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Controlling Nitrosamine Impurities in Pharmaceutical Formulations by Exploring Use of Spray Dried Expients

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ABSTRACT

N-Nitrosamine risk assessment and control have become an integral part of pharmaceutical drug product development and quality evaluation. Initial reports of nitrosamine contamination were linked with the drug substance and its manufacturing process. Subsequently, the drug product and aspects of the formulation process have shown to be relevant. Regarding specific formulation contributions to nitrosamine content in a product, one risk lies in possible interactions between nitrosating agents, derived from nitrite in excipients, and vulnerable amines, either present as moieties of the active molecule or as impurities / degradants. However, the limited validated information on nitrite levels in excipients available until now has been an obstacle for scientists to assess the risk of nitrosamine formation in pharmaceutical products. This has driven the creation of a database to store and share such validated information. The database, maintained by Lhasa Limited, constitutes a central platform to hold the data donated by the pharmaceutical company members on the nitrite concentrations in common excipients measured with validated analytical procedures. The goal of this data sharing initiative is to provide a common framework to contextualize and estimate the risk posed by presence of nitrites to contribute to the formation of nitrosamines in drug products. The major findings from the database analyses are: (1) average nitrite content and batch to batch variance differ among excipients, (2) for solid dosage forms, the nitrite contribution is dominated by the highest formula % excipients, e.g., the fillers (diluents), which are typically used in larger proportion, and are characterized by low nitrite levels and low variability, leading to an average value of 1 mg/g nitrite in a typical formulation, (3) substantial differences in average nitrite content in batches from different excipient vendors potentially reflecting differences in source materials or processing methods for excipient manufacturing. That final point suggests that future selection of raw materials or processing by excipient manufacturers may help reduce nitrite levels in finished drug product formulations, and thus the overall risk of nitrosamine formation in cases where the product contains vulnerable amines.

Key words: Nitrosamine, Excipient, Pharmaceutical Products, Nitrosating agents

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INTRODUCTION

N-nitrosamines are a class of organic compounds that include examples that are associated with a potential for a significant carcinogenic risk (part of the "cohort of concern" in ICH M7) [1]. Beginning in July 2018, the European Medicines Agency (EMA) reported the recall of several products containing Valsartan due to *N*-nitrosodimethylamine (NDMA) contamination [2]. This initiated investigations by several regulatory agencies resulting in the discovery of N-nitrosamine impurities in sartans and other unrelated compounds [3, 4]. Because the presence of N-nitrosamines in final drug products is a global issue, there have been requests from multiple regulatory agencies for drug product manufacturers to complete risk assessments for the presence or formation of N-nitrosamines in marketed drug products containing chemically-synthesized APIs [5, 6] All pharmaceutical goods, including biologics, vaccines, Advanced Therapeutic Medicinal Products (ATMPs), and recombinant therapeutic proteins, were included in the scope of the nitrosamine risk assessment when the EMA released an Article 5(3)

assessment report in July 2020 [7]. Biologics are now included in the scope of nitrosamine risk evaluations by other regulatory bodies, including Health Canada, Swiss Medic, and ANVISA. The US Food and Drug Administration (FDA) released its nitrosamine recommendations in September 2020 [8]. Any drug product incorporating chemically generated APIs and drug products at risk are covered by the FDA's recommendations.

A nitrosating agent, a secondary or tertiary amine, and the proper circumstances (for example, increased temperatures, acidic conditions, or liquid phase) for the aforementioned to react are what pose the greatest danger for the existence or creation of N-nitrosamines in pharmaceutical goods.

However, epidemiological research have shown less proof of a connection between nitrosamines and carcinogens in people than toxicology literature has. Nitrosamines have been linked to carcinogens in laboratory animals [9, 10, 11]. Based on (1) the permitted daily intake of nitrites/nitrates, (2) the naturally occurring nitrosamine content in foods and reported levels of daily nitrosamine exposure in the diet, and (3) the daily endogenous nitrosamine production, any exposure to nitrites and/or nitrates in an excipient would result in humans being exposed to nitrosamine levels that are significantly lower than the current limits established for food consumption.

The possible sources of nitrosamine contamination and generation during the production of drug products should be evaluated in risk assessments by the maker of the drug product. Although there is very little chance that excipients themselves contain nitrosamine compounds, many excipients do include amounts of nitrites, which under certain circumstances in the drug product can lead to the creation of nitrosamines. The manufacturing process, susceptible amines, and nitrosating agent are the checkpoints identified by the IPEC questionnaires (IPEC-Americas Template, IPEC-Europe Template) that need to be evaluated.

Manufacturers of excipients are many. Large multinational chemical businesses that produce goods for the pharmaceutical sector make up a tiny portion of certain manufacturers' total sales. Other producers are smaller, but they concentrate on industries with strict regulations, such the food, dietary supplement, and pharmaceutical industries. Manufacturers of excipients may obtain their goods from natural sources like mining or botanical sources, while others may create their products through the synthesis of smaller chemical building blocks. Simple mixes of excipients from different excipient producers may also be produced by some excipient manufacturers. In these situations, the excipient producer frequently finds itself in a position similar to that of the Marketing Authorization Holders (MAH), in that they are reliant on other excipient manufacturers for technical and regulatory information. And even excipient producers, who create goods by combining smaller components, will frequently contract out their raw material needs, so they are once again reliant on those raw material suppliers for information.

With such a wide selection of excipient providers, there are several ways to tell clients about goods and address their regulatory and technical inquiries. To reduce the risk in the production of pharmaceutical products, excipient producers might be proactive and provide clients with a declaration that includes all pertinent and accessible information on nitrosamine impurities for an excipient. IPEC surveys can offer the precise information needed for such analyses. To offer the right context for any perceived danger, it is important to put the risk related to the potential existence of nitrosating agents, susceptible amines, or nitrosamines in excipients in perspective. The risk coming from an excipient will depend on the formulation components in the drug product, including the active pharmaceutical ingredient (API), and the amount of the excipient used in the formulation.

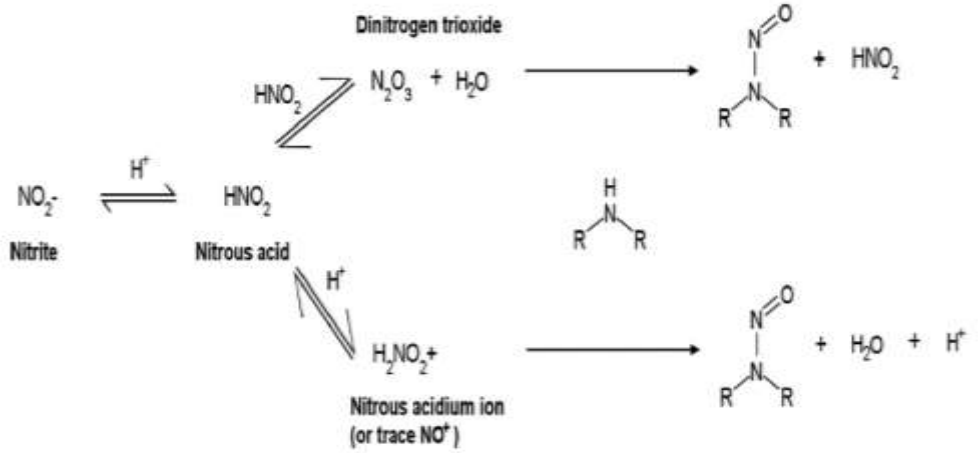

Fig. 1 Example formation of a Nitrosamine from a secondary amine. Depending on conditions, the actual nitrosating agent is the nitrous acidium ion, the nitrosonium ion or dinitrogen trioxide. Tertiary amines are less reactive than secondary amines, therefore the focus here is on secondary amines

IPEC Federation Position

Nitrosating Compounds in Excipients

Nitrites and nitrates have received the most attention due to concerns about nitrosating compounds in excipients. Although neither of these substances is a strong nitrosating substance on its own, it is possible that under specific circumstances they could interact with other substances to form nitrosamines. Under slightly acidic conditions, nitrite can produce the reactive species nitrous anhydride (N_2O_3) [12]. Nitrates can undergo an enzymatic reduction to produce nitrite, which can subsequently produce the reactive nitrous anhydride under acidic circumstances [13].

In the study by Wu et al., nitrates and nitrites were detected in samples of lactose, lactocrystalline cellulose (MCC), sodium starch glycolate (SSG), sodium croscarmellose, hydroxypropyl cellulose (HPC), silicon dioxide, povidone, and crospovidone [14]. Nitrite levels in the excipients were reported to vary from 0.9 ppm (in a sample of HPC) to 285.6 ppm (in a sample of SSG). Nitrate concentrations varied from 3.5 ppm (HPC) and 183.1 ppm (SSG).

Nitrites and nitrates may be produced as a result of processing of excipients, raw materials, and water. Purified or drinkable water can be used in the manufacture of excipients. Potable water typically has nitrite levels below 0.1 ppm and nitrate levels of 10 ppm; as such, it is unlikely to be a source of concern for nitrosating agents [12]. Where purified water is used to make excipients, this likelihood is much lower. Regular testing and reporting of control levels for a variety of chemical moieties, such as nitrite and nitrate monitoring and controls, are usually conducted on purified water and drinking water.

As previously mentioned, nitrites are a frequent precursor for nitrosating compounds that have been found at ppm levels in several excipients [14]. Even though nitrites are present in excipients that are often used at ppm levels, getting rid of nitrites from excipients is not simple. The impact of nitrites in a specific excipient should be carefully assessed for each therapeutic product for any possible harm rather than being removed or limited. Depending on the ingredients used in the drug product formulation will determine if the presence of nitrites in an excipient poses a substantial danger.

So, is it necessary to introduce limits for nitrites in excipients? In general, no, for the following reasons:

- Implementing general limits for nitrites will not alleviate the risk of nitrosamine formation
- The amount of nitrite present in a drug product as a result of an excipient is dependent upon the amount of excipient used in the formulation

Table -1 Data Fields in the Database with their Respective Permitted Values.

Field header	Permitted value
Excipient information	
Excipient Name	Name of excipient (USP) and National Formulary names are preferred
Supplier	Three letter blinded code
Batch	Four digit blinded code
Donated	Version of the database during which the data were entered
Date of manufacture	Date of excipient manufacture (in MMMYYYY)
Date of test	Date of test (in MMMYYYY formate)
Intended use	Multiple use Oral solution/Suspension Solid oral dosage form Sterile injectable
Analytical study method	
Sample preparation	Complete dissolution Suspension Full validation as quantitative method Reduce validation as quantitative method Limit test
Analytical study results for each study	
Nitrite (/Nitrate) value	Report actual value
LOQ	Limit of quantization result

However, a complete risk analysis of the drug product by the MAH or drug product maker may find that the development of nitrosamine is at risk in the presence of nitrites in an excipient (at any quantity). In these

circumstances, the maker of the MAH or medicinal product should work with the excipient provider to reduce any risk (s). In this case, a nitrite limit could be suitable.

Vulnerable Amine Containing Excipients

A drug product may contain vulnerable amines due to the active drug ingredient, its impurities, counterions from pharmaceutical salts, and excipients. Can an excipient directly introduce a nitrosamine or a reactive amine that can convert to a nitrosamine within a drug product? These are the concerns that should be taken into account with regard to excipients. Or are there known excipients that include nitrosamines? The nitrosamine impurity is N-nitrosodiethanolamine, and trolamine (triethanolamine) is an example of an excipient known to contain it. The limit for N-nitrosodiethanolamine in the European Pharmacopeia is set at 24 ppb [15]. Although this specific excipient could have a nitrosamine impurity, there is very little chance that an excipient will introduce a nitrosamine into a medicinal product.

In particular for biologics where the final drug product is typically a solution formulation, amino acid excipients (e.g., L-histidine, L-proline, and L-arginine) and other vulnerable amine containing excipients (e.g., triethanolamine) have the potential to react with nitrosating agents and form nitrosamines within the drug product. Although nitrosation of amino acids is a possibility, these nitroso compounds have not been found to be carcinogenic in the literature [16-20]. Similar to nitrites, the potential risk that may come from a vulnerable amine present in trace amounts in an excipient will depend on the formulation composition and should be evaluated accordingly.

Responsibilities of Excipient Suppliers

As the preceding sections have shown, nitrosating agents and susceptible amines may be present in excipients, but, depending on the location, the MAH or the manufacturer of the medicinal product is responsible for the overall risk assessment for the presence of nitrosamines in a drug product. What could excipient suppliers and manufacturers do to help MAHs with global supply networks in their risk assessments? First, it should be made apparent that excipient producers are not required by law to give risk evaluations of nitrosamines to regulatory bodies. However, it is in the manufacturers' best interests to offer details that would make it easier for people to utilise their excipients safely overall and equally for nitrosamine risk assessments. When levels of nitrites or vulnerable amine impurities are known to be present in an excipient, that information should be provided to the drug product manufacturer, drug product distributor, and/or MAH, by the excipient manufacturer or supplier.

Available Information on Nitrosamines

There was no need for excipient makers to think about the possibility of nitrosamines or nitrosating agents in excipients until recent reports from regulatory agencies that nitrosamines were identified in drug goods. As a result, nitrosamine information is often not readily available from excipient producers. Excipient producers, on the other hand, often have a thorough grasp of the production procedures as well as the fundamental chemistry of the raw materials utilized. Based on this knowledge, it is frequently able to rule out the possibility of nitrosamine production. In conclusion, excipient manufacturers might be able to supply data that might rule out the presence of nitrosamines, nitrosating agents (nitrites), or vulnerable amines, but they often won't have analytical testing information on these chemicals.

Format for Providing Information

For the purpose of informing the risk assessments of the makers of medicinal products, IPEC-Americas and IPEC-Europe have created questionnaire templates that lead an excipient producer through a series of questions concerning a specific excipient and its production process. These templates or other comparable forms have been used by several excipient producers to communicate with pharmaceutical producers. Despite the differences between each template, each one may be utilised as a starting point for giving clients information about excipients. These templates are accessible to the general public on the relevant regional IPEC website (IPEC-Americas Template, IPEC-Europe Template).

Reasonable Expectations / Misperceptions

Over the past few of years, excipient producers have responded to numerous inquiries about nitrosamines and identified a few misconceptions that need to be clarified.

The MAH or the manufacturer of the drug product is exclusively responsible for determining the risk of the drug product, even though excipient manufacturers typically provide data to support such evaluations. Although the MAH is responsible for regulatory oversight, the excipient provider should carefully consider any hazards associated with its excipient. Suppliers of excipients are not legally required to do risk assessments for their products, although they may participate in doing so. Testing is required - certain producers of pharmaceutical products have said that excipient makers should test their excipients to ensure that nitrosamines and nitrites are absent or offer. Manufacturers of excipients are not required to test their products for these compounds. Manufacturers of excipients may voluntarily offer such information in circumstances where it is regarded justified.

The majority of excipient producers are open to providing information on how their goods are made in order to possibly rule out the possibility of nitrosamines. The use of the IPEC questionnaire templates is recommended for excipient producers that wish to give information on this subject.

Responsibilities of Excipient Users

According to regulatory agencies, it is the duty of the drug product maker and/or MAH to do a thorough risk assessment for the finished drug product and to share it with the relevant regulatory authorities as instructed. It is important to carefully consider the sources and procedures that might lead to the production or contaminating of nitrosamines. Although excipients are typically not regarded as a significant risk factor in terms of being a direct source of nitrosamines, it is important to understand any residual levels of nitrites that may be present in an excipient and that may be capable of interacting with other substances, such as an API. In addition, the excipients may include weakly reactive amines, such as amino acids, which may be exposed to trace levels of nitrites and undergo a chemical reaction to produce nitrosamines in the final product. As nitrosamine development would rely on the API and formulation components, it should not be expected that the presence of nitrites or susceptible amines in an excipient will inevitably result in their creation. Additionally, certain reaction circumstances (such as a low pH, a high temperature, etc.) are required for the creation of nitrosamines. To ensure accurate conclusions are drawn, care should be taken when excipients are assessed as a component of the drug product nitrosamine risk assessment. Collaborative discussions between the excipient manufacturer and the drug product manufacturer, drug product distributor, and/or MAH should occur when needed to ensure available excipient information is understood within its proper context. The ultimate goal is to ensure safe and effective medications are available for the treatment of patient ailments.

Path forward / Summary

IPEC continues to keep a close eye on any regulatory changes pertaining to nitrosamines, drug products, and any potential effects on excipients or excipient producers. Nitrosamine production in a drug product is not always caused by the presence of nitrogen-containing components in an excipient. Excipient suppliers should, however, carefully assess the potential risk associated with their excipients to help drug product manufacturers comply with their regulatory obligations to conduct risk assessments for their drug products, as components of excipients may contribute to the formation of nitrosamines in the final drug product. The possibility of nitrosamine development in certain formulations and under particular manufacturing, packing, and storage circumstances can only be ascertained by the drug product manufacturer, distributor, and/or MAH. Therefore, IPEC is in favour of the existing regulatory approach that places the emphasis on the medicinal product rather than on the excipient producers' risk assessments or data.

Future mitigation tactics should concentrate on preventing the production of nitrosamine in pharmaceutical goods. Excipients are currently thought of as risk factors to be taken into account during the risk evaluation of medicinal products. Excipients can be investigated as potential nitrosamine inhibitors in medication formulations, however. Updates on potential methods to lower the danger of nitrosamine contaminants in pharmaceutical goods were recently released by the FDA [22]. The FDA urges drug product producers to investigate cutting-edge methods to lessen the development of nitrosamines in drug goods in the update. This is consistent with the study that Nanda just presented [21]. The inhibition of nitrosamine formation in drug products may be possible with the careful evaluation of suitable inhibitors and excipients. However, for existing approved drug products this likely is a major investment and not a short-term solution.

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