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Review Article.

A Study of Nitrosamine Impurities and Regulations Governing their Presence in Drug Products

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ABSTRACT

The seriousness of presence of nitrosamines came to Limelight after USFDA and EMEA declared in July 2018 that N-Nitroso dimethylamine and N-N-NDMA are focused on the pharmaceutical medicinal products and particularly used in case of SARTANS that are used in the treatment of Hypertension and Angiotensin II receptor blockers. Later the list was expanded to include Histamine-2 blocker Ranitidine and Diabetes drug Pioglitazone. Reaction of Urea Derivatives, Secondary amide carbamates and amines with Nitrogenous agent and nitrates lead to formation of Nitrosamines. The Oxidation state of nitrogen is +3. The Reasons for Presence of Nitrosamines in Pharmaceutical Products can be due to Product Degradation, Catalysts, solvents, Chemical reagents, Cross Contamination, Manufacturing Process and Contamination of Raw Materials. Technologies like Gas Chromatography, Mass Spectroscopy, Light Chromatography Mass spectroscopy are used to detect Nitrosamine Contamination. N-Nitrosamines categorized as "Cohort of concern" in ICH guidelines due to their potential mutagenic and carcinogenic nature. N-Nitroso dimethylamine and N-Nitroso diethylamine are classified as Class 2A human carcinogens by IARC-International Agency for Research and Cancer. This study focused on profile of nitrosamine impurities and regulations governing their presence in drug products.

Keywords: Nitrosamine impurities, Carcinogenicity, Limits, Regulations, Global risk.

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INTRODUCTION

Unwanted substances that are still present in Active Pharmaceutical Ingredients (APIs) or drug product formulations are referred to as pharmaceutical impurities.[1] The impurities found in pharmacological compounds could have been generated during synthesis. A variety of frequently used excipients contain nitrite impurities at ppm level, which can cause nitrosamine impurities to develop in drug materials during the manufacturing process and storage-life. Pharmaceutical companies are identifying nitrosamine impurities in their products as these molecules are a cause of worry since nitrosamine impurities are responsible to cause cancers in humans.[2] The fundamental circumstances that lead to the formation of nitrosamine in the drug products are the sources of contamination from amines that can form secondary, tertiary and quaternary nitrosamines; raw materials obtained from vendors; recycled materials; the searing process, and loss of method management and control.[3]

Even though they are also found in various foods and liquid sources, their inclusion in pharmaceuticals is however seen as inappropriate. Guidance discusses probable origins of nitrosamine production and suggests API and medicinal product producers follow:[4]

- Carry out a risk analysis of their commercialized or qualified Medicinal Products.
- Take steps to reduce or total elimination of nitrosamines in Medicines based on the Agency's current understanding.

The FDA and other international agencies conducted a thorough study of these contaminants in the impacted pharmaceutical products after nitrosamines were found in various types of drug products. The FDA has been researching at the nitrosamine impurities that are present in some drugs. The FDA has established internationally accepted recommended daily intake levels for nitrosamines in cooperation with regulatory counterparts throughout the world. In medications, nitrosamine levels below this limit are tolerable. The FDA advises the producer to recall medications if nitrosamine levels are higher than the allowable daily ingestion limit. Some pharmaceutical companies have recalled specific medications out of an abundance of caution, while others have done so because tests revealed nitrosamine levels over the permitted daily intake limits.[5-7] Numerous pharmaceutical items containing the APIs metformin,[7] valsartan,[8] losartan,[8] ranitidine (also known as zantac),[9] were removed off

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from the market or have been recalled as a result of the discovery of nitrosamine impurities over the threshold limit.

History and milestones of nitrosamine impurity profiling

Nitrosamines, or more formally N-Nitrosamines, are organic substances having the chemical formula $R_2N=O$, where R is often an alkyl group.[10] They contain a Nitroso group (NO+) coupled to a deprotonated amine.[11] Over a generation back, the chemical literature published the first characterization of a class of chemicals named nitrosamines. Since diethyl amine hydrochloride and sodium nitrite were combined to produce Nitrosodiethylamine (NDEA), nitrosamines have been well known. However, until 1954, the scientific community paid little attention to these chemicals.[12] When two cases of liver cirrhosis among three persons working in a research facility at an industrial company where NDMA (N-Nitroso Dimethyl Amine) had been introduced as a solvent first appeared that year, John Barnes and Peter Magee reported that the compound had hepatotoxic effects. The hepato-carcinogenicity of NDMA in rats was also discovered a few years later, in 1956, by Barnes and Magee.[13]

The toxicity of N-Nitroso compounds attracted a tons of attention after it was discovered that NDMA was carcinogenic.[13-15] The oral cavity, esophagus, stomach, urinary bladder, and brain are the most popular targets where tumors are formed in animals. Since NDMA was detected in some few valsartan products made in China in July 2018, pharma manufacturers and the FDA have been grappling with the issue of contamination with NDMA and related nitrosamine chemicals. Later, the recalls included losartan and irbesartan as additional ARBs (Angiotensin II receptor antagonists). In order to prevent the introduction of nitrosamines into these agents, the agency has been collaborating with manufacturers. Certain production procedures were deemed to be at fault. Angiotensin II Receptor Antagonists (ARBs), which include sartans like candesartan, irbesartan, losartan, olmesartan and valsartan, are being tested for the presence of NDMA. Patients with hypertension, as well as those with specific cardiac or renal conditions, are treated with these medications. When liver abnormalities were noticed in a variety of farm animals that had taken feeds containing herring that had been preserved by the addition of high amounts of sodium nitrite in the early 1960s, nitrosamines became a new topic of worry. It was possible to isolate and identify the harmful chemical in the diet as NDMA. The existence of that contaminant was later determined to be the consequence of an interaction between dimethylamine, an amine that naturally occurs in fish, and even a nitrosating agent created from sodium nitrite. As a result, scientists started to investigate if nitrosamines could also be present in food for humans. They then started to measure the levels of nitrosamines in the human food supply, which revealed that a number of different meals included some quantity of these contaminants. Tetrazole, a particular ring structure of these ARBs, has the potential to produce nitrosamine impurities during production. When particular reactions occur during the synthesis of ARBs, nitrosamines can emerge. The FDA had publicly revealed the procedure for checking ARBs against nitrosamine contaminants in the APIs, like valsartan, which has been the source of recalls and inquiries since 2018. However, the FDA has continuously exaggerated the risk that the contamination causes to the patients, citing studies that indicated a minimal to no increase in cancer risk. Nevertheless, ARB continued to issue additional recalls until 2019. Impurities containing nitrosamine have recently been observed in products containing pioglitazone and ranitidine.[16]

Ranitidine is a recent medication molecule that the FDA is closely monitoring for patient safety due to the high amounts of NDMA. According to the US Regulatory update from October 2, 2019, ranitidine formulations produced very high amounts of NDMA when tested at higher temperatures using a test method modified by a third-party laboratory. Ranitidine samples have so far tested positive for unacceptable amounts of NDMA in the agency's preliminary, constrained testing. The FDA stated in its announcement of the ranitidine contamination that it was still assessing the degree of patient risk.[16]

Sources of nitrosamine

There are many ways that people might be exposed to nitrosamines, including through drinking water, food, tobacco, personal care items, rubber goods, pesticides and industrial exposure. The second biggest source of nitrosamine exposure, after cigarettes, has been found as nitrosamine absorption through food intake, regardless of dietary preferences.[17-19] These substances can be produced endogenously in addition to being exposed to nitrosamines exogenously. Nitrite and nitrate are used in the endogenous synthesis, which predominantly takes place in the stomach from the latter, which is converted to nitrite by bacteria in the oral cavity. According to reports, it may be responsible for between 45% and 75% of all N-Nitroso compound exposure in humans.[20-22] However, a recent study found that it might represent 97% of the total nitrosamine load that a person might encounter.

The potential sources of Nitrosamine is descripted in Figure 1.[23-36] The production of nitrosamines as contaminants in pharmaceutical medicines can be caused by a number of methods.

There are few cases of sources/pathways published[37]

- Cross-contamination, which happens when many processes are performed one after the other on the same production line.
- Using particular packing materials. Finished pharmaceutical preparations kept in blister packs with Nitrocellulose-containing lidding foil have been found to have the nitrosamine contaminant.

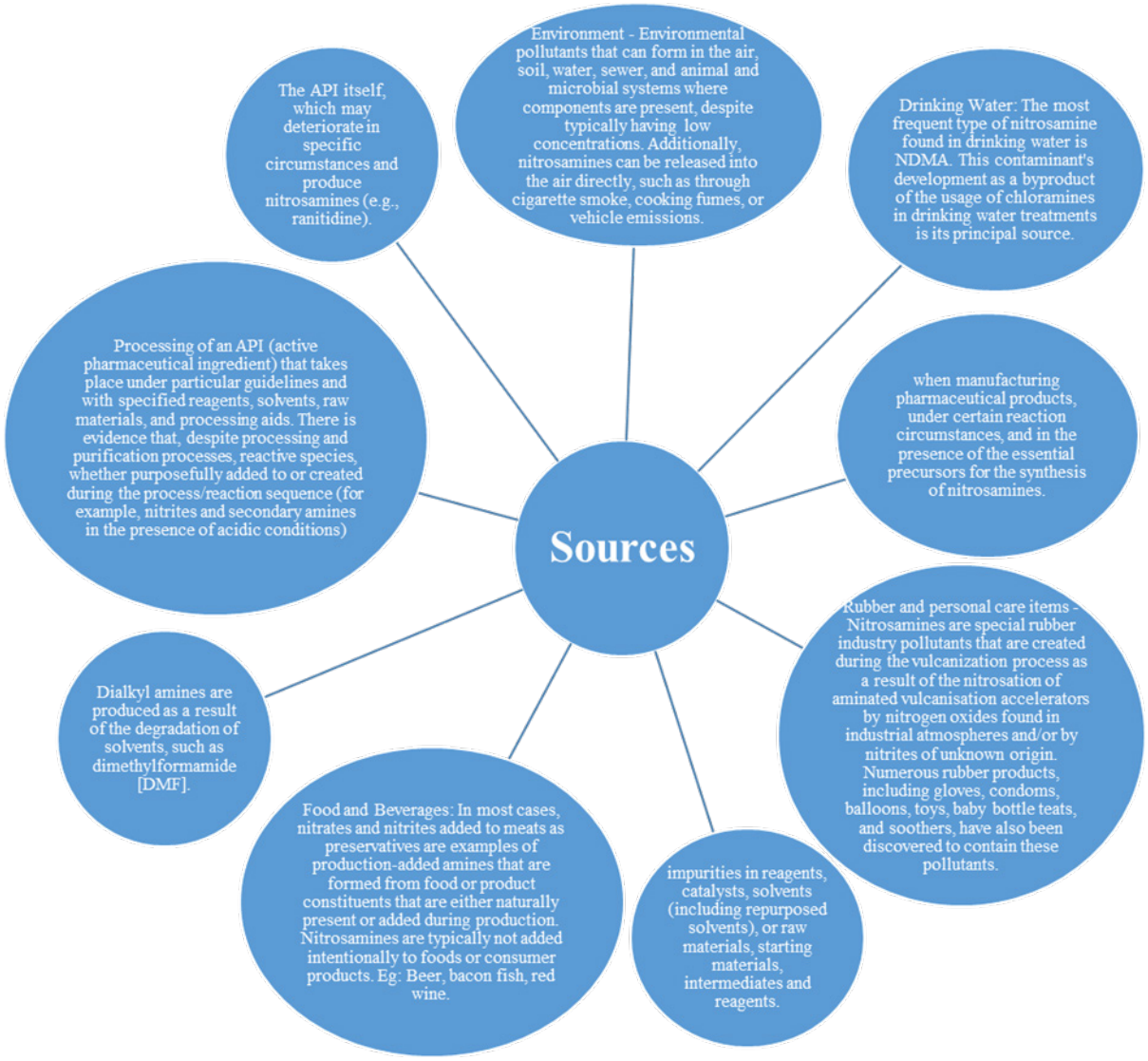


Figure 1: The potential sources of Nitrosamines.

- Nitrosating agents incorporated in drug product components react with the nitrosatable nitrogen functionality in APIs or their contaminants during formulation or storage.

Limits of nitrosamine

The FDA recommended Acceptable Intake (AI) limits as given Table 1. It suggest the manufacturers to use these AI technologies when determining nitrosamine impurity limits for APIs and pharmaceutical products.

Tests for determining the presence of nitrosamines[38]

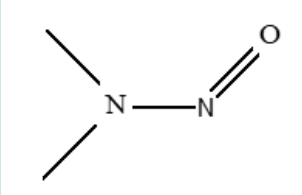
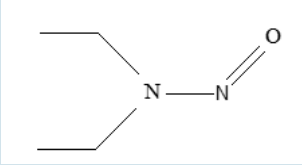
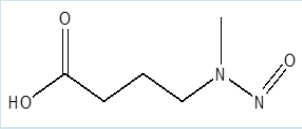
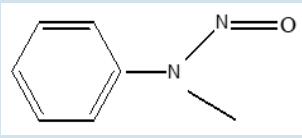
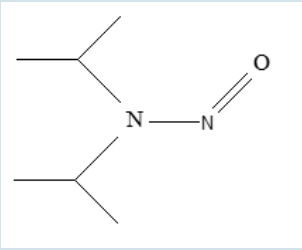
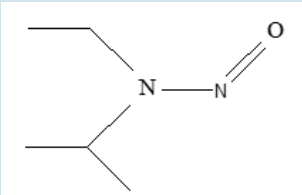
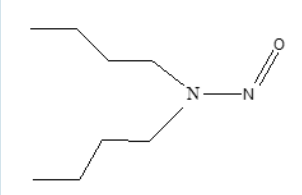
The risk assessment's findings and suggested control approach may need to be verified through exploratory testing when it is finished.

Regulations related to nitrosamine

EU[39]

Manufacturers were requested to review and modify their manufacturing processes to reduce nitrosamine impurities to the degree practically possible in the European Union (EU) following an Article 31 evaluation of sartans at risk of harbouring nitrosamine impurities (those containing a tetrazole ring). The implementation of these measures has been given a two-year transitional period. Interim limitations, as shown in Table 1, are being imposed to items during this transitional phase. Batches of product that contain both NDMA and NDEA or that exceed these limits for a single impurity are prohibited in the EU. The European Pharmacopoeia's drug substance descriptions for the sartan series are currently being updated to include nitrosamine testing. The general monograph for APIs (General monograph 2034), which is currently being revised, will also provide the necessary tests. Several sartan drugs were temporarily removed

Table1: Acceptable intake limits for various nitrosamines like NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products.

Nitrosamine	Structure	AI Limit (ng/day)
NDMA (N-Nitrosodimethylamine)		96
8NDEA (N-Nitrosodiethylamine)		26.5
NMBA (Nitrosomethyl-N-butylamine)		96
NMPA (N-Nitrosomethylphenylamine)		34.3
NIPEA (N-Nitrosoisopropylethylamine)		26.5
NDIPA (N-Nitrosodiisopropylamine)		26.5
NDBA (N-Nitrosodibutylamine)		26.5

from the EU market as a result of these actions. Many have now re-entered the market, although the EU encouraged consumers not to cease. Taking their medications. Similar to how the FDA sought to identify and recall medications with nitrosamine content over what was considered appropriate, it has published a list of ARB drugs.[10] The USFDA emphasized, as did the EMA, that the low risk of continuing the prescriptions with these impurities outweighs the consequences of abruptly stopping them (such as a stroke). More recently, ranitidine and nizatidine product batches have been found to contain NDMA impurity levels. For individuals with diseases like heartburn and stomach ulcers, ranitidine medications are frequently used to control the production of stomach acid. Both over-the-counter and prescription versions are offered. Reactions from regulatory

Table 2: List of drug products recalled due to presence of nitrosamines.

Date	Product Name	Company Name
22/03/2022	Quinapril and Hydrochlorothiazide.	Pfizer
25/10/2022	Quinapril and Hydrochlorothiazide.	Aurobindo Pharma, USA, Inc.
21/12/2022	Quinapril 20 and 40 mg tablets.	Lupin Pharmaceuticals.
01/12/2022	Metformin Hydrochloride tablets.	Viona Pharmaceuticals, Inc.
14/10/2021	Irbesartan and Hydrochlorothiazide USP.	Lupin Pharmaceuticals, Inc.
01/04/2021	Metformin HCl extended release USP 750 mg.	Nostrum Laboratories.
23/09/2022	Metformin HCl oral suspension.	Sun Pharmaceuticals Laboratories.
20/08/2020	Metformin HCl 500 and 750 mg.	Bay shore Pharmaceuticals, LLC.
07/08/2020	Metformin HCl 500 and 1000 mg.	Lupin Pharmaceuticals, Inc.
06/05/2022	Metformin HCl extended release 500 mg.	Markans Pharma Limited, India.

agencies have ranged. Swiss medic, Health Canada, and a few specific national regulatory bodies in Europe took preventative actions to either or prohibit the sale of all ranitidine products until batch analyses show that NDMA levels were below permissible ranges. In order to determine if patients using ranitidine are at any risk from NDMA, the EMA is presently assessing the data that is available. Only if test findings indicate NDMA levels above the intermediate levels have[11] other bodies, including the USFDA, asked for voluntary recalls of items.[12] The majority of ranitidine and nizatidine products have levels of DMA that, according to the USFDA, are comparable to those that would be present in typical foods such grilled or smoked meats.Many companies have initiated voluntary ranitidine product recalls as a preventative measures The EMA has asked all FPPs to analyse the possibility of nitrosamines being present in all products containing chemically synthesised active components, as a precautionary measure. Despite the fact that the vast majority of medicines are not expected to produce nitrosamines, firms have been asked to do this precautionary review due to the possibility of cross contamination or accidental introduction of amines and nitrites. These reviews should include all facets of the manufacturing process, including the production of FPP, and should be comprehensive in scope. The EMA has asked MAHS to finish this review in six months.

USFDA[40-42]

The FDA has been tasked with "protecting the public health by maintaining the safety, efficacy, and assurance of human and veterinary medication products, biological products, and medical devices...," and is housed within the US Department of Health and Human Services. Brand name prescription pharmaceuticals, generic medications, and non-prescription (over-the-counter) drug items are all regulated by the FDA. FDA approval of a drug indicates that the FDA has deemed the drug to be both safe and effective. Nevertheless, issues that affect the safety of certified items do arise. A drug recall may result when issues arise that influence the efficiency of drug goods. "A voluntary action performed by the corporation at any moment to remove a deficient drug product from the market" is the concept of a drug recall. When a pharmaceutical product is deemed harmful for patients or when FDA regulations have not been followed, a recall is either announced by the FDA or the medication company. Mislabeling, contamination, the existence of contaminants, and a lack of sterility are a few of the many causes of drug recalls. According to one count, the FDA has declared 226 medicine recalls in the last two years. Given that "...not all recalls are published on FDA.gov or in the mainstream media," the total number of drug recalls is probably far higher. FDA was informed of valsartan by one source in June 2018 the manufacturing of pharmacological compounds regarding the existence of an impurity identified as N-Nitrosodimethylamine (NDMA). Additional FDA investigation revealed that N-Nitrosodiethylamine (NDEA), another Nitrosamine impurity, was also detected in prescription substances from various manufacturers of valsartan and other medications at levels that were inadequate. The FDA announced "interim acceptable limits" for these Nitrosamine impurities in ARB medications as a key measure because there was no acceptable limit in the specification for Nitrosamines. It was advised to remove drug substances and drug products from the market if they exceeded certain limit levels. The FDA suggested that the producers of pharmaceutical products analyze samples from each batch or lot of pharmaceutical ingredients used in the production of pharmaceutical products for the US market to see if any nitrosamine impurities were present. Additionally, FDA has released validated techniques for locating and measuring NDMA and NDEA components in all ARB medicinal ingredients as well as some medication products.

Other Regulatory Authorities[40-42]

The Therapeutic Goods Administration (TGA) of Australia issued guidelines for "sartan" blood pressure medicines with respect to presence of Nitrosamine impurities.

Recall of pharmaceutical products because to nitrosamine impurities

In recent years, there has been an increase in the number of medicinal product recalls. This is now a pervasive problem, and

manufacturers need to be ready for any crises that may arise from unsuccessful product recalls. Both regulatory agencies and patients have severe concerns about the occurrence of nitrosamine impurities in prescription goods. Over 1400 product batches have been withdrawn or recalled, because the amount of nitrosamines present is greater than the daily permissible limit, from the markets in the previous two years.[43-45] Numerous pharmaceutical products containing the APIs valsartan, irbesartan, losartan, metformin, ranitidine, and nizatidine were removed off from the market or were recalled as a result These drug products were found to contain three different types of nitrosamine impurities.[46] To avoid a scarcity on the market, the FDA did not recall the life-saving drugs rifampin and rifapentine. These medicinal products' MNP and CPNP sources are still being looked into. According to the FDA, the range of daily nitrosamine intake that is considered to be safe for most people is 26.5 to 96 ng per day. Losartan has been related to the most product recalls (almost 24% of the total), with 324 batches containing this medication being taken off the market. A careful investigation of the FDA information finds that medication items containing "sartans" are to responsible for almost 81% of the recalls. In addition to sartans, combination products containing sartans co-formulated with other APIs accounted for around 42% of the total.[47] Numerous blood pressure drugs are being withdrawn by Pfizer and other organizations because they contain higher quantities of nitrosamine.[48] The various drug products recalled by the companies for the presence of nitrosamine are mentioned in Table 2.

EMA request to assess the possibility of nitrosamine presence

The results of sartans review suggested that, depending on API and drug product production methods, there is a possibility that nitrosamines will be present in APIs for other drugs. As a result, in September 2019, EMA formally requested that all MAHs for medications containing chemically synthesized active ingredients assess the risk of N-Nitrosamines in their products and implement the necessary risk mitigation strategies.[49,50] The following actions should be taken in the call for review:[51]

Step 1: To identify active ingredients and drug products at risk of N-Nitrosamine production or (cross-) contamination, perform a risk evaluation. The current cut-off date for chemical medications is 31 March 2021, and the topic of this dissertation is focused on this step.

Step 2: Confirmatory testing should be carried out on the items that were shown to be susceptible to Nitrosamine contamination or production.

Step 3: MAHs should make any necessary revisions to the dossier if the presence of nitrosamine(s) is confirmed (e.g. changes to their manufacturing processes). Steps 2 and 3 for chemical medicines must be finished by September 26, 2022.[52]

Global risk determination[53]

According to their anticipated significance in the global risk, various impact factors (ratios) were assigned to each of the mentioned potential causes in order to establish a classification of the global risk. As previously indicated, the drug Ranitidine Generis 150/300mg, which has been recently prohibited from the EU due to the presence of low quantities of NDMA, was subjected to this technique after it was produced while testing the medication Losartan Generis 50mg/100mg. The drug Losartan Generis 50mg/100mg was selected because, at the time this research was initiated, it was one of the few medicines for which Generis Farmecêutica, S.A. already possessed a sizable amount of data on the API production process. In addition, this medication is used to treat hypertension, one of the most prevalent long-term medical conditions, therefore it was thought that the existence of nitrosamine impurities in this medication would have a significant negative influence on public health. The choice of Ranitidine Generis 150/300mg was made since it was one of the products for which a greater quantity of information was already accessible and because, at the time, it was one of the newest products with proven nitrosamine impurity presence.

CONCLUSION

Awareness in the mutagenic and carcinogenic potential has increased in consequence to the latest discovery of Nitrosamine impurities on several commercially available medications. Due to the solvent, catalyst, and raw materials utilized throughout the production process, these impurities developed on the drug product. To manage various nitrosamine impurity, the various regulatory agencies have issued to alter the production process's control procedures, so that these impurities can be avoided. Impurities in manufactured biological and pharmacological products are located using validated analytical techniques. Based on the maximum daily dose, the overall amount of nitrosamine impurities should not be more than 26.5 ng/day (acceptable intake of nitrosamine).

The carcinogenic properties of nitrosamines, which are genotoxic contaminants, make them a grave danger to all life on earth. Regulatory organisations including CDSCO, the US-FDA, and the European Medicines Agency (EMA) have continuously worked to quantify the amine impurities found in food products and other intermediates in chemical synthesis in an effort to address this global problem. Researching novel approaches and methodologies for the accurate estimate of nitrosamine impurities from diverse pharmaceutical APIs, however, is a difficult challenge for scientists, researchers and industrialists.

Their high hydrophilicity and low molecular weight are the main issues.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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