Review Article

Nitrosamine Impurities Present in Drugs

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ABSTRACT

Nitrosamines The FDA requires that the manufacturer gets in touch with the organization for review if more than one nitrosamine impurity is found and the overall amount of nitrosamine impurities exceeds 26.5 ng/day (the allowed intake for the most potent nitrosamines). An analysis of the nitrosamine impurity found in drugs. When determining the risk of human cancer, the control of potentially mutagenic contaminants in pharmaceutical products is crucial. Interest in their mutagenic and carcinogenic potential has grown in response to the re-cent discovery of Nitrosamine impurities in several commercially available pharmaceuticals. Chemical classes that are deemed to be a "cohort of concern" indicate that the normal control technique cannot be performed when using the threshold of toxicological concern (TTC). Drugs like ranitidine and nizatidine are Spartans. These impurities developed in drug prod-ucts as a result of the production process's utilization of raw ingredients, catalysts, and sol-vents. The press release or notification regarding the interim control of these contaminants has been published by various regulatory bodies. By altering the manufacturing process or taking care of the production of drug substances or drug products, nitrosamine impurities can be avoided. Validated analytical techniques are employed to determine the characteristics of these contaminants. The analytical techniques include liquid chromatography, gas chromatography, and mass spectrometry. The first time a European medical organization finalized the Nitrosamine impurities present in Sartan medicine, these impurities were caused by secondary, tertiary, ammonium salt with a nitrosating agent.

Keywords: Nitrosamine, NDMA, Sartans, Angiotensin 2 Receptor Blockers (ARB), Ranitidine, Histamine 2 Re-ceptor Blockers, Food and Drug Administration (FDA), European Medicines Agency (EMA), Met-formin, Chromatography.

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INTRODUCTION

A family of carcinogenic contaminants includes nitrosamine. These are produced when nitrite and other nitrogenous agents react with secondary amide carbamates, amines, and urea derivatives. The oxidation state for nitrogen is +3. [1] In trace concentrations, nitrosamines are present in the soil, water, and outdoor air. In foods, the nitro sating agent responsible for forming NDMA is usually nitrous anhydride, which arises from nitrite in an acidic aqueous solution, as in the stomach.[2] Beer, cured meats such as bacon or sausage, and even water contain nitrosamines in small amounts. Tobacco (either smoke or smokeless) contains nitrosamines.[3,4] As a result of its covalent interaction with DNA and metabolic activation, nitrosamine seems to cause pro-mutagenic DNA adducts, which is thought to be the mechanism of nitrosamine carcinogenicity. Different DNA repair pathways can help damaged DNA regain its structural and functional integrity. However, if they are unsuccessful or overwhelmed by large exposures and adducts continue accumulating over time during DNA replication, point mutations at important DNA locations may ensue. [3]

Numerous factors contribute to the presence of Nitrosamine in the medication. The production and packaging of drugs are the sources of nitrosamine. Nitrosamine impurity is present in the medication throughout this procedure. We use HS-GC-MS and LC-MS/MS as generic methods for detecting nitrosamine impurities. [1]

Nitrosamine Impurities Present in Drugs are:

- NDMA: N-Nitrosodimethylamine
- NDEA: N-Nitrosodiethylamine
- NDIPA: N-Nitrosodiisopropylamine
- NEIPA: N-Nitrosoethylisopropylamine
- 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
- NMPA: N-Nitrosomethylphenylamine
- NIPEA: N-Nitrosoisopropylethylamine

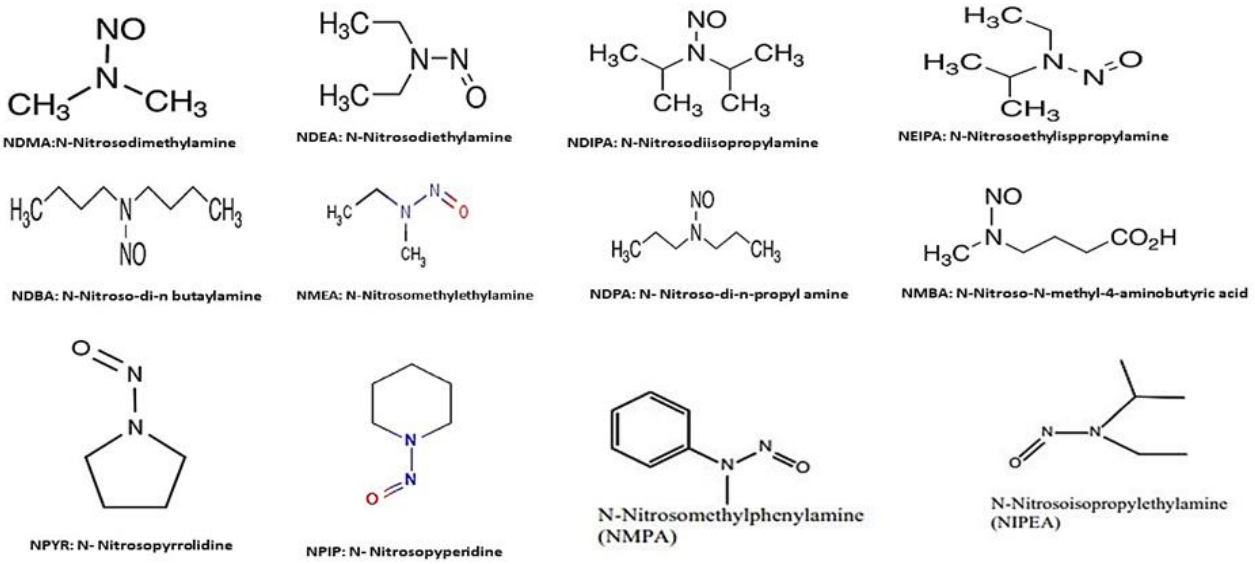

Figure 1: Nitrosamine Impurities Present in Drugs

The Food and Medication Administration and the European Medicines Agency, In July 2018, confirmed that N-nitrosodimethylamine (NDMA) and N-nitrosodimethylamine are generic substances found in drug products and include carcinogenic contaminants. In particular, in medicines from the Sartan or angiotensin 2 receptor blocker (ARB) family, which are used to treat heart failure and hypertension (high blood pressure). An investigation by the Food and Drug Administration and European Medicines Agency in 2019 resulted in the discovery of nitrosamine impurity in pioglitazone, a medication used to treat diabetes. Use of ranitidine H2 (histamine-2) Blocker for Stomach Acidity Low levels of nitrosamine impurity is being investigated by the FDA and EMA in metformin drugs. [6,7]

FORMATION OF NITROSAMINE IMPURITY

Nitrosamine Impurities' Sources

Impurities containing nitrosamine may be detected in pharmaceutical drugs. The formation process comprises raw materials, intermediate, solvent and catalyst, chemical and reagent, cross-contamination, product degradation, and direct introduction.

Drug goods may include nitrosamine impurities owing to carbamates, amide, N-alkyl amide, secondary or tertiary, and quaternary ammonium salts. The type, structure, and concentration of the nitrosating agent all affect how much nitrosamine impurity is present. Other nitrosating agents are less reactive than secondary amide.

Impurities including nitrosamine are created when the recovered solvent and catalyst are utilized in a procedure. These solvents were treated with nitrites or nitric acid to eliminate any remaining azide, which caused the generation of the contaminant nitrosamine.

Vendor-supplied contaminated starting materials or authorized supplies may introduce nitrosamine contaminants into the drug product.

The creation of Nitrosamine impurities in drug substances or drug products is also produced by cross-contamination across various manufacturing processes or products on the same production line.

These contaminants can have developed as a result of the solvent and other materials employed in the production process decomposing. Nitrosamine impurities are produced as a byproduct of medication production.

For instance, a solvent like dimethylamine or diethylamide might create nitrosamines like NDMA and NDEA.

Nitrosamine impurities can emerge when specific packing materials are used and final goods are produced. Nitrosamine impurities are created when printing priming and nitrocellulose-containing packaging materials like lidding foil react with an amine in printing ink. These impurities could get into medicinal products.

When reaction conditions, such as temperature, pH, or the order in which reagents, intermediates, or solvents are added, are incorrect or poorly regulated, this can create nitrosamine impurities.

The European Medical Agency (EMA) and the Food and Drug Administration (FDA) have identified these sources of nitrosamine, and they have determined that nitrosamine impurities are created in drug substances or goods for a variety of reasons. [8,9]

Food and Drug Administration (FDA)

The guideline advises manufacturers to complete a risk assessment for products that are approved or already on the market, the first three steps manufacturers must take

to reduce nitrosamine contamination in their products, within six months of the publication of the guide, to ensure the safety of the U.S. drug supply. According to the FDA, an industry standard titled "Control of N-Nitrosamine Contamination in Human Drugs" is now available. This guidance offers recommendations for makers of active pharmaceutical components and medicinal products to identify and stop harmful levels of nitrosamine contamination in pharmaceutical goods. The manual also goes through situations where nitrosamine contamination could occur. [10,11]

European Medicines Agency (EMA)

The European Medicines Agency (EMA) evaluated the likelihood that nitrosamine would develop or be present during the production of human medicines and gave market-authorized authorities instructions on how to prevent nitrosamine contamination.

Biological investigations on nitrosamines in animals have led to their classification as carcinogens, which may also apply to humans. In the middle of 2018, nitrosamine contamination, particularly N-Nitrosodimethylamine (NDMA), is found in blood pressure medications known as "Sartans," which has been linked to human cancer. [10]

RESTRICTION AND ACCEPTABLE FOOD

The European Medical Agency (EMA) and the Food and Drug Administration (FDA) have discovered these sources of nitrosamine, which indicate that impurities containing nitrosamine can develop in drug substances or goods for a variety of causes.

These restrictions only apply if a medicine product includes just one nitrosamine. The manufacturer should get in touch with the Agency for review if more than one of the nitrosamine impurities listed in Table:1 is found and the total amount of impurities exceeds 26.5 ng/day (the AI for the most powerful nitrosamines), according to the maximum daily dosage (MDD). A suggested limit for total nitrosamines of 0.03 ppm is not more than 26.5 ng/day for pharmaceutical goods having an MDD of less than 880 mg/day and is regarded as appropriate.[5,12]

Table 1: Nitrosamine impurity upper limit

Nitrosamine	AI Limit (ng/day)
NDMA	96
NDEA	26.5
NMBA	96
NIPEA	26.5
NIPEA	26.5
NDIPA	26.5

Advice for Those in Possession of a Marketing Authorization:

- The manufacture of all goods containing organic matter should be reviewed by authorized marketing authorities to spot any nitrosamine contamination and, if required, limit the danger**.**
- By Article 5(3) of Regulation (EC) No 726/2004 of June 2020, the EMA has completed an assessment to offer recommendations to market authorization authorities on how to prevent the occurrence of nitrosamine contaminants in human medicines**.**
- To check for the potential presence of nitrosamine and test items that may be in danger, the Committee for Medicinal Products for Human Use (CHMP) has requested market permission holders to examine all human chemical and biological medications.
- Companies must implement effective control measures to prevent or decrease the occurrence of these pollutants and, if required, improve their production process.
- In cooperation with regulators outside the European Union (EU), the EMA and appropriate national authorities will continue to keep an eye out for the existence of nitrosamine contaminants in pharmaceuticals. They will also engage with marketing authorities to address any issues as soon as they arise.
- When marketing license holders have finished a risk assessment for their goods, the European Medicines Regulatory Network urges them to submit the results of step 1 before the deadline.
- Additionally, they must evaluate the hazards to patients and take the necessary steps to prevent or minimize patients' exposure to a nitrosamine.[1213]

PRODUCTION PROCESS

A template for marketing authorization managers to utilize when compiling product findings for nitrosamine pollution testing is provided by the European Medical Agency. The producer must take the following actions to manage the nitrosamine contamination that exists in human pharmaceutical goods.

Step 1: Risk Assessment:

Risk assessment for the identification of active components and products at risk of N-nitrosamine production or (discontinuation) contamination and reporting effect on March 31, 2021, for chemical pharmaceuticals, and July 1, 2021, for biological medicines. Marketing authorization owners should ideally provide a step-by-step response template and go on to step 2 of the final product verification test. Marketing authorization holders should undertake a product risk assessment if there are no obvious risks associated with the active ingredient and submit a 1-step result only after coming to a final determination about the active ingredient and completed product. Products can be submitted by Marketing Authorization Managers for a single email notification group.

Step 2: Verification Evaluation:

Authorized marketing authority fulfill at least one of the following requirements to utilize the "Step 2 - Nitrosamine obtained above allowable take" or "newly obtained nitrosamine response template:

• Goes over the allowed tolerance level.

• Exceeds the 1 in 100,000 cancer risk threshold.

• Newly detected nitrosamine, regardless of quantity obtained, is not covered by CHMP article 5 (3).

They should send this template together with the "Step 2 - Nitrosamine discovered response" in these situations.

Step 3: Examine the Marketing Permit:

Apply for any modifications to the manufacturing process that are required as a consequence of this evaluation by seeking a change of marketing authorization by accepted control procedures. Authorities to permit the sale of goods that have received national approval. Owners of marketing permissions must pass a verification exam and submit their applications by the following deadlines: 1 July 2023 for biological products; 26 September 2022 for chemical medicines.

To adequately ensure that the conditions for the authorized sales of sartan drugs that they must adhere to avoid the presence of nitrosamine contaminants in their products are the same in all human medicines, it is necessary to complete step 2 of the activities to meet these final days.

The medication that gives rise to nitrosamine contaminants:

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

Ranitidine

The medication ranitidine is used to alleviate stomach acidity. The European Union (EU) has recommended the suspension of ranitidine after testing showed that some of these products contain low quantities of the toxin N-Nitroso dimethylamine (NDMA). Based on research done on animals, NDMA is classified as a probable human carcinogen (possibly carcinogenic). It is found in various foods and water and is not anticipated to be harmful if ingested in extremely small amounts. Patients with diseases like heartburn and stomach ulcers can utilize ranitidine to reduce gastric acid. [14] Histamine H2-receptors are competitively inhibited by ranitidine. Both the volume and the concentration of stomach acid are reduced as a result of the reversible inhibition of H2-receptors in gastric parietal cells. [1,5]

Unfortunately, a comprehensive examination of ranitidine synthetic pathways cannot provide a precise explanation for the mystery surrounding nitrosamine contamination in ranitidine. Nevertheless, since it acts as an NDMA precursor when water is chlorinated, this H2-blocker has been implicated as a potential source of nitrosamine pollution in water systems.[16] The ranitidine dimethylamine molecule is substituted by the monochloramine (NH2Cl) in a nucleophilic manner to generate a hydrazine intermediate, which is then further oxidized to produce NDMA. Ranitidine has been identified as the most reactive NDMA precursor in several research. [16, 17, 18] Additionally, this medicine tended to raise the amount of NDMA in urine when taken orally. When the U.S. assessed the stability of a few ranitidine products, based on these published findings both in vitro and in vivo, the degradation process of NDMA was determined by the FDA to be correlated with expiry dates.[19] Thus, ranitidine may be the source of NDMA contamination. One hypothesis is that a small quantity of nitrosating agents may have gotten into the ranitidine during its manufacturing, and over time, these chemicals will react with the drug molecules to produce nitrosamines. An alternative theory is that ranitidine nitro functionality's inherent instability is what leads to nitrosation. This theory is based on a report by Bauer and Fung [20] stating that nitro-containing compounds release nitric oxide when exposed to light, along with the NO/O2-triggered nitrosation described by Itoh et al. [21] On the other hand, some nitro compounds, such as bromonitromethane [22] and nitromethane [23], have been demonstrated to mediate direct nitrosation of secondary and tertiary amines, albeit with the requirement. Following the discovery of NDMA, nizatidine, an isostere of ranitidine with comparable dimethylamine and nitro substituents, was also remembered. [24, 25] This further supports the theory that the instability of H2-blockers with a nitro group might result in nitrosamine production. To determine the reason for the nitrosamine contamination in both ranitidine and nizatidine, in-depth studies into the mechanism causing NDMA generation will be necessary.

Alternatives exist, and individuals should speak with their healthcare providers for guidance on which drug to take. To identify possible sources of pollution and enforce stronger producer standards, EU officials have taken action. [14]

Rifampicin

A drug called rifampicin is used to treat leprosy or TB. Authorities in the EU are looking into whether rifampicin contains the nitrosamine pollutant 1-nitroso-4-methyl piper zine. In the ongoing EU drug research, competent national authorities collaborate closely with businesses and official pharmaceutical regulatory laboratories (OMCLs). Competent national authorities are requesting owners who allow the marketing of medications containing rifampicin in February 2021 to test their medications before putting them on the market. The initial line of defense against TB is rifampicin. Leprosy and a few other severe disorders including blood diseases are also treated with it. Any possible harm from 4-methyl-1-nitrosopiperazine (MeNP) is

greatly outweighed by the risk associated with patients failing to take their prescribed dose of rifampicin. [26] Rifampin is thought to inhibit bacterial DNA-dependent RNA polymerase, which appears to occur as a result of drug binding in the polymerase subunit deep within the DNA/RNA channel, facilitating direct blocking of the elongating RNA. [27]

Sartans

High blood pressure is treated with sartan medication (high blood pressure). All human medications must adhere to the same standards that sartan pharmaceutical market authorities do to prevent the existence of nitrosamine contaminants in their goods. In January 2019, it published its initial advice for sartan. The findings of research on the presence of nitrosamine in sartan medications were disclosed by a European drug authority in June 2020. (Also known as angiotensin II receptor antagonists). ARBs function by obstructing the hormone's receptors, especially the AT1 receptors present in the kidneys, blood arteries, and heart. Angiotensin II blockade lowers blood pressure and guards against heart and kidney damage. This offers suggestions to lessen the chance of medication tampering.[26]

The structures of the ARB medication compounds are shown in Fig: 3. to create biphenyl analogs with an acidic core, multistep processes are typically used. Five sartans, including valsartan, losartan, irbesartan, olmesartan, and candesartan all include a Tetrazole ring Fig: 2. This acidic functional group and a carboxyl moiety in ARB structures have been hypothesized to replicate the Tyr4 phenol or the Asp1 carboxyl group of angiotensin, respectively, and hence appear to be essential for their pharmacological action. But a biphenyl tetrazole has better bioavailability and metabolic stability than the other two. Because of this, it is present in the majority of ARB compounds that are currently on the market, except for eprosartan, telmisartan, and azilsartan, which have carboxyl substituents instead.

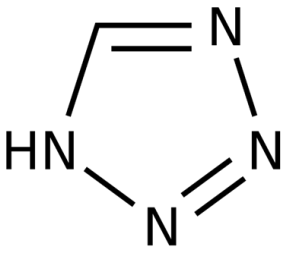

Figure 2: Tetrazole Ring

Unfortunately, it has been suggested that nitrosamine contamination originated with the installation of a tetrazole. [28] Biphenyl nitrile may be readily converted into biphenyl tetrazole in one step by adding it to an azide, [29] such as trimethyltin azide (Me_3SnN_3), sodium azide (NaN_3), or tributyltin azide (Bu_3SnN_3) (Fig: 4). The unreacted azides are frequently quenched with nitrite under acidic circumstances, when nitrogen gas and nitrous oxide are produced, due to their explosive nature and potential for human toxicity.[30] Unfortunately, some trace dialkyl amines can easily react with nitrite in an acidic environment to produce nitrosamines if they already exist as leftovers from previous processes or impurities in other reagents. While N, N-dimethylformamide (DMF) was also used in the synthesis process, it is stated that Bu_3SnN_3 was used as the azide source in the instance of valsartan to form the drug's tetrazole ring. Dimethylamine, the first nitrosamine to cause valsartan recalls, is an amine source for NDMA and a frequent precursor as well as a potential breakdown product of DMF. It is plausible that dimethylamine occurs in this solvent as an impurity. Triethylamine is sometimes purposefully employed as an amine source in the production of valsartan. The second nitrosamine discovered in valsartan is NDEA, which might be produced if this reagent is contaminated with diethylamine.

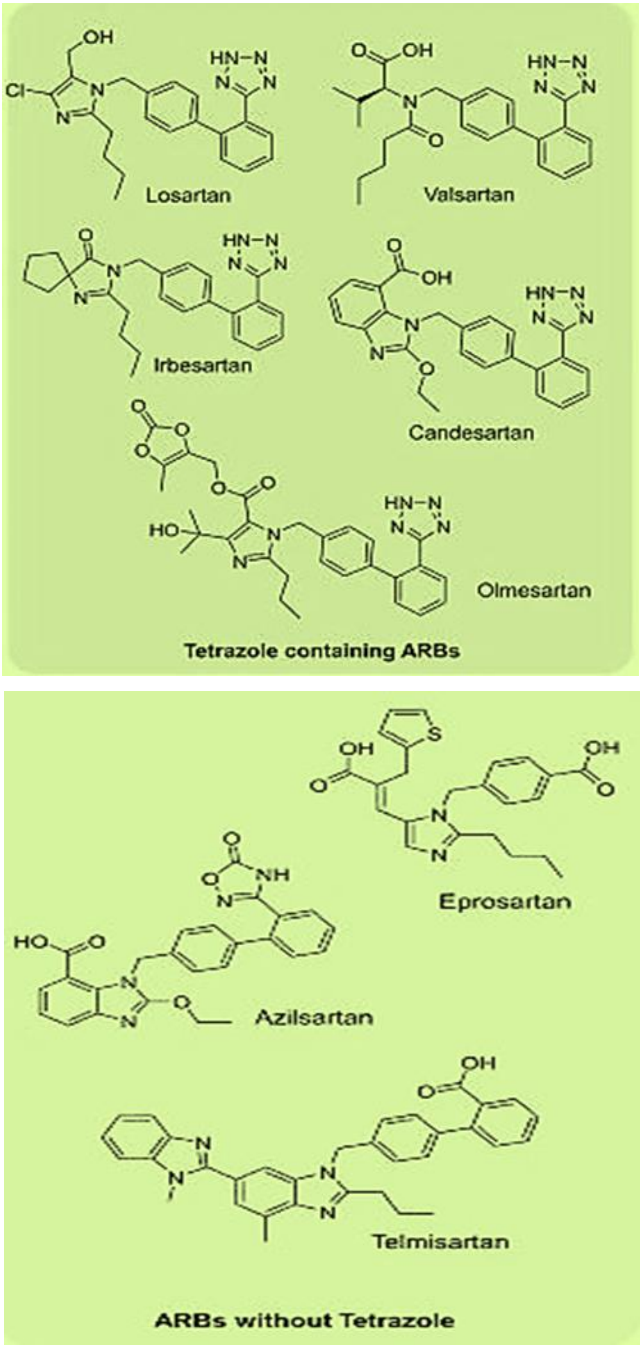

Figure 3: ARB with/without Tetrzole

Given the underlying reason for the NDMA and NDEA contamination in valsartan, it is anticipated that additional tetrazole-containing ARBs would be subject to comparable dangers. Several synthetic processes for losartan use DMF and need NaN3 to produce tetrazole.[31] In addition, comparable risk factors for nitrosamine contamination have been proposed since the synthesis methods for irbesartan[32, 33] and candesartan[34] both depend on the azide-nitrile coupling to create tetrazole. N-methyl pyrrolidinone (NMP), an organic solvent used in the manufacturing processes of several ARBs like losartan, may be the cause, however, NMP is not reactive in and of itself. Additional nitrosamine species can be rationally anticipated given the range of amines employed in ARB synthesis and the present knowledge of the dangers of contamination resulting from a procedure.

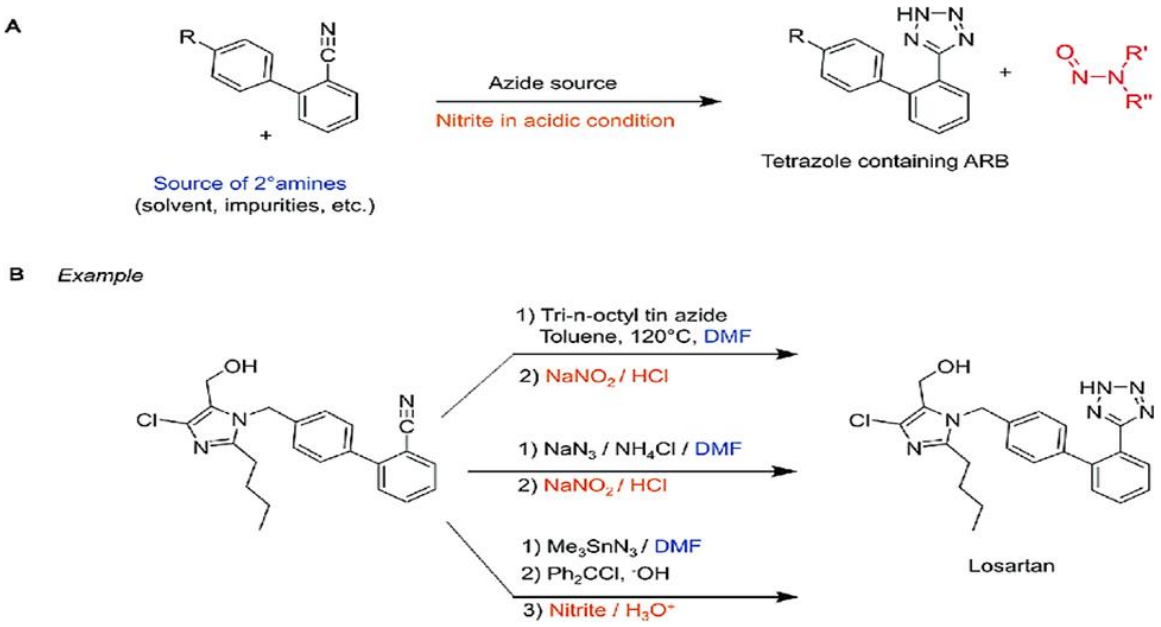

Figure 4

Metformin

Metformin is used to treat diabetes. The EMA has revealed that NDMA was found in a few batches of the pioglitazone produced by Hetero Labs in India, although at permissible trace levels. [35] In contrast, Health Canada has issued a voluntary recall of metformin from several companies led by Apotex Inc. as a result of NDMA contamination above its acceptable limit in many batches of finished products.63 Although such a problem was not detected in any batches of metformin investigated by the U.S. FDA[36] and EMA,[37] this issue has been under close monitoring by both authorities. Metformin can break down via oxidation to produce NDMA in the presence of alkali, heat, and high-pressure oxidative conditions. Metformin being deemed a Crucial medicine, the EMA and national authorities work closely together to minimize any shortages so that patients can continue to receive the therapy they need.[13,14]

Champix Medicine

Champix drug used for smoking cessation helped CHMP EMA conduct a review of the presence of contaminants of nitrosamine, N nitroso-varenicline, and Champix (varenicline) (varenicline). 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 by ICH M7 guidelines. Presence of Champix Pollution such as N-nitroso varenicline. [26]

Methodologies for Identification of Nitrosamine Toxins:

The following techniques for identifying NDMA impurities in drugs have been made public by the FDA.

- Headspace Gas Chromatography / Mass Spectroscopy Approach. (Using a predetermined temperature profile, a sample is heated in a closed sampling vessel, and the vapor inside the vessel is sampled for examination.)
- Liquid Chromatography-Tandem Mass Spectroscopy (LC-MS / MS) which is a powerful analytical technique that combines the separating power of liquid chromatography with the highly sensitive and selective mass analysis capability of triple quadrupole mass spectrometry for the Determination of NDMA in Ranitidine Drug substances and Solid Dosage Drug Product.

Analytical Method

Methods of nitrosamine testing in sartan include the use of chromatographic methods (reversed-phase liquid chromatography - RP - LC or gas chromatography - GC), combined with mass spectrometry (MS), and spectrophotometry (UV) (UV). or nitrogen chemiluminescence (NCD) (NCD). USP suggests four analytical procedures that producers can utilize to identify probable nitrosamine in their products:

• For testing NDMA, NDEA, NDIPA, NEIPA, NMBA, and NDBA, the first technique suggests using high-performance liquid chromatography-high resolution mass spectrometry (HPLC-HRMS).

• For NDMA, NDEA, NDIPA, and NEIPA, the second suggests using gas chromatography-mass spectrometry (GC-MS).

• HPLC-Tandem Mass Spectrometry is advised by the third party for the analysis of NDMA, NDEA, NDIPA, NEIPA, NEIPA, and NMBA.

• Fourthly suggests GC-Tandem Mass Spectrometry for NDMA, NDEA, NDIPA, NMBA, and NDMA. [14,38]

CONCLUSION

Nitrosamine exposure is a carcinogenic and mutagenic pollutant leading to cancer. So, the amount of pollution that our nation needs has a limit. The European Medical Agency and the Food and Drug Administration are also taking strong action against these pollutants so that these contaminants can be minimized through alternatives. These contaminants are generated when catalyst sources, solvents, and raw materials react with nitrosating agents. Avoid utilizing catalysts and solvents. First, the Sartan drug exhibits nitrosamine contamination. There are limitations to the acceptance of the daily diet of nitrosamine contamination. Utilizing technologies like gas chromatography, mass spectrometry, and liquid chromatography, nitrosamine contamination is detected. These techniques assist in reducing the number of Nitrosamine impurities in drug substances or drug products used in human treatment.

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