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Review

Nitrosated Active Pharmaceutical Ingredients – Lessons Learned?

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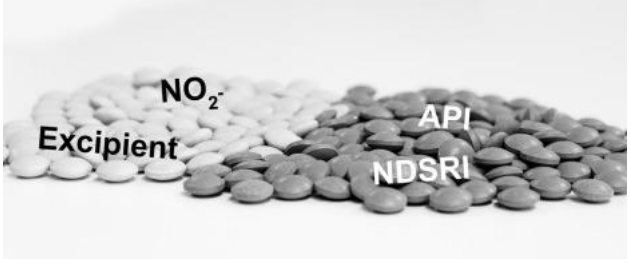
Abstract

The occurrence of *N*-nitrosodialkylamines in active pharmaceutical ingredients (APIs) and drug products in the last years was a kind of eye opener with regard to quality of drugs. We became aware of the fact that quality control tests described in the international pharmacopoeias might not be sufficient. The *N*-nitrosodialkylamines found were neither so-called (structurally) related substances, nor residual solvents or heavy metals; hence they were not limited by a compendial test, but by the ICH guideline M7 of mutagenic impurities. Additionally, nitrosamine drug-substance-related impurities (NDSRIs) were detected, mostly within the process of risk assessment required by regulatory authorities. Here, the APIs containing a vulnerable amino moiety had reacted with nitrites being a contaminant of an excipient. This review deals with the formation, toxicity, and mitigation of NDSRISs.

Graphical abstract



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Introduction

N-Nitrosamines are potentially carcinogenic and mutagenic often at a very low concentration level. They are controlled by the guidelines of the “International Council for harmonisation of Technical Requirements for Pharmaceuticals for Human Use” ICH M7 on mutagenic compounds. They occur upon a reaction between an amine, best a secondary one, and a nitrosating agent, mostly summarized as nitrite. Regarding drugs, the amines can be the

drug itself, a synthesis intermediate, which might be a potential impurity, as well as amine impurities of solvents, such as the high boiling point amide solvents *N*-dimethylformamide, *N*-methylpyrrolidone, and *N*-dimethylacetamide. The nitrites can be synthesis reagents, they might by formed by degradation of a drug or an excipient, e.g. oxidation of amines by means of peroxides and hydrogen peroxide, or an impurity of the excipient as will be discussed later.[1,2]

In 2018, *N*-nitrosodimethylamine (NDMA), which is formed by the reaction of a dimethylamine and nitrite, was first found in Valsartan. Fastly, it became clear that NDMA was an unexpected by-product of one step of the synthesis pathway, in which the tetrazolyl ring of the sartans is established. This was due to a change in synthesis, i.e. the usage of sodium azide, DMF and $NaNO_2$ (the latter to destroy the excess of the NaN_3), instead of the formerly used tin azide reagent. DMF, which is used in the new procedure, easily releases dimethylamine. The latter reacted with $NaNO_2$ and to formed NDMA. Since the variation of the production was not reported to the regulatory authorities, the monographs of the international pharmacopoeias did not cover the nitrosamine. Beside the development of appropriate LC/MS and GC/MS analysis methods, which are sufficiently sensitive to limit even low amounts of the nitrosamine, regulatory authorities as well as scientists all over the world started to look for nitrosamines in other active pharmaceutical ingredients (APIs) and drug products. In rapid succession, NDMA and other related nitrosamines, such as *N*-nitrosodiethylamine, *N*-nitrosoethyl-isopropylamine, *N*-nitrosodiisopropylamine, and *N*-nitroso-*N*-methylamino butyric acid, were found in all tetrazolyl-containing sartans, which was more or less expected.[e.g.3] Moreover, *N*-nitrosamines were also found in other APIs. 1-Nitroso-4-methyl piperazine (NMP) was detected in Rifampicin and might originate either from the synthesis or upon storage.[4,5] The same holds true for the corresponding 1-cyclopentyl-4-nitrosopiperazine (CPNP) in Rifapentine.[6] The antidiabetic API Pioglitazone also contains NDMA, albeit in a very small amount.[7] It was well-known that Ranitidine contains NDMA, which is due to a kind of self-degradation[8] upon storage. The occurrence of the very small amounts of NDMA in nizatidine might be explained similarly.[9] Moreover, high amounts of *N*-nitrosomorpholine were found in molsidomine tablets, because a synthesis reagent - methane sulfonic acid - was contaminated with the nitrite.[10] Whereas in the aforementioned cases the nitrosamines were related to the API itself and its synthesis or storage, two root causes of NDMA in metformin could be identified: the dimethylamine, being a starting material of the metformin synthesis and simultaneously be discussed as a degradation product by oxidation, has reacted with a nitrite coming from an excipient, e.g. hypromellose and povidone. Consequently, NDMA was found in the final drug product only and not in the API.11, 12, 13, 14 Recently, nitrosated APIs (NDSRIs) were detected in several drug products, because the drug itself contains an amino function and the excipients used the nitrite. The NDSRIs are in the focus of this review with regard to formation, toxicity, and mitigation.

Even though it is well-known since more than 10 years that excipients contain reactive impurities,[15] the regulatory authorities did not draw obvious conclusions from this fact. The quality of excipients is evaluated in the international pharmacopoeias by the determination of bulk parameters, such as acid value, iodine value, ester value, hydroxyl value, saponification value,[16] and others, which characterize the composition of the excipient products, mostly of natural origin, and their derivatives rather than providing information about the purity of the excipient. Only the peroxide value is related to degradation, i.e. the autoxidation of fatty acid moieties, giving hydroperoxides which are further degraded to reactive aldehydes, and carboxylic acids. All these tests are related to the structures of the excipients, which are often fatty acids, sorbates, macrogols, sugars, and derivatives thereof.

However, as mentioned above, many excipients are natural products and hence a mixture of compounds.[17] They do not only contain the main ingredients, but also other salts such as nitrites and nitrates.[15] Therefore, a consortium of scientists from Pharmaceutical Industries under the umbrella of Lhasa Limited, a non-profit organization, recently took the proactive initiative to collect data of the nitrite content in excipients commonly used in the drug formulation process.[2] The concentration of nitrites in drugs products is a key piece of information for the risk assessment for nitrosamine formation, because a very high percentage of APIs contain a vulnerable amine, which can be converted to a nitrosamine in presence of nitrites (see below).

The Lhasa Limited consortium agreed on two validated methods for the determination of the nitrite concentration, being an ion chromatography using conductivity detection and the Griess method of nitrite detection coupled with liquid chromatography employing a UV detection. With these data they can provide high-quality information which are the basis of the platform being established. Moreover, since nitrite and nitrate are a redox pair and a reduction of nitrate to nitrite is possible, the consortium also collected nitrate content data. The members of the consortium perform the testing after each analysis laboratory has met the validation criteria. This is an extremely important

requirement in order to avoid false positive results, which are often published in the literature.[18] The anonymous data then enter the platform at Lhasa Limited, which can be accessed by the members.

Meantime (January 2023), the Excipient Database "Vne" (Vitic nitrites in excipients) contains of about 804 "data points" on some 85 excipients from different lots.[19] The content of nitrites in an excipient of different manufacturers was found to be different, due to diverse source materials and processing.[2,12] This is not astonishing, but indicates that each and every batch of an excipient has to be tested for nitrites if the variation observed is found to be significant to nitrosamine formation risk.

Among the excipients studied in 2021, especially crospovidone and magnesium stearate contained substantial amounts of nitrite.[2] The sum of nitrite in a final drug product depends on both the portion of the nitrite in the excipient and the amount of the excipient in the formulation. E.g., since an oral formulation does not contain a lot of magnesium stearate, it does not contribute significantly to the sum of nitrite in the formulation; in contrast to crospovidone whose nitrite content will govern the final nitrite concentration. Additionally, the amount of API present in a tablet has to be considered because most likely, the ratio of API to nitrite-containing excipient will determine the probability of the nitrosamine formation. Moreover, the particle size of the API as well as its molecular lattice properties - crystalline or amorphous - play a decisive role: the smaller the particles, the higher is the surface area and the chance of nitrosamine formation. However, no official data are currently available for the likelihood of the reaction, which has to take place in the solid state. Moreover, the water content may support the *N*-nitrosamine formation. The nitrosation can also take place upon both the formulation because the mixture of excipients and APIs might be warmed up during this procedure, and upon storage, which can be years. Of course, the nitrosamine formation is also dependent on the fact whether the vulnerable amine is used as a free base or acid salt.

Of note, the manufacturers do not only produce their excipients for the highly regulated Pharmaceutical Industries, but also for the food and cosmetic industries to name only a few. The manufacturer may synthesize the excipients from smaller building blocks or derive them from natural sources such as botanicals or mines. Other manufacturers may produce simple mixtures of excipients purchased from other producers.[20] It has to be stressed that excipient manufacturers and suppliers are not necessarily under specific regulatory requirements and the quality requirements of the various industrial branches might be different. In other words, manufacturers of excipients are not obliged to test their products for nitrites or nitrosamines. According to the position paper of the International Pharmaceutical Excipients Council (IPEC), they may voluntarily, but not necessarily provide corresponding data.[20]

This makes quality assurance difficult, especially against the background that the fraction of excipients used for pharmaceutical purposes is rather small and the suppliers are often not economically dependent on the pharmaceutical business. Hence, it might be difficult to obtain excipients of the required quality for drug formulation on the market. Taken together, the aforementioned Vne platform fills a gap of information important for all drug product manufacturer and Marketing Authorization Holders (MAHs), who have to perform a nitrosamine risk assessment (see below).
In the aforementioned cases the amine source was mostly dimethylamine, e.g. released from the solvent dimethylformamide or the API ranitidine, or a starting product. However, a large portion of drugs contains secondary and tertiary amines, which can easily be nitrosated by nitrites from the excipients. As early as 2003, Adachi et al. reported the occurrence of *N*-nitrosofenfluramine in a Chinese weight-loss dietary supplement.[21] More recently, the nitrosation of the vulnerable amine function has been observed for the following drug (cf. Fig. 1):

In July 2021, *N*-nitroso-Vareniclin was found in Champix® (Vareniclin tartrate)[22]; the smoking cessation drug was withdrawn from the market, because the amount found was above the daily limit.[23]

In March 2022, *N*-nitroso-Quinapril was detected in antihypertensive drug Accuzide®, consisting of Quinapril hydrochloride and Hydrochlorothiazide. This drug was also voluntarily recalled from the market by Pfizer.[24] However, the withdrawal is not critical, because the drug can easily be replaced by other ACE inhibitors, but only after consultation of the medical doctor.

In the same month, propranolol nitrosamine was reported by Pfizer (Inderal-LA® capsules). The government of Canada wants to keep the prescription drug on the market, because there is no other provider.[25]

Again, in March 2022, Sandoz withdrew Orphenadrine citrate extended-release tablets, a skeletal muscle relaxant, from the market because 13 batches contained NO—Orphenadrine exceeding the daily limit of 26.5 ng. The drug was shipped to customers between August 2019 and April 2021.[26]

In May 2022, the antiparkinsonian drug Rasagiline was withdrawn by Heumann due to the occurrence of nitrosation.[27]

This is a small collection of APIs being reported to as NDSRIs in the last two years. For sure this number will increase, and because of the currently running risk assessment, more NDSRIs will be found to be present in drugs. In all cases the excipients seem to be the root source of nitrite, necessary for nitrosation of the API. The group of Parr has studied the potential of nitrosation of some 70 drugs and were able to prove a nitrosation for some 40 drugs experimentally,[28] impressively indicating the risk of the NDSRIs formation. These findings were confirmed by a substructure-based screening approach, performed by Kao et al.,[29] who uncovered more than 190 drug substances with a theoretical likeliness of the formation of a nitrosamine by employing the open-source software DataWarrior. Some 140 were not reported before. A similar, even more comprehensive *in silico* study considering more than 12,000 compounds was performed by Schlingemann et al.[30] and revealed a very high prevalence of the nitrosamines. Some 40 percent of the APIs and 30 percent of the API impurities have the potential to form nitrosamines. The workflow applied identified mostly API-related nitrosamine (NDSRIs). Among them are beta-adrenoreceptor blockers and sympathomimetics, ACE inhibitors, SNRIs, tricyclic antidepressants, triptans, and thienopyridines such as clopidogrel.
However, the EMA is aware of the fact that there are far more drugs which are “at higher risk of formation of active substance derived nitrosamine impurities”.[31] In October 2022, the Questions and Answers document of the CMDh/EMA, Rev. 12, already provides a couple of additional NDSRIs - including an acceptable daily intake (AI), i. e. the NO derivatives of Rifampicin (26.5 ng), Varenicline (37.0 ng), Methylphenidate (1300 ng), Rasagiline (18 ng), Sitagliptin (37 ng), Amitriptyline and Nortriptyline (8 ng), Dabigatran (18 ng), and Duloxetine (100 ng). Of note, the limits given are only valid if a single *N*-nitrosamine is present and they are partially derived from structure-activity relationships or class specific threshold of theoretical concern (TTC). This points to the fact that the evaluation of the toxicity of the *N*-nitrosamines is an ongoing yet just started process. The current nitrosamine limits for the Acceptable Intake (AI) are calculated from substance-specific carcinogenicity data, which might have been extrapolated from rodent TD_{50} values.[32,33] However, we have to keep in mind that more than one nitrosamine might be “eaten” via food or drug intake. In this case “the total intake of all identified nitrosamines should not exceed the most potent nitrosamine”, and “the total risk level of the sum of all detected N-nitrosamines should not exceed a 1 in a 100,000 lifetime risk.”[33] This sounds very theoretical, because do we really know all *N*-nitrosamines consumed per day regarding both amount and type, even if we consider drugs only?

In order to set limits for the nitrosamines with unknown carcinogenicity, which however are regarded to as a “cohort-of-concern” by the ICH guideline M7 (R1) “Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk”,[34] the toxicity of nitrosamines needs to be determined. The NDSRIs might not necessarily be detected by the Ames test, because many NDSRIs might be minor or non-mutagenic. This prompted Lhasa Limited to set up the platform Vcn Vitic of structurally-complex (API-like) nitrosamines, in order to be able to derive structure-activity (toxicity) relationships based on results of the Ames testing and to predict toxicity.[35]

Why are nitrosamine mutagenic? The toxification of the nitrosamines occurs upon biotransformation. It starts with the hydroxylation of the α-carbon by means of a cytochrome P450 enzyme (e.g. 2E1, 1A6, 2C9, 2C19, 2D6, 2A4). This step might be sterically negatively influenced by substituents at this atom as the active side of the enzyme can be small. As can be seen in Fig. 2 for NDMA, the hydroxylation is followed by the release of an aldehyde, OH^- or water, depending on the pH. The remaining highly reactive diazonium ion and finally carbo cation can form DNA adducts. This alkylation reaction, being a nucleophilic substitution, might be influenced by steric hinderance in case the substituents of the initial *N*-nitrosamine are large.

Cross and Ponting[36] studied more than 350 dialkyl *N*-nitrosamines, of which more than 200 are characterized by carcinogenicity data (TD_{50} values) and some 280 by Ames test data. In general, structure-activity (toxicity) relationships revealed that large *N*-nitrosamines, as is often the case of the NDSRIs, have TD_{50} value covering 4 orders of magnitude and often the mutagenic potency is rather low. This can be explained by the inhibition of the metabolism by the mostly bulky substituent on the α-carbon atom. Furthermore, electron withdrawing groups

attached to the β-carbon atom decrease carcinogenicity potential. However, even though the findings are rational from the chemistry point of view, more experimental toxicology data are needed to validate these first outcomes.

Dobo et al.[37] tried to estimate the AI by organizing nitrosamines, derived from secondary amines, in 13 groups based on the nitrosamine substituents, which is similar to structure-toxicity approach of Cross and Ponting. Since in each group are members of known mutagenicity/toxicity, an AI and TTC might be derived.

Even though this is the best we can do currently because of missing data, we urgently need toxicity data, such as TD_{50} values for rodents, and we need information not only on acute toxicity but also data for long-term toxicity after years of administration of nitrosamines. However, a longitudinal cohort study including more than 780.000 patients who had administered NDMA-contaminated valsartan for many years revealed no increased overall risk of cancer and only a slight increase of hepatic cancer.[38] Mansouri et al., who considered 1.4 million patients treated with NDMA-contaminated valsartan between January 2012 and December 2017, report in their nationwide study (France) the same outcome.[39]

The small molecule *N*-nitrosodialkylamines such as NDMA, NDEA and others, which were found in some APIs, can be detected and quantified by very sensitive LC/MS/MS, GC/MS/MS and GC/MS methods, which were fastly developed, especially within the OMCL network. They are already described in the European Pharmacopoeia in the new general chapter 2.5.42 “N-nitrosamine impurities in active substances”.[40] A large number of related HPLC, SFC and GC separations using mass detection and dealing with the small nitrosamines were published in the last years. Since they are outside the scope of this perspective, no details are given here.

However, the analysis of the more complex NDSRIs might be more difficult, and it would be preferable to have general methods which can be applied to nitrosamines of different structure. Wang et al.[41] suggest a coulometric mass spectrometry (CMS): first, the *N*-nitrosamines have to be reduced by zinc in acidic media to give a hydrazine which is then quantified by CMS. The advantages of this method are that no internal standards are necessary, and that the method is very sensitive and can be applied to many nitrosamines. However, it needs a pre-column derivatization, which required an extensive validation, and CMS is not a method available in each quality assessment laboratory.

Currently the market authorization holders (MAH) have to perform a risk assessment of the manufacturing process for presence of nitrosamines which includes three steps. In step 1, the risk of nitrosamine formation upon production had to be evaluated “on paper”. This had to be done till the end of March 2021 in case of chemically defined drugs and end of July 2021 for biologicals. In step 2, the possible risks found in step 1 have to be experimentally confirmed, the nitrosamines quantified (= confirmatory testing) and the competent authorities have to be informed. The deadline was by 26th September 2022 for chemically defined drugs and will be 1st July 2023 for biologicals. And finally in step 3, in case nitrosamines are present, the production of the APIs or the drug products has to be changed in order to avoid the formation of nitrosamines upon formulation or storage and/or nitrosamine-contaminated APIs have to be further purified. In case of changing the manufacturing process, the regulatory authorities have to be informed. This has to be performed till end of September next year. The entire risk assessment process and the action to be taken are described by the FDA, the EMA and other regulatory authorities.[42,43] The EMA deadlines are given here.

NDSRIs in drug products may be formed upon the formulation process as well as upon storage during the shelf-life. As described before, they often occur, because the excipients used contain nitrites. An obvious solution to the problem seems to be the qualification of the excipient supplier, i.e. the search for nitrites by the aforementioned analytical methods and eventually the search for nitrite-free excipients (of another supplier), which might be difficult due to the fact, that the excipients are used by other industrial branches and the sometimes the market share of the pharmaceutical industries, as has been discussed above.

Another mitigation strategy, to be applied if the drug concomitantly contains of a vulnerable, mostly secondary amine, and the excipient nitrites, is the inhibition of the NDSRIs formation, by e.g. controlling the pH value or by addition of an antioxidant or a primary amine.

Nitrosamines are mainly formed under acidic conditions, where nitrous acidium ions, dinitrogen trioxide and nitrosium ions are present and can act as nitrosating agents.[44] Figure 3 displays the reaction with the NO^+. The reaction is far slower in neutral or basic environment. The addition of sodium carbonate to the formulation mixture might shift the pH value towards a basic milieu and thus avoid the nitrosation of the API. The power of Na_2CO_3

addition upon the tablet formulation has been demonstrated by Jires et al.[1] Even batches spiked with an amine and H_2O_2 did not show substantial nitrosamine contamination in the dosage form when Na_2CO_3 is added.

Making use of the redox pathway by means of antioxidants was shown to effectively prevent the nitrosamine formation, because the nitrosating agents will be converted to the non-nitrosating nitric oxide NO. Nanda et al.[45] have applied the strategy to a model tablet system consisting of 1-phenylpiperidine hydrochloride and 0.57 and 5.7μM of an antioxidants, respectively. They have chosen ascorbic acid, sodium ascorbate and α-tocopherol, because they are regarded by the FDA as inactive ingredients, and caffeic and ferulic acid, as they are frequently present in food. Stressing the tablets at 50 °C and 75% relative humidity for one month resulted in a very efficient inhibition of the nitrosamine formation of mostly up to 80% in presence of the antioxidant, especially when using the higher inhibitor concentration.

Furthermore, Nanda et al.[45] added amino acids, namely histidine, glycine, and lysine, to a solution of the phenylpiperidine at a pH of 3 and 60 °C. Here, the primary amino group consumes the NO^+ by diazotation. Especially, histidine was able to inhibit the nitrosation. From the formulation point of view, it might also be possible to isolate the vulnerable amine, i.e. the API, from the nitrite-containing excipients, e.g. by coating the API or by a bilayer approach. However, this has to be considered in an early stage of drug development, otherwise a change of the approval is necessary.

These are only a few examples of chemical mitigation strategies to prevent the nitrosamine formation, which are obviously very efficient in keeping the nitrosamine levels below the acceptable intake.
Beside the potential mutagenicity/carcinogenicity of the NDSRIs, which seems likely to be not too high, we do not have any information about the pharmacological effect of the nitrosation.

Let us make a wild guess in order to demonstrate possible toxicological problems. In the case a drug product contains only a low amount of a very active drug, which has a vulnerable amine, and which is surrounded by one or more excipients having a high nitrite content, a substantial amount of the API might be nitrosated and only a smaller amount NO-free. If the NDSRIs does not have any pharmacological activity, the treatment of a patient might be in danger, because it is unlikely, that a NDSRIS may bind effectively to the target molecule due to a different distribution of charges. Even though this is a pure intellectual game only, because we neither consider the pH nor the water content, we have to keep this idea in mind and the future will show whether it becomes true.

Finally, it has to be stressed that drug products are not the only source of nitrosamines. Food contains nitrosamines, e.g. fats, oils, fish, sweets, vegetables, meat and here especially fried and broiled meat contain increased nitrosamine levels, as well as tobacco products. Gushgari and Halden recently reported a detailed analysis.[46] These nitrosamines have to be added to the nitrosamine which are possibly contained in drugs administered. Hence it is important to limit the drug nitrosamine content as they may contribute to the overall daily intake on *N*-nitrosamines, especially when a drug is supposed to be administered for a long period of time, such as antihypertensive or antidiabetic drugs. A key step is the development of better quality control of the excipients, which considers not only the composition of the excipients but also their potential impurities. Since the source of the excipients can be rather different, this will be a challenge. Ironically, patients frequently eating broiled meat and/or smoke do not take advantage of the pure APIs.

Currently we can state that the nitrosamine problem is identified, measures are partially taken, and more investigations are initiated. Regulatory authorities, such as the BfArM, have looked closely to the synthesis manually as far as they are publicly available, and some screening and *in silico* studies have been performed to evaluate the risk of *N*-nitrosamine formation.28, 29, 30 However, to guarantee the quality of APIs and drug products, a more in-depth analysis of impurities has to be performed. We should not only look at possible side and starting products of the synthesis. The impurities of solvents, which are often redistilled, and of reagents should be considered as well as the possible reaction products of all impurities. High resolution mass spectrometric techniques, such as qTOF measurements, being well established in the field of proteomics, can help for this targeted analysis. Maybe upon development of a new synthesis pathways, an untargeted analysis might be worthwhile to find “unknown unkowns”. A typical description of such a procedure was recently exemplified for bisoprolol and cetirizine.[47,48] Such analyses might protect us from unexpected impurities, which might be mutagenic in the worst case.

Section snippets

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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