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RECENT APPROACHES TO DECREASE NITROSO IMPURITIES FROM PHARMACEUTICAL AND CARCINOGENIC DRUGS

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ABSTRACT

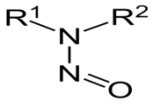
The control of Nitrosamine impurities which are potentially mutagenic and carcinogenic found in Pharmaceutical products play important role in evaluating carcinogenic risk to humans. The recent discovery of nitrosamine impurities in some marketed pharmaceutical drugs has increased mutagenic and carcinogenic potential. As per International Agency for Research on Cancer (IARC), nitrosamine is the chemically classified as a probable human carcinogen.[1] The various regulatory authorities have published the press release or notice regarding the control of nitrosamine impurities with the interim limit. Validated analytical methods are used to identify and quantify the nitrosamine impurities to the trace level at a given interim limit.[2,20] Medicine regulatory authorities like FDA, EMA, TGA and Health Canada have published several public notices to guide the manufacturer to control and limit these impurities to acceptable intake level.[22,24]

KEYWORDS:- Nitrosamine, Carcinogenic Drugs, Impurities, Analytical Methods and Guidelines.

INTRODUCTION

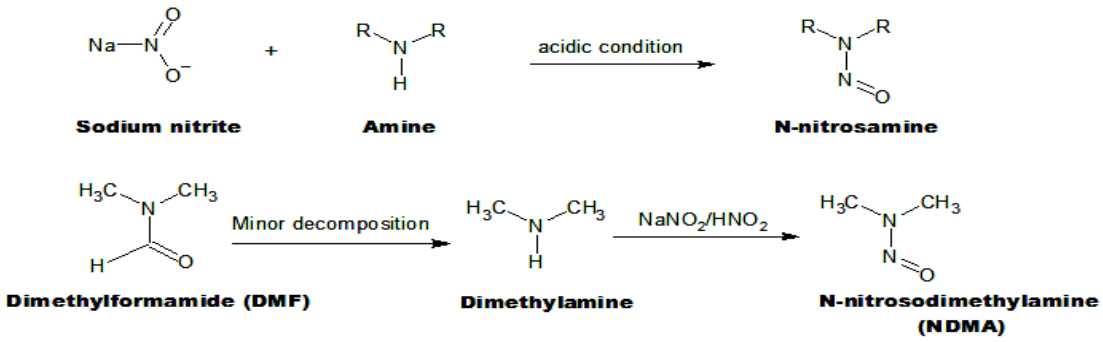
Nitrosamines[1,2,21]

Any molecule containing nitroso functional group known as Nitrosamine or more commonly N-nitrosamine. Nitrosamines are a family of carcinogen impurities which are formed by reaction of secondary amines, amides, carbamate derivatives of urea with nitrite or other nitrogenous agent like fuming nitric acid, N_2O_4, & $NOBF_4$in the +3 state.



Nitrosamine forms a large group of genotoxic chemical carcinogens which occurs in human diet and other environmental media and can be formed endogenously in the human body. N-nitroso compounds can induce cancer in experimental animals.[3]

Formation of nitrosamine impurities[1,21]



Some of secondary amines and their corresponding nitrosamine impurities are formed are given in table below-

Table 1: Amines and Corresponding nitrosamine impurities.[1]

Secondary Amines	Nitroso impurity	Abbreviations
Dimethyl amine	N-Nitrosodi-methylamine	NDMA
Diethyl amine	N-Nitrosodiethylamine	NDEA
Dipropylamine	N-Nitroso di-propylamine	NDPA
Di-isopropylamine	N-Nitrosodi-isopropylamine	NDIPA
Di-butylamine	N-Nitrosodi-butylamine	NDBA
Ethyl methylamine	N-Nitroso-N-methyl-4-aminobutyric acid	NMEA
4-(methyl amino) butanoic acid	N-Nitroso-N-methyl-4-aminobutyric acid	NMBA

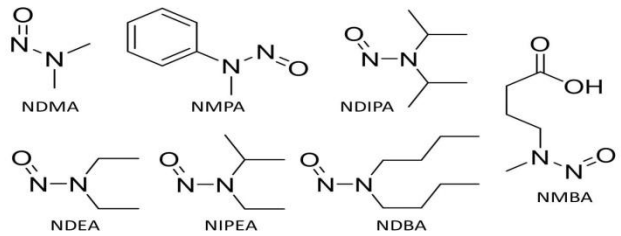


Fig. Chemical Structures of Seven Potential Nitrosamine Impurities in API′s and Drug Products.

Carcinogenic drugs[1,5,13]

Carcinogenic drugs are also known as anticancer drugs. These are the drugs which act by alkylation process &/or by binding tightly to the DNA which frequently causes cancer in experimental animals & it may be carcinogenic in mans. Certain anticancer drugs also act as co-carcinogens in experimental systems and increase the tumorigenicity of chemical carcinogens. In short, Carcinogens or Carcinogenic drugs are the chemicals or substances which are able to produce cancer or to cause cancer.

Classification of carcinogenic agents[1,3,13]

The International Agency for Research on Cancer (IARC) has devised a system of categories for evaluation of carcinogenicity of an agent in human beings. An agent is classified based on scientific evidence derived from experimental animal studies and humans and other relevant data.

Table 2: IARC Classification of carcinogenic drugs.

Groups	Description
Group 1	Carcinogenic to humans
Group 2 A	Probably carcinogenic to humans
Group 2B	Possibly carcinogenic to humans
Group 3	Drugs which are not classifiable as to its carcinogenicity to humans
Group 4	Probably not carcinogenic to humans

Hazard assessment includes an initial analysis of actual and potential impurities by literature searches and conducting database for carcinogenicity and bacterial mutagenicity data for its classification as class 1, 2 or 5 according to given in below table.[1,3]

Table 3: Impurity Classification according to Mutagenic and Carcinogenic potential.

Class	Definition
1	Impurities with known mutagenic carcinogens.
2	Impurities like known mutagens with unknown carcinogenic potential (bacterial mutagenicity (+ve) no rodent carcinogenicity data).
3	Impurities having altering structure unrelated to the structure of the drug substance and with absence of mutagenicity data.
4	Impurities having altering structure, same alert in drug substance or compounds which are related with drug substance. (Eg. Process intermediates) which have been tested and are non-mutagenic.
5	Impurities do not having structural alert, or alerting structure with adequate data to demonstrate lack of carcinogenicity or mutagenicity.

Toxicity[6,7,13,25]

N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) belongs to `control of concern′ which is a group of highly potent mutagenic carcinogens that have been classified by WHO′s International Agency for Research on Cancer as probably human carcinogens. Along with the potency of these impurities, there is still low risk of nitrosamine impurities at the level found could cause cancer in humans.

Impurity specific toxicity data available for NDMA & NDEA is limited. Based on this info, interim acceptable intakes for nitroso impurities have already been adopted by major regulators are listed in below table.

NDIPA, NEIPA and NMBA have similarities in their structure and due to their similarities, they are considered by International Regulators for exhibiting a toxicological profile like NDMA and NDEA.

Table 4: Interim allowable daily intake limit for selection of N-nitrosamine Impurity.[1,3,13]

Name of Impurity	Chemical Name	Allowable Daily Intake(ng/day)
NDMA	N-nitrosodimethylamine	96.0
NDEA	N-nitrosodiethylamine	26.5
NMBA	N-nitroso-N-methyl-4-amino butyric acid	96.0
DIPNA	N-nitrosodiisopropylamine	26.5
EIPNA	N-nitrosoethylisopropylamine	26.5
MeNP	1-Methyl-4-nitrosopiperazine	26.5
NDBA	n-nitrosodi-n-butylamine	26.5
NMPA	N-nitrosomethylphenylamine	34.3

The limits are calculated based on harmonic mean TD_{50} value which is derived from carcinogenic potency database (CPDB) and these limits are derived using Structure-Activity-Relationship (SAR)/read-across approach.

Analytical methods

To determine nitroso impurities, it was a challenging step to develop analytical technique due to very low levels of impurities present in complex matrices. The developed methods needs to be validated and must comply to cGMP requirements. The extension of measure to be detected.

Carcinogenic impurities found in pharmaceutical drugs

Sr. No.	Name of Impurity	Class of Impurity	Impurity found in drug	Detection Method
1	NDMA(N-nitrosodimethylamine)	NA	Ranitidine, Valsartan, Metformin	GC-MS/MS, LC-MS, LC-HRMS, Rapid Fire MS/MS, HPLC
2	NDEA(N-nitrosodiethylamine)	NA	Valsartan, Irbesartan	GC-MS/MS, LC-HRMS, Rapid Fire MS/MS
3	NMBA(N-nitroso-N-methyl-4-aminobutyric acid)	NA	Losartan Potassium	LC-HRMS, Rapid Fire MS/MS
4	MNP(1-methyl-4-nitrosopiperazine)	NA	Rifampin	LC-ESI-HRMS
5	CPNP(1-cyclopentyl-4-nitrosopiperazine)	NA	Rifapentine	LC-ESI HRMS
6	DMF (Dimethylformamide)	Solvent	Valsartan	GC-MS
7	EMS (Ethyl Methanesulphonate)	Sulphonate Ester	Viracept	GC-MS

Review of manufacturing process[17,18,19]

The European Medicines Agency (EMA) has issued one template for marketing authorization holders to use when filing results of product testing for nitrosamine contamination.[15,17,24]

The steps required by the manufacturer to control the assessment of nitrosamine in human medicinal products are as follows[27]

Step I	Risk Evaluation	As per ICH Q9 and ICH M7 guidelines within 6 months.
Step II	Confirmatory testing	Confirmatory testing of all the concerned drug products should be concluded at the latest within 3 yrs of publication of the notification or otherwise justified.
Step III	Changes to the marketing authorization	If there is a risk to public health, the competent authorities must be informed immediately.

All steps must be completed within 3 Yrs in a prioritized manner.

Recent approaches to decrease nitrosamine impurities from pharmaceutical Drugs and Drug products[1]

All amines with nitrosating agents like fuming nitric acid, N_2O_4, $NOBF_4$ are considered to be prior in the generation of nitrosamine impurities in the drug substance or drug products. Thus, with the help of following precautions, we can minimize these nitroso impurities in human medicinal products.[1,26]

1) Nitrosamine impurities are formed when nitrites or other nitrosating agents reacts with the secondary or tertiary amines or quaternary ammonium salts are used within the same or different steps of the manufacturing process of drug substances. Thus, avoiding the use of these reagents, we can prevent the Nitrosamine impurity formation.
2) Contaminated raw materials, intermediates and reagents used in manufacturing of drug substance are also the major source of nitrosamine impurities. In presence of traces of nitrites, the degradation product of raw materials and intermediate upon storage may lead to formation of Nitrosamine impurities. Hence, these materials should be properly stored and tested for Nitrosamine impurities.
3) Along with solvent, many of the impurities get purged out. If these solvents are recovered and reused, there is possibility of reintroduction of these impurities in the drug synthesis process. Therefore, the use of recovered solvents must be avoided in the manufacturing process of drug product. In same manner, if we reuse the recovered catalyst, it may contaminate the drug with nitrosamine impurities.
4) If the equipments are not properly cleaned and checked for contamination, then the equipments used for the manufacturing of drug substance may be cross contaminated with Nitrosamine impurities due to previous products. So to overcome this problem, equipments should be properly cleaned and checked for contamination prior to use for manufacturing of new drug product.
5) At various stages of manufacturing, to purge out amines, nitrites and nitrosamine impurities, the manufacturer should modify the process of manufacturing. To detect and control Nitrosamine impurities in intermediate or drug substances, the control strategies should be implemented.
6) The manufacturer of drug substances should test and check the carryover of Nitrosamine impurities in various intermediate stages and if the impurities are present, it should be controlled with the proper limit.
7) If the Nitrosamine impurity is found to be above the LOQ, the manufacturer should develop a strategy which helps in ensuring the nitrosamine level remains within the Acceptable Intake(AI) limit. The control strategy must include specification limit for the identified Nitrosamine. When the introduction of nitrosamine is inherent due to API structure, the API ROS, or the manufacturing process of API or drug product.
8) If drug product batches having unacceptable level of Nitrosamine impurities have already in distribution, the drug product manufacturer should contact to FDA so the agency can determine the regulatory action for the specific drug products. If any drug product batch

found to contain the Nitrosamine impurities at or above the recommended AI should not be released by the Drug Product Manufacturer for the distribution. Manufacturer should contact the Agency if a recall is initiated.

9) It is necessary to heat mixtures containing N-nitroso-pendimethalin in Pendimethalin to a temperature greater than or equal to 120° C. and hold the Pendimethalin at that temperature for a period of time sufficient to breakdown the N-nitroso-pendimethalin present in the mixture. It is advantageous to remove volatile breakdown products from the mixture.[28]
10) Manufacturers can find further information about the identification, analysis, and management of quality risks in the ICH guidance for industry Q9 Quality Risk Management (June 2006). Manufacturers of APIs and pharmaceutical products should take the necessary precautions to avoid include amounts of nitrosamine contaminants in their goods that are too high.[29]

CONCLUSION[1,29]

Nitrosamine impurities which are highly carcinogenic and mutagenic need to limit it to the acceptable limit in drug substances and pharmaceutical drug products. The potential source for Nitrosamine impurities like raw material, reagent, catalyst, solvents used and cross-contamination which are used in manufacturing process should be identified to control its presence in drug substances. Medicine Regulatory Authorities like FDA, EMA, TGA and Health Canada have published some public notices to guide the drug manufacturer to control and limit these nitrosamine impurities to acceptable intake level. These regulatory Authorities also issued a template for Marketing Authorities for assessment of these impurities in human medicinal products. Nitrosamine impurity formation can be avoided by selecting proper reagent, catalyst and solvents in the process of manufacturing of drug substances. The analytical method for the Determination and Quantification of Nitrosamine impurities is by GC or LC using Mass Spectroscopy.

These methods should be well developed and well established and validated as per ICH guidelines to determine these impurities upto very low levels.

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