim.Nitrosamine impurities can be avoided by change in manufacturing process or precautions in drug substance or drug products manufacturing. Validated analytical method are used in identify and qualities of these impurities. The analytical methods are Gas chromatography technique , mass spectrometry, liquid chromatography.these impurities formed due to secondary , tertiary, ammonium salt with nitrosating agent first time European medical agency finalize the Nitrosamine impurities present in Sartanmedicine.

Keywords : *Chromatography, medicine, nitrosating agent, European medical Agency, food and drug administration .*

Introduction:

Nitrosamine are family of carcinogenic impurities. Which are formed by reactions of secondary amide carbamates , amines, derivatives of urea with nitrite and other Nitrogenous agent. Nitrogen has +3 Oxidation state. There is different reasons Nitrosamine present in the drug.source of Nitrosamine is During manufacturing of drug and packaging of Drug . During this process Nitrosamine impurity present in drug. We have general method for detection of nitrosamine impurities are HS-GC-MS , LC-MS/MS. [1]

Nitrosamine present in drug are:

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- NDMA:N-Nitrosodimethylamine
- NDEA: N-Nitrosodiethylamine
- NDIPA: N-Nitrosodiisopropylamine
- NEIPA: N-Nitrosoethylisppropylamine
- NDBA: N-Nitroso-di-n butaylamine
- NMEA: N-Nitrosomethylethylamine
- NDPA: N- Nitroso-di-n-propyl amine
- NMBA: N-Nitroso-N-methyl-4-aminobutyric acid
- NPYR: N- Nitrosopyrrolidine
- NPIP: N- Nitrosopyperidine

Food and drug administration and European medical Agency in July 2018 acconuced that carcinogenic impurities are present in N- Nitrosodimethylamine (NDMA) and N- N-Nitrosodimethylamine are generic substance present in drug product. Especially in angiotensin ii receptors Blocker(ARBs) or Sartans class medicine which are used to treat hyper tention

(high blood pressure) and heart failure. Food and drug administration and European medical Agency investigation in year 2019 leads to detection of nitrosamine impurity present in pioglitazone are used in treatment of diabetes. Ranitidine H2 (histamine-2) Blocker used in acidity in stomach. Low level of nitrosamine impurity present in metformin drug investigation under FDA and EMA.[2,3]

Formation of nitrosamine impurity:

Source of nitrosamine impurity :

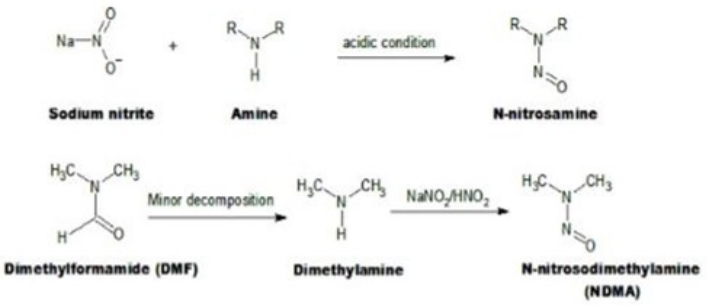

Fig 1: Formation of nitrosamine impurity[4]

Nitrosamine impurities can incorporate into drug product Basically through manufacturing process, cross contamination, degradation of product, direct introduction, process of formation involved raw materials, intermediate, solvent and catalyst, chemical and reagent.

The nitrosamine impurities formed due to carbamates, amide, N-alkyl amide , secondary or tertiary and quaternary ammonium salts with drug products.the extent of nitrosamine impurity depends on the type , structure, concentration of nitrosating Agent. Secondary amide is more reactive than other nitrosating agent.

Recovered solvent and catalyst are used in process leads to formation of Nitrosamine impurities. These solvents treated with nitrites or nitric acid in order to destroy residual azide to leads to formation of Nitrosamine impurity.

Contaminated starting or law materials supplies by vendor may be introduced Nitrosamine impurities in drug product.

Cross contamination between different manufacturing process or product on same production also leads to formation of Nitrosamine impurities in drug substance or drug products.

These impurities may formed due to decomposition of solvent and other material used in manufacturing process. By product formed in drug synthesis leads forward formation of Nitrosamine impurities. For example, solvent such as Dimethylamine or Diethylamide lead to formation of Nitrosamine like NDMA and NDEA.

Use of certain packaging materials and finished good product may be formed nitrosamine impurities. Packaging materials lidding foil containing nitrocellose, printing primer reacts with amine in printing ink to formed Nitrosamine impurities. These impurities may transfer to drug products.

Another potential source of formation of nitrosamine impurities is lack of optimization of the manufacturing process for APIs when reaction conditions such as temperature, pH, or the sequence of adding reagents, intermediates, or solvents are inappropriate or poorly controlled.

These sources of nitrosamine found European medical Agency and food and drug administration . nitrosamine impurities formed in drug substance or product different reasons . [5,6]

European medical Agency -

The European Medicines Agency (EMA) assessed the risk of formation or presence of nitrosamine during the manufacture of human medicines and provided guidance to market-authorized authorities to avoid the presence of nitrosamine contamination.

Nitrosamines are chemical compounds that are classified as carcinogens that humans may be based on in animal studies. EU regulators begin noticing nitrosamine in medicines in mid-2018 when nitrosamine contamination, including N-Nitrosodimethylamine (NDMA), is detected in blood pressure drugs known as 'Sartans'. cancer in humans.[7]

Food and drug administration -

Ensuring the safety of the U.S. drug supply, the guideline recommends that manufacturers must complete a risk assessment for approved products or on the market, the first three steps manufacturers must take to reduce nitrosamine contamination in their products, within 6 months of publication of the guide. With today's review of the directive, the FDA extended the recommended time for the completion of the risk assessment to 31 March, 2021. Manufacturers do not need to submit the risk assessment documents to the facility, but must keep these documents available on request. [9/1/2020] The FDA announces the availability of an industry guideline, entitled "Control of N-Nitrosamine Contamination in Human Drugs." This guide recommends steps that manufacturers of active pharmaceutical ingredients and drug products take to detect and prevent adverse levels of nitrosamine contamination in pharmaceutical products. The guide also describes conditions that may present nitrosamine contamination.[7, 8]

Restrictions and acceptable food:

Food and Drug Administration recommends the

following table acceptance table (AL) for Nitrosamine contamination by NDMA, NDEA, NMBA, NMPA, NIPEA, NDIPA. Determining the limit of APIs for contamination of nitrosamine and drug products is as follows:

Table 1: Limit Of Nitrosamine Impurity[9]

Nitrosamine	AL limit (ng/ Day)
NDMA	96.0
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

Guidance for marketing authorisation holders:

- Authorized marketing authorities should review their production processes to identify all products containing organic matter in order to identify and, if necessary, reduce the risk of the presence of nitrosamine contamination.
- The EMA has finalized a review under Article 5 (3) of Regulation (EC) No 726/2004 of June 2020 to provide guidance to market authorization authorities on how to avoid the presence of nitrosamine contaminants in human medicines.
- CHMP has asked market permit holders to review all human chemical and biological drugs to determine the possible presence of nitrosamine and test products at risk.
- Companies need to have appropriate control strategies in place to prevent or reduce the presence of these pollutants and, where necessary, improve their production process.
- The EMA and competent national authorities will continue to monitor the presence of nitrosamine contaminants in medicines, in collaboration with regulators from outside the European Union (EU), and will work with marketing authorities to find quick solutions to any deficiencies.
- The European Medicines Regulatory Network encourages marketing license holders to submit the outcome of step 1 before the deadline once they have completed a risk assessment or risk assessment for their products.
- They should also assess the risks to patients and take appropriate action to avoid or reduce patients' exposure to nitrosamine.[9, 10]

Production process:

The European Medical Agency has included a template for marketing authorization managers who use it when completing product results for nitrosamine pollution testing. The following steps are required by the manufacturer to control the nitrosamine contamination present in human pharmaceutical products[10]

Step 1: Risk assessment:

Risk assessment for the identification of active ingredients and products at risk of N-nitrosamine formation or (discontinuation) contamination and reporting effect on 31 March 2021 of chemical drugs, 1 July 2021 with biological medicines. Ideally, marketing authorization owners should submit a step-by-step response template and proceed with step 2 of the finished product verification test. If there is no apparent risk of the active ingredient, marketing authorization holders should conduct a product product risk assessment and submit a 1-step result only when they reach the final conclusion of the active product and finished product. Marketing Authorization Managers may submit products for a single email notification group.[11]

Step 2: Verification test:

Authorized marketing authorities should only use" Step 2 - Nitrosamine obtained above acceptable take or a newly obtained nitrosamine response template 'if they have acquired nitrosamine in their product and meet at least one of the following criteria:

- Exceeds acceptable acceptance limit.
- Exceeds the risk of cancer excess of 1: 100,000.
- Freshly identified nitrosamine not included in CHMP article 5 (3), regardless of the amount obtained.

In these cases, they should submit this template in addition to 'Step 2 - Nitrosamine detected response'.[11]

Step 3: Review the marketing authorization:

Apply for any necessary changes to the production process resulting from this review, by requesting a change of marketing authorization using standard control procedures. Authorities to authorize marketing of nationally approved products. Owners of marketing permits must complete a verification test and submit their separate applications by:

- 26 September 2022 on chemical medicines.
- 1 July 2023 on biological drugs.

In order to meet these last days, it is necessary to carry out step 2 of the activities to adequately ensure the requirements for the authorized sales of sartan drugs that they must follow to avoid the presence of

nitrosamine contaminants in their products are the same in all human medicines.[10, 12]

The drug from which nitrosamine contaminants are derived:

- Sartan medicine
- Rifampicin drug
- Ranitidine
- Metformin - Containing medicine
- Champix medicine

Sartan medicine :

Sartan medicine used to treat high blood pressure (high blood pressure). The requirements that sartan pharmaceutical market regulators need to follow to avoid the presence of nitrosamine contaminants in their products are the same across all human medicines. The CHMP reviewed the requirements of the Sartans in November 2020, which are in line with the outcome of its Article 5 (3) vision. It first issued a recommendation for sartan in January 2019. In June 2020, a European drug regulator published the results of studies conducted on the presence of nitrosamine in sartan drugs (also known as angiotensin II receptor antagonists). This includes recommendations to help reduce the risk of drug contamination.[11]

Rifampicin :

Rifampicin drug used to treat tuberculosis or leprosy. EU authorities are investigating the presence of contaminants of nitrosamine, 1-nitroso-4-methyl piperazine, in rifampicin. Competent national authorities work closely with companies and official pharmaceutical regulatory laboratories (OMCLs) in the ongoing EU drug research. February 2021, competent national authorities are asking owners who authorize marketing with rifampicin-containing drugs to test their drugs before releasing them on the market.

Rifampicin is the first line of treatment for tuberculosis. It is also used to treat a few other serious illnesses, including blood diseases and leprosy. The risk for patients not taking their rifampicin medication far outweighs any potential risk from MeNP.[11]

Ranitidine medicine :

Ranitidine used in the treatment of acidity in stomach review of ranitidine drugs has led to a recommendation for its suspension after tests showed that some of these products contain NDMA. in the EU due to the presence of low levels of pollutants called N -Nitrosodimethylamine (NDMA). NDMA is classified as a possible human carcinogen (potentially carcinogenic) based on animal studies. It is present in other foods and water and is not expected to cause harm if absorbed at very low levels. Ranitidine is used to reduce stomach acid in patients with conditions such as heartburn and stomach ulcers. Alternatives are available and patients should contact their healthcare professionals for advice on which medication to take.2018 NDMA and similar compounds known as nitrosamine have been found in several drugs. EU regulators have taken steps to identify potential sources of pollution and impose stricter producer requirements.[13]

Metformin-Containing a drug :

Metformin is used to treat diabetes. The EMA and competent national authorities are investigating the impact of experiments found on NDMA in other EU units of metformin-containing drugs, used to treat diabetes. This follows the ratification of NDMA in other non-EU clusters by the end of 2019.EMA and competent national authorities are working closely with companies and official pharmaceutical regulatory laboratories (OMCLs) in the ongoing EU drug research. In October 2020, the EMA and competent national authorities asked holders of metformin-licensed drug dealers to test their drugs before releasing them on the market. Metformin is considered a critical drug, the EMA and national authorities work closely together to avoid potential shortages so that patients can continue to receive the treatment they need.[10, 13]

Champix medicine :

Champix drug used for smoking cessation help CHMP EMA conducted a review of the presence of contaminants of nitrosamine, N nitroso-varenicline, Champix (varenicline), a smoking cessation drug. The CHMP concluded that the authorized marketing owner must make changes to Champix's authorization to ensure that it complies with the acceptable thresholds for taking nitrosamine of EU drugs, calculated in accordance with ICH M7 guidelines. Presence of Champix Pollution such as N-nitroso varenicline.[11]

Methods for detection of Nitrosamine impurities :

The FDA has released the following methods for the determination of NDMA impurities in drugs.

- GC / MS Headspace Chromatography Mass Spectrometry Approach.
- Liquid Chromatography - Tandem Mass Spectrometry (LC - MS / MS) Method for the Determination of NDMA in Ranitidine Drug Substance and Solid Dosage Drug Product.[7]

Analytical methods :

Methods of nitrosamine testing in sartan include the use of chromatographic techniques (reversed phase liquid chromatography - RP - LC or gas chromatography - GC), combined with mass spectrometry (MS), spectrophotometry (UV).) or nitrogen chemiluminescence (NCD). USP proposes

four analytical methods that manufacturers can use to identify potential nitrosamine in their products:

- The first method recommends high-performance liquid chromatography-high resolution mass spectrometry (HPLC-HRMS) for measuring NDMA, NDEA, NDIPA, NEIPA, NMBA and NDBA.
- The second recommends gas chromatography-mass spectrometry (GC-MS) for NDMA, NDEA, NDIPA, and NEIPA.
- Third party recommends HPLC-Tandem Mass Spectrometry for NDMA, NDEA, NDIPA, NEIPA, NEIPA, NEIPA, and NMBA.
- Fourthly recommends GC-Tandem Mass Spectrometry for NDMA, NDEA, NDIPA, NMBA and NDMA.12,13

Conclusion:

Nitrosamine contamination is a carcinogenic and mutagenic contaminant leading to cancer. So there is a limit to this pollution need in our country. The European Medical Agency and the Food and Drug Administration are also taking strong action against these contaminants so that these contaminants can be controlled through alternatives. Sources of these catalysts catalysts, solvent, raw materials react with nitrosating Agent lead to the formation of these contaminants. Avoid the use of solvent and catalyst. First the Sartan drug exhibits nitrosamine contamination. There are limits to and acceptance of the daily diet of nitrosamine contamination. Nitrosamine contamination is detected using technologies such as Gas chromatography, mass spectrometry, liquid chromatography process. These methods help in to low level of Nitrosamine impurities in drug substance or drug product in human medicine.

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