MITIGATING THE RISK OF NITROSAMINE IMPURITIES IN DRUG SUBSTANCES AND PRODUCTS: ANALYTICAL APPROACHES AND REGULATORY GUIDELINES

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Abstract
Nitrosamine impurities, known to be highly toxic and capable of causing cancer, can have carcinogenic effects even in small quantities when present in the body. To prevent the presence of these impurities, precautions should be taken during the manufacturing and development of drug substances and products. Regulatory authorities such as the World Health Organization (WHO) and the US Food and Drug Administration (USFDA) have provided guidelines and notifications on controlling these impurities, aiming to prevent their spread in drug substances. Validated analytical techniques like gas chromatography (GC) and liquid chromatography (LC) should be employed to detect and measure these impurities. Nitrosamine impurities can be introduced into the drug substance or product through reagents, catalysts, solvents, or raw materials used during the manufacturing process. Detecting these impurities at trace levels requires sophisticated instruments, such as LC or GC combined with mass detectors, which are commonly used for this purpose.

Keywords: Nitrosamine impurities, Impurity profiling, Side effects, Analytical methods, etc.

1. INTRODUCTION [(1) (2) (3)]
Nitrosamines, specifically N-nitrosamines, are formed when molecules containing the nitroso functional group react with nitrous acid. These impurities are a concern because they have the potential to be harmful to humans. While nitrosamines can be found in some food and beverage substances, their presence in medications is considered unacceptable.

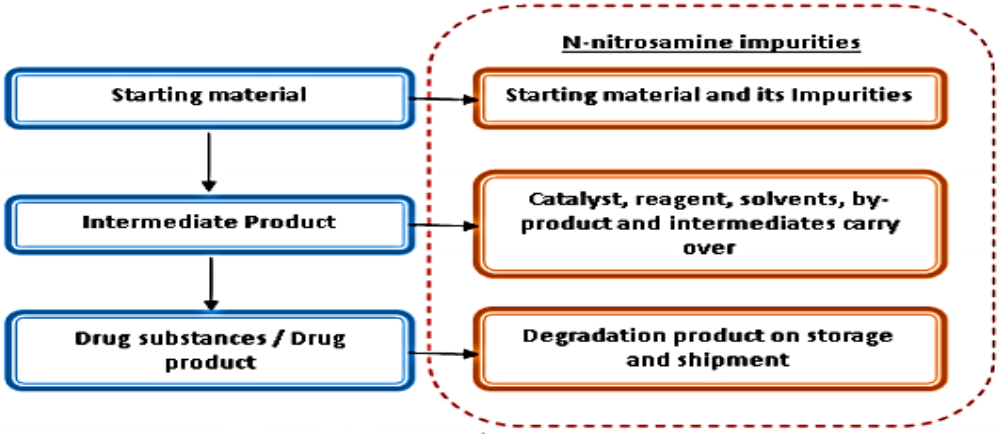
Nitrosamine formation occurs when secondary or tertiary amines react with nitrous acid, which is often generated in situ from nitrites (NO2) under acidic conditions. In the case of sartan compounds, which commonly contain a tetrazole ring, the use of sodium nitrite in the formation of this ring has been implicated. The exact source of N-nitrosodimethylamine (NDMA) in batches of ranitidine is currently unclear.

According to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Nitrosamine impurities are classified as Class 1, indicating their potential toxicity and carcinogenicity based on data from rodent studies and mutagenicity testing.
These impurities can affect genetic material through mutations caused by chromosomal breaks, rearrangements, covalent binding, or insertion into DNA during replication. Exposure to very low levels of Nitrosamine impurities can lead to these genetic changes, potentially resulting in cancer. Therefore, it is crucial to detect Nitrosamine impurities in medications at extremely low levels to ensure public safety.

1.1 Source of Impurities [(3)]
Nitrosamine impurities can be introduced into drug substances and products through various routes, including during the manufacturing process. These impurities may be incorporated through process formation, direct introduction, degradation, or cross-contamination. The manufacturing of drug materials

involves the use of raw materials, intermediates, solvents, chemicals, and reagents. If Nitrosamine impurities are present or persist throughout these stages, they can become embedded or carried forward into the final drug product. It is important to identify and prevent the presence of these impurities at every step of the manufacturing process to ensure the safety and quality of the drug.

Figure 1: Sources



1.2 Occurrence [2] [4]:

March 2018: A risk assessment was conducted for genotoxic impurities. The issuance of the agreed document M7 (R1) helped in outlining the threat assessment.

June 2018: NDMA (N-nitrosodimethylamine) was discovered in an API (Active Pharmaceutical Ingredient) producer of valsartan. Voluntary reporting of the issue began. This incident raised concerns among regulatory authorities and ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) standards.

July 2018: Voluntary recalls of products containing valsartan were announced. Manufacturing of the API was halted, and investigations were initiated. The presence of NDMA impurity led to a significant product recall. Distribution of affected medicines was stopped, and alternative medications were recommended. Testing of valsartan for NDMA impurity was conducted, and a list of unaffected valsartan products was issued.

August 2018: Evaluation of processes to prevent the presence of unsafe impurities continued. Collaborative efforts were focused on preventing the presence of NDMA in the future. The investigation expanded to include other batches of affected products. Lists of recalled and unaffected products were issued. The manufacturing process was challenged to address the presence of genotoxic impurities specific to each product.

September 2018: The investigation into the issue continued and gained momentum. The search for NDMA impurity was intensified. FDA inspection concluded, emphasizing the responsibility of manufacturers to develop and utilize methods for detecting impurities.

October 2018: FDA issued an analytical document regarding various products and materials. A new GCMS (Gas Chromatography Mass Spectrometry) technique was introduced, offering a more reliable method for detecting impurities. The GC-MS/MS (Gas Chromatography-Tandem Mass Spectrometry) method was also issued. NDEA (N-nitrosodiethylamine) was identified in irbesartan in FDA laboratories.

December 2018: The list of affected and unaffected products continued to be updated. Focus remained on nitrosamine impurities. Testing methods were uploaded. The scope of the methods covered API, finished products, and other ARBs (Angiotensin Receptor Blockers). Daily acceptable intake levels were established.

August 2019: Proposed method adjustments were evaluated. Facility inspections and sample testing were conducted. Compliance was assessed, and investigations were carried out to address any arising issues.

1.3 Root causes formation & infection of Nitrosamine [(5)]:

Nitrosamine impurities can be formed during the processing of APIs (Active Pharmaceutical Ingredients) under specific processing conditions and when certain raw materials, starting substances, and intermediates are present. This means that the formation of nitrosamines is not inherent to all processing methods or materials but depends on specific circumstances.

The use of sodium nitrate or other nitrates, in the presence of secondary or tertiary amines, can contribute to the formation of nitrosamines. Secondary amines, which are compounds containing an amino group bonded to two carbon atoms, can commonly be found in common bases used in the manufacturing process. Inflamed raw materials, such as recycled solvents, reagents, and catalysts, can pose a risk due to the presence of amines in waste streams. If these materials contain amines, which are organic compounds containing a nitrogen atom, there is a potential for nitrosamine formation during the production process.

The use of third-party suppliers to obtain higher-quality materials, including solvents, reagents, and catalysts, can introduce a risk if these suppliers do not provide sufficient information on the content of the substances. Additionally, if the recovery techniques used for these materials are not specifically dedicated to preventing contamination, it can increase the chances of nitrosamine impurities being present.

The use of contaminated starting materials, including intermediates supplied by companies that use processes resulting in nitrosamine formation, can lead to the presence of nitrosamine impurities. If the starting materials or intermediates used in the manufacturing process contain substances or undergo processes that generate nitrosamines, it can contribute to the overall contamination.

1.4 Types of drug affect [(3)]

As per the latest update, the European Medicines Agency's (EMA) human medicine committee (CHMP) is conducting a review to investigate the presence of a nitrosamine called NDMA in certain batches of ranitidine. The purpose of this review is to gather evidence and understand how NDMA was detected in these ranitidine batches. Furthermore, the EMA, along with national authorities, is also assessing the implications of recent tests that have identified the presence of NDMA in some batches of metformin medications used to treat diabetes. This assessment aims to evaluate the extent and potential risks associated with the presence of NDMA in these metformin batches. The objective of these ongoing reviews and assessments is to gather all relevant information, investigate the origin of NDMA contamination in ranitidine and metformin, and determine the potential impact on patient safety. The EMA and national authorities are working to ensure that appropriate measures are taken to address any identified risks and protect the health and well-being of patients.

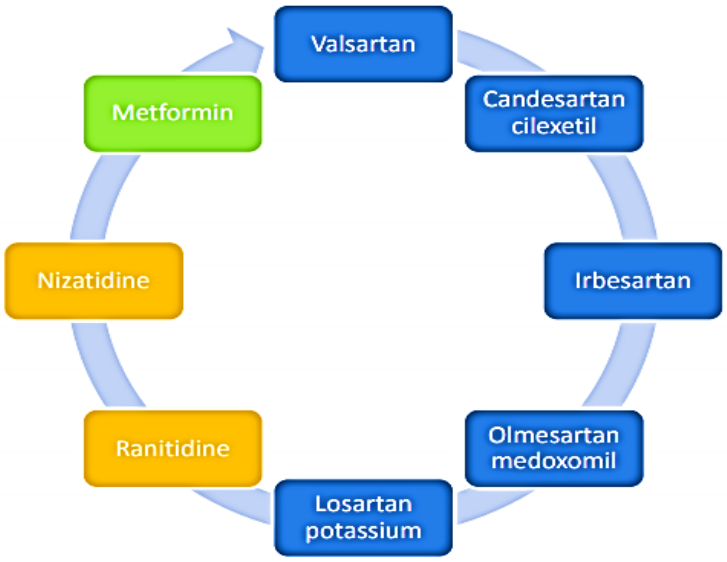
1.4.1 Drug category:

Table 1:Data category [3]

Medication name	Indication
ARB (Angiotensin Receptor Blocker) s (Sartans): Valsartan, Candesartan, Losartan and Olmesartan	High blood pressure
Ranitidine	Over the counter: • Heart burn • Sour stomach • Acid indigestion Prescription: • Heartburn • Ulcers of the stomach and intestine • Gastroesophageal reflux disease
Metformin	Type 2 diabetes (diabetes mellitus)
Nizatidine	Ulcers of stomach and intestines Gastroesophageal reflux disease
Pioglitazone hydrochloride	Type 2 diabetes (diabetes mellitus)

1.4.2 Impacted molecules [6–8]:

Figure 2: Impacted molecules



Ranitidine:

Ranitidine is a medication classified as an acidity inhibitor, primarily used for short-term treatment. It was commercially introduced in 1981 and has since become available in over 120 countries worldwide. The World Health Organization (WHO) recognizes the importance of ranitidine and includes it on the List of Essential Medicines. The inclusion of ranitidine on this list signifies its relevance in addressing essential healthcare needs and its importance in public health systems globally.

Sartans:
Certain sartan medications have been found to contain nitrosamine impurities, specifically NDMA (N-nitrosodimethylamine) and NDEA (N-nitrosodiethylamine). The presence of these nitrosamine impurities in sartans has raised concerns regarding the safety and quality of these medications. Nitrosamines are classified as potentially carcinogenic substances, meaning they have the potential to cause cancer in humans.

The detection of nitrosamine impurities in sartans originated in 2018 when NDMA was identified in valsartan, an angiotensin II receptor blocker (ARB) used to treat high blood pressure and heart failure. Subsequently, investigations expanded to other sartan medications, including losartan, irbesartan, and candesartan, where varying levels of nitrosamine impurities were also detected. The presence of nitrosamine impurities in sartans is believed to be linked to specific manufacturing processes and the use of certain raw materials. Regulatory authorities worldwide, such as the FDA (U.S. Food and Drug Administration), EMA (European Medicines Agency), and other national agencies, have issued recalls, warnings, and guidelines to address the issue. Manufacturers have been instructed to implement measures to prevent or minimize the presence of nitrosamine impurities in sartan medications, ensuring their safety for patients.

Ongoing efforts are focused on enhancing manufacturing processes, conducting rigorous testing, and implementing strict quality control measures to ensure that sartans are free from nitrosamine impurities and meet the required safety standards.

Figure 3: Data of Sartans:

	NDMA		NDEA	
Active substance (max daily dose)	**Maximum daily intake (ng)**	**Limit (ppm)**	**Maximum daily intake (ng)**	**Limit (ppm)**
Candesartan (32 mg)	96.0	3.000	26.5	0.820
Irbesartan (300 mg)	96.0	0.320	26.5	0.088
Losartan (150 mg)	96.0	0.640	26.5	0.177
Olmesartan (40 mg)	96.0	2.400	26.5	0.663
Valsartan (320 mg)	96.0	0.300	26.5	0.082

Nizatidine and metformin:
According to literature review the drug cutoff in September 2021, there have been no reports or recalls specifically related to nitrosamine impurities in nizatidine or metformin. Nizatidine is another medication used to reduce stomach acid, similar to ranitidine, but it has not been widely associated with nitrosamine impurities.

However, it's important to note that the presence of nitrosamine impurities in medications can evolve over time, and new information may have emerged since my knowledge cutoff. It is always advisable to stay updated with the latest information from regulatory authorities and consult healthcare professionals for the most current guidance on specific medications.

1.5 Limits and acceptable intake

To determine the acceptable levels of nitrosamine impurities in APIs (Active Pharmaceutical Ingredients) and drug products, the median toxic dose (TD50) is used as a basis for calculation. The TD50 is a well-established international standard recommended by the ICH M7 (R1) guidelines for assessing the acceptable extra risk associated with mutagenic and carcinogenic impurities.

For NDMA, the TD50 value is reported as 0.096 mg/kg/day for the most sensitive species, which is the rat. This translates to a dose of 1.92 ng/kg/day for NDEA. Based on these values, the acceptable intake (AI) levels for an individual with a body weight of 50 kg would be 96 mg/day for NDMA (50 kg x 1.92 mg) and 26.5 mg/day for NDEA.

The FDA (U.S. Food and Drug Administration) has provided recommendations for AI limits for various nitrosamine impurities, including NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA. Manufacturers are advised to use these Acceptable Intakes when determining limits for nitrosamine impurities in APIs and drug products. These recommendations serve as guidelines to ensure the safety of medications with respect to nitrosamine contamination.

Figure 4: AI for various types of Nitrosamines

Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

1.6 Side effect of overdose [1,2,4]

1.6.1 Toxicity Profiling:

NDMA and NDEA are classified as part of a group of potent mutagenic cancer-causing agents known as the "cohort of concern." These substances have been identified by the International Agency for Research on Cancer (IARC) of the WHO as likely human carcinogens. There is limited available data on the specific toxicity of NDMA and NDEA. Based on this information, interim acceptable intakes for these impurities have been established by major regulatory bodies. NDIPA, NEIPA, and NMBA are structurally similar to NDMA and NDEA, and therefore, international regulators consider them to have a toxicological profile similar to these two impurities.

Contamination:
Contamination of nitrosamine content can occur from external sources. Recycled materials and solvents that already contain nitrosamine levels can contribute to contamination. For instance, the use of recycled DMF (Dimethyl formamide), which is treated with sodium nitrite to remove residual azide during the recovery process, serves as an example. If equipment is not adequately cleaned between uses, materials and solvents can become cross-contaminated with nitrosamines or with impurities that have the potential to react and form nitrosamines downstream.

1.6.2 Elimination of impurities (How can get rid from the impurities) [3]*:*

1. The presence of nitrosamine impurities in drug substances or products is primarily associated with the use of nitrosating agents and amines. To minimize these impurities, it is recommended to avoid the use of such reagents during the manufacturing process.
2. Nitrosamine impurities can be eliminated through the solvent used. However, if these solvents are recovered and reused, there is a risk of reintroducing the impurities. Therefore, it is advisable to refrain from using recovered solvents in the manufacturing process.
3. Contaminated raw materials, intermediates, and reagents used in drug substance production can contribute to nitrosamine impurities. Storage of these materials in the presence of trace amounts of nitrites may lead to impurity formation. It is important to properly store and test these materials for nitrosamine impurities.
4. Equipment used in drug substance manufacturing may be cross-contaminated with nitrosamine impurities from previous products. Thorough cleaning and contamination checks of the equipment are necessary.
5. Manufacturers should test and monitor the presence of nitrosamine impurities in various intermediate stages and establish appropriate limits if detected.
6. Manufacturers should adjust their processes to minimize the presence of amines, nitrites, and nitrosamine impurities at different stages.

In conclusion, the formation of nitrosamine impurities in finished products can be effectively managed by selecting synthesis routes that minimize their formation, adhering to strict good manufacturing practices (GMP) including equipment cleaning, and controlling the recovery process for solvents. API and drug product manufacturers should assess the risk, conduct confirmatory testing, and report any changes made to prevent or reduce nitrosamine impurities to regulatory authorities.

2. ANALYTICAL METHODS:

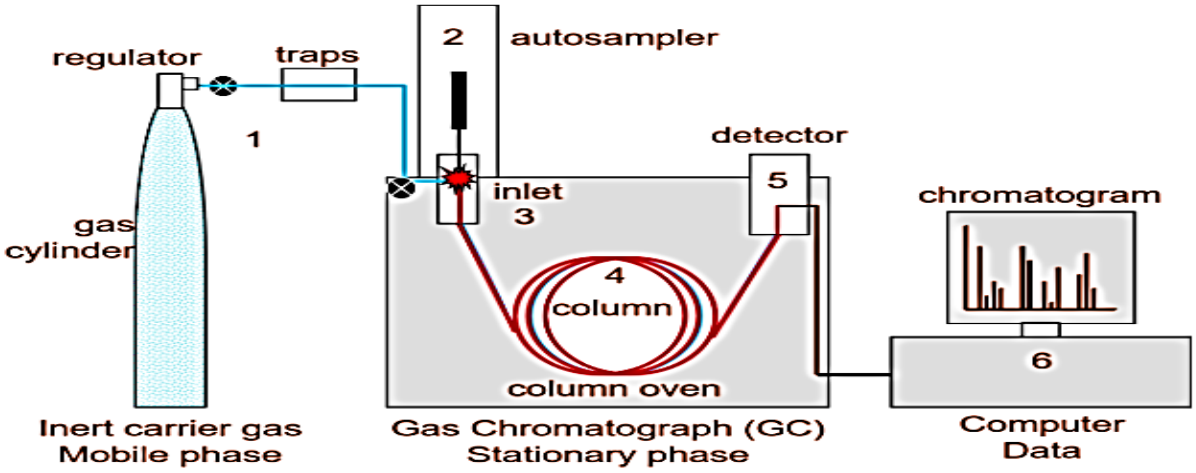
2.1 By USFDA [3,10]:

Developing analytical methods for detecting nitrosamine impurities is indeed a challenging task, primarily because these impurities exist in very low concentrations within complex matrices. The methods developed for this purpose also need to undergo validation to ensure they meet the requirements of good manufacturing practices (GMP). The FDA has published several methods to detect NDMA and NDEA in various 'sartans', addressing the specific concern at the time. The EMA has expressed the need to expand these measures to include additional nitrosamines, indicating a broader approach to addressing the issue of nitrosamine impurities.

2.1.1 Gas Chromatography

Gas chromatography coupled with mass spectrometry (GC-MS) is widely used for the analysis of nitrosamine impurities with lower molecular weights. It is a frequently employed technique due to its high selectivity and sensitivity. The FDA has developed and validated a combined GC-MS/MS method specifically for the simultaneous determination of four nitrosamine impurities (NDMA, NDEA, NDIPA, and NEIPA) in Valsartan drug substance and drug products. This method meets all the necessary requirements, including sensitivity, repeatability, and surpasses the expected control limits. Many recent publications also utilize GC-MS or GC-MS/MS techniques, which offer excellent selectivity and low detection limits, making them suitable for nitrosamine analysis and complying with modern regulatory standards.

Figure 5: Gas Chromatography



The use of Thermal Energy Analysis (TEA) provides excellent selectivity for nitrosamines. However, when it comes to high molecular weight nitrosamines, these molecules are relatively unstable and cannot be effectively detected using gas chromatography (GC) alone.

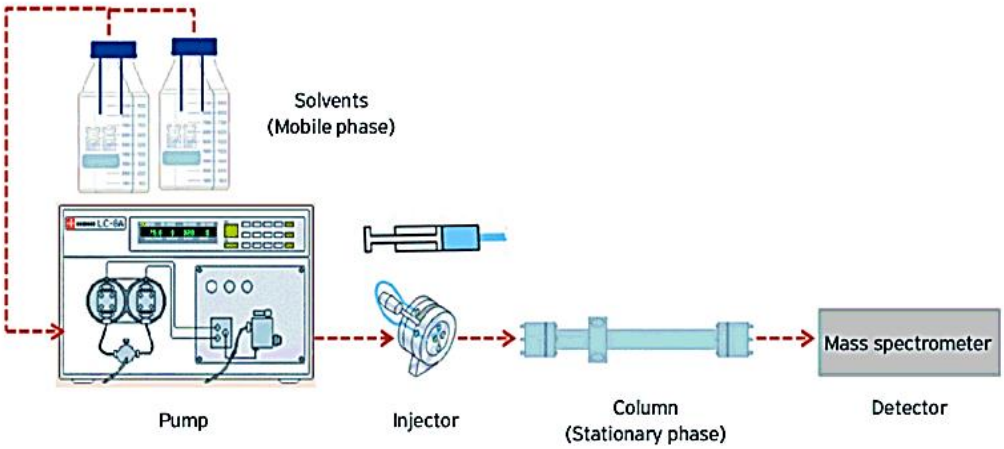
2.1.2 Liquid Chromatography

The utilization of liquid chromatography (LC) methods provides a faster alternative to traditional GC-MS techniques. By employing high-resolution accurate mass spectrometry, these methods offer good selectivity for detecting both GC-detectable and GC-undetectable compounds, including thermally stable and unstable nitrosamines.

The FDA has recognized that the GC-MS method commonly used for testing nitrosamine impurities in angiotensin II receptor blockers (ARBs) may not be suitable for analyzing ranitidine due to the generation of NDMA during sample heating. As a result, an LC-HRMS method was developed by the FDA to accurately measure NDMA levels in ranitidine drug substance and drug products in accordance with ICH Q2 (R1) guidelines.

The method has a limit of detection (LOD) of 0.011 ppm, a limit of quantitation (LOQ) of 0.033 ppm, and a range of 0.033-3.33 ppm. Furthermore, various scientific literature reports have described multiple methods utilizing liquid chromatography-mass spectrometry (LC-MS) or LC-MS/MS.

Figure 6: Liquid Chromatography[(11)]



Although limited, a few studies have documented the analysis of NDMA in drugs using conventional high-performance liquid chromatography (HPLC).
HPLC is widely employed for routine analysis and quality control of active pharmaceutical ingredients (APIs) and products. It is advantageous to have the capability of detecting NDMA impurities alongside drug substances in a single HPLC analysis. Therefore, it is crucial to develop a rapid and straightforward analytical method for the determination of NDMA in drugs using HPLC.

2.2 By Various Companies [10]:

2.2.1 International Agency for Research on Cancer (IARC):

Nitrosamine compounds are potent genotoxic agents that are known to cause cancer in various non-human species. They have been classified as probable human carcinogens by the International Agency for Research on Cancer (IARC).

Starting from June 2018, the presence of N-nitrosamines has been detected in multiple batches of drug substances, primarily in Sartans. However, the focus of health authorities has now expanded to encompass all drug substances and drug products.

Initially, N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) were identified, but subsequently, other N-nitrosamines were discovered in addition to these two.

Health agencies have mandated pharmaceutical companies to conduct a risk assessment to determine the potential presence of N-nitrosamines in their products. Companies are required to experimentally demonstrate the absence of these impurities based on the risk assessment. The specific list of N-nitrosamines to be tested should be obtained from the risk assessment.

The IARC has established general methods for analyzing N-nitrosamines in API and drug products using techniques such as HS-GC-MS and LC-MS/MS. These methods can be adjusted with minor modifications to suit the client's specific API or drug product.

Kymos offers a proposal to meet the regulatory agencies' requirements while optimizing costs and time. The proposal consists of two steps:

- Screening of the target nitrosamines requested by the client from the provided list. A default limit of 0.03 ppm is set for this screening, which aligns with the future limit established by health agencies. Higher limits can be established based on the product or client's requirements.
- If one or more nitrosamines are found to be at or above the established limits, the development and validation of a quantitative method will be necessary and agreed upon with the client.

2.2.2 Agilent [12]:

Sample preparation:

- The analysis involved testing APIs and drug products such as valsartan, olmesartan, irbesartan, and losartan. A 500 mg portion of the API was accurately weighed into a disposable 15 mL glass centrifuge tube. Then, 5 mL of the internal standard solution was added using a volumetric pipette.
- After vortexing the samples for one minute, they were placed in a centrifuge and spun at 4,000 rpm for 2.5 minutes. Subsequently, approximately 2 mL of the dichloromethane layer was filtered through

a 0.45 µm nylon filter using a disposable pipette. The filtered solution was then transferred to a GC vial for further analysis.

Standard preparation:

Paraphrased:

- The standard stock solution was appropriately diluted to create calibration solutions with the following concentrations: 100, 80, 40, 20, 10, 5, and 2.5 ng/mL. Each calibration solution was prepared in dichloromethane and included NDMA: C13-d6 as an internal standard.
- The GC system utilized a 7697A headspace sampler connected to a multimode inlet (MMI). From the inlet, a GC capillary column, specifically an Agilent J&W VF WAXms column with dimensions of 30 m × 0.25 mm and 1.0 µm particle size, was connected to the mass spectrometer (MS). Tables 2 and 3 display the GC and MS parameters.

Figure 7: GC parameters.

Parameter	Value
MMI Injection Mode	Pulsed splitless: 12.285 psi until 0.5 min
Inlet Temperature	250 °C
Oven Temperature Program	40 °C (0.5 min) 20 °C/min to 200 °C (0 min) 60 °C/min to 250 °C (3 min)
Total Run Time	12.33 min
MS Transfer Line Temperature	250 °C
Injection Volume	2 µL
Carrier Gas	Helium, 1 mL/min

Figure 8: Mass Parameters

Parameter	Value	
Mode Source	Electron ionization, 40 eV	
Temperature	250 °C	
Quadrupole Temperature	Q1 and Q2 = 150 °C	
MRM Mode Conditions		
MS1 Resolution	All compounds Unit	
MS2 Resolution	All compounds Unit	
Collision Gas Flow	Nitrogen at 1.5 mL/mi	
Quenching Gas Flow	Helium at 4 mL/min	
Detector Gain	1	
Quant./Qual. Transitions (FDA method)	Start time: 6.5 min	NDMA 74 → 44, CE 15, dwell 150 ms 74 → 42, CE 20, dwell 50 ms NDMA:C13-d6 82 →48, CE 20, dwell 100 ms
	Start time: 7.60 min	NDEA 102 →85, CE 10 V, dwell 150 ms 102 →56, CE 18 V, dwell 150 ms
	Start time: 8.03 min	NEIPA 116 →99, CE 10 V, dwell 150 ms 71 →56, CE 10 V, dwell 150 ms
	Start time: 8.25 min	NDIPA 130 →88, CE 10 V, dwell 150 ms 130 →42, CE 10 V, dwell 150 ms
	Start time: 8.70 min	NDBA 158 →99, CE 10 V, dwell 150 ms 84 →56, CE 22 V, dwell 150 ms

2.3 Results and Discussion:

In the analysis, the compounds were effectively separated from each other, and the peaks of interest were clearly distinguished from other components such as the solvent and matrix species. The retention times of all five compounds aligned with the values specified in the FDA regulations, ensuring accurate identification and quantification.

To establish the concentration levels of the impurities, calibration curves were constructed using a linear regression model. The FDA mandates that the correlation coefficient, R^2, should be equal to or greater than 0.998 to ensure the reliability and precision of the calibration curve. In this study, the obtained calibration curves demonstrated excellent linearity, with R^2 values exceeding 0.999 for all five impurities. This high degree of linearity indicates a strong relationship between the concentration of the impurities and their corresponding peak areas, allowing for accurate and precise quantification of the impurities in the samples.

2.4 Nitrosamine Impurity Testing and Analysis, consisting N-nitrosodimethylamine (NDMA), in drugs by LC-MS and GC-MS Methods by Intertek [(13)] :

GC/MS Headspace Chromatography Mass Spectrometry Approach
The FDA Office of Testing and Research has formulated a comprehensive method combining gas chromatography (GC) and mass spectrometry (MS) using the headspace technique. This method was specifically developed to simultaneously detect and evaluate four nitrosamine impurities in drug substances and drug products belonging to the angiotensin receptor blocker (ARB) class. The targeted impurities encompass N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosodiisopropylamine (NDIPA), and N-nitrosoethylisopropylamine (NEIPA). The method's development and validation process were carried out using valsartan as the representative drug substance and drug product.

Liquid Chromatography High Resolution Mass Spectrometry (LC-HRMS) Technique for the Determination of NDMA in Ranitidine Drug Substance and Drug Product
The FDA has recognized that the existing testing method used for evaluating nitrosamine impurities in angiotensin II receptor blockers (ARBs) is not suitable for the examination of ranitidine due to the production of NDMA upon sample heating. As a result, the FDA has developed a new method using liquid chromatography-high-resolution mass spectrometry (LC-HRMS) to measure the quantities of NDMA in ranitidine drug substance and drug product, following the guidelines outlined in ICH Q2 (R1). The method's limit of detection (LOD) is 10 ng/g, with a lower limit of quantitation (LOQ) of 33 ng/g and an upper LOQ of 3333 ng/g.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Method for the Determination of NDMA in Ranitidine Drug Substance and Solid Dosage Drug Product
The method employed is a liquid chromatography-tandem mass spectrometry (LC-MS/MS) technique specifically designed for the analysis of NDMA in ranitidine drug substance and drug product. This LC-MS/MS method, which utilizes a triple-quad platform, serves as an alternative or confirmatory approach to the liquid chromatography-high-resolution mass spectrometry (LC-HRMS) method.

A Rapid Detection Approach

Ultra-Performance Liquid Chromatography, Low Resolution Tandem Mass Spectrometry (UPLC-LR/MS/MS) technique for the determination of NDMA, NDEA, NMBA and NDIPA in valsartan drug substance.

Intertek has also developed an alternative method utilizing ultra-performance liquid chromatography with low-resolution mass spectrometry (UPLC-LR/MS/MS). This approach enables the swift detection and quantitation of several nitrosamine impurities, including NDMA, NDEA, NMBA, and NDIPA. The method offers a limit of detection (LOD) of 5 ng/g, lower limit of quantitation (LOQ) of 15 ng/g, and upper LOQ of 75 ng/g. This method is highly suitable for a rapid initial screening to identify common nitrosamine impurities, facilitating and expediting the risk assessment process. If required, the method can be further optimized and validated for your specific APIs or drug products.

3. CONCLUSION

The significance of ensuring the quality of drug products for human health cannot be overstated. The presence of impurities in pharmaceuticals can have a direct impact on their safety and efficacy. Therefore, it is essential to detect and analyze impurities in every drug product that may be affected. In recent years, there has been an increasing emphasis on the impurity profile of pharmaceuticals, with drug safety receiving significant attention from the public and media. This article provides valuable insights into various analytical techniques employed for the determination and qualification of impurities in pharmaceuticals. It also highlights the critical factors that need to be considered during the preparation of bulk drugs.

Isolation and characterization of impurities play a crucial role in acquiring and evaluating data that establish the biological safety of drugs. This underscores the importance and scope of impurity profiling in pharmaceutical research. By identifying and understanding impurities, researchers and manufacturers can ensure the development and production of safer and more reliable drugs.

Overall, the detection and analysis of impurities in drug products are essential steps in maintaining the quality, efficacy, and safety of pharmaceuticals. The continuous advancement of analytical techniques and the focus on impurity profiling contribute to improving drug safety standards and meeting the expectations of both the scientific community and the general public.

Abbreviations

- WHO: World Health Organization
- USFDA: United states food and drug administration
- ICH: International conference of harmonization
- NDMA: Nitroso di-methyl amine
- DNA: Deoxyribose nucleic acid
- API: Active pharmaceutical ingredient
- FDA: Food and drug administration
- GCMS: Gas chromatography Mass spectroscopy
- NDEA: Nitroso di ethyl amine
- ARB: Angiotensin receptor blocker
- DMF: Dimethyl formamide
- CFR: Code of federal registration

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