Nitrosamine
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Nitrosamines in pharmaceuticals

Mitigate risk with ascorbic acid or alpha-tocopherol

dsm-firmenich

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Nitrosamines are chemical compounds formed by a reaction between nitrites and certain amines. These substances can be found in a large variety of consumer products – such as processed meats, alcoholic beverages, cosmetics and pharmaceuticals – as well as in air, water and soil. Nitrosamines are known carcinogens, and exposure can lead to increased risk of various cancers, including lung, brain, liver, kidney, bladder, stomach, esophageal, and nasal and sinus.[1] Although these risks have been well known for over 40 years,[2] only recently have nitrosamines been found in common drug products prescribed for high blood pressure (valsartan), type 2 diabetes (metformin) and heartburn (ranitidine). This discovery led to thousands of product recalls, loss of revenue for many companies and, more critically, patients being deprived of vital treatment.[1] Since 2018, drugs containing these compounds or precursors have been regulated, putting nitrosamine mitigation on the agenda of drug developers around the world.[3,4]

This whitepaper discusses the role of nitrite scavengers – such as ascorbic acid and alpha-tocopherol – as one solution to this issue, working as functional excipients to block nitrosation reactions.

What are nitrosamines?

The term 'nitrosamines' refers to a group of compounds that all have a nitroso group (formed of nitrogen and oxygen) bonded to an organic group, with N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) being the most common.

Cancer risk and regulations

More than 90% of the 300 known nitrosamines are carcinogenic,[2] reacting with DNA in a way that can cause mutations, increasing the risk of developing cancer.[1]

Some nitrosamines are therefore classified by the ICH M7 guidelines as belonging to the 'cohort of concern' (CoC), which means that they are considered highly potent mutagenic carcinogens and require strict control to minimize human exposure.

While the FDA does not expect a patient to have an increased cancer risk when exposed to nitrosamine levels at or below the acceptable daily intake limits, long-term exposure to these impurities or exposure above the acceptable daily limit may increase the risk of cancer. The allowed intake of NDMA, for example, is limited to no more than 96 ng per day when taken regularly over a lifetime of 70 years.[5,6]

The requirements developed by various regulatory bodies – including the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) – now guide drug manufacturers on risk assessment and control strategies, which might require product reformulation in some cases.[7,8]

Nitrosamines in pharmaceuticals

Nitrosamines are formed through a chemical reaction between a nitrosating agent and a secondary or tertiary amine, which can occur at any stage of drug manufacturing, making controlling their presence particularly challenging. Additional factors can also influence the risk of nitrosamine formation, such as the chemical structure of the active pharmaceutical ingredient (API), excipients in the formulation, solvents, water, manufacturing processes, and even choices related to packaging and storage.

There are several sources of nitrosamines in drug formulations, but the most common include[9]:

- using sodium nitrite ($NaNO_2$) or other nitrosating agents in the presence of secondary or tertiary amines, or quaternary ammonium salts, either within the same or different steps of the production process;
- using $NaNO_2$ or other nitrosating agents with reagents, solvents or catalysts that degrade into secondary or tertiary amines;
- using contaminated raw materials, starting materials and intermediates supplied by manufacturers whose processes or materials allow nitrosamine formation;
- degradation of starting materials, intermediates and drug substances, particularly in the presence of carryover nitrosating agents;
- the presence of nitrosamine precursors in raw materials, excipients or packaging;
- exposure to nitrogen oxides (NO_x) during production and storage.

Blocking nitrosamine formation

There are various strategies to mitigate the risk of nitrosamine formation, including rigorous qualification programs for new ingredients and maintaining low levels of nitrosating agents in formulations. Optimizing the processing of drug products can help to keep the nitrosamine burden as low as possible, but even this might not completely inhibit these compounds from forming. Nitrosamines that are formed during drug manufacturing may need to be eliminated through additional purification steps if their levels exceed the allowed limit. However, this isn't always possible, and blocking nitrosamine formation during the manufacturing process is a more desirable solution, and one that is proving critical for the long-term control of contamination in pharmaceuticals.

One approach that addresses the multiple nitrosamine generating scenarios listed above is the use of nitrite scavengers. Nitrite scavengers quench reactive nitrites to prevent them becoming nitrosating agents like nitrous acid, blocking the nitrosation reaction. Although there are many known nitrite scavengers, not all are suitable for use in drug products, and only a few are listed on the FDA's inactive ingredient database (IID). There is also a lot of variability between approved nitrite scavengers, such as differences in activity, the environment in which they can work, and their interactions with external compounds.[4]

Alpha-tocopherol and ascorbic acid have shown good results as nitrite scavengers (see Figures 1 and 2) and have both been endorsed by the FDA.[10–12] This is supported by recent literature which concluded that these vitamins are suitable inhibitors of nitrosamine formation, demonstrating greater than 80% inhibition when spiked at 1% levels in solid oral dosage forms.[12] Studies have demonstrated their efficacy while showing no significant effects on the permeation of certain Schedule III drugs, suggesting minimal impact on the bioequivalence of products reformulated with these scavengers.[13,14] Ascorbic acid in particular has extensive literature supporting its use as a nitrite scavenger, demonstrating that it effectively reduces nitrite levels in placebo tablets produced by both direct compression and wet granulation.[15] This effect is dose dependent, showing a greater reduction with higher concentrations, up to one percent. Another study evaluated the impact of ascorbic acid in a standard tablet formulation using a model API.[15] Both a control tablet and one containing 1% ascorbic acid were subjected to two weeks of stress testing under elevated temperature and humidity conditions. The results indicated that ascorbic acid substantially decreased nitrosamine levels in the tablets, with similar findings observed in two other drug models with different formulations and properties.[8,15]

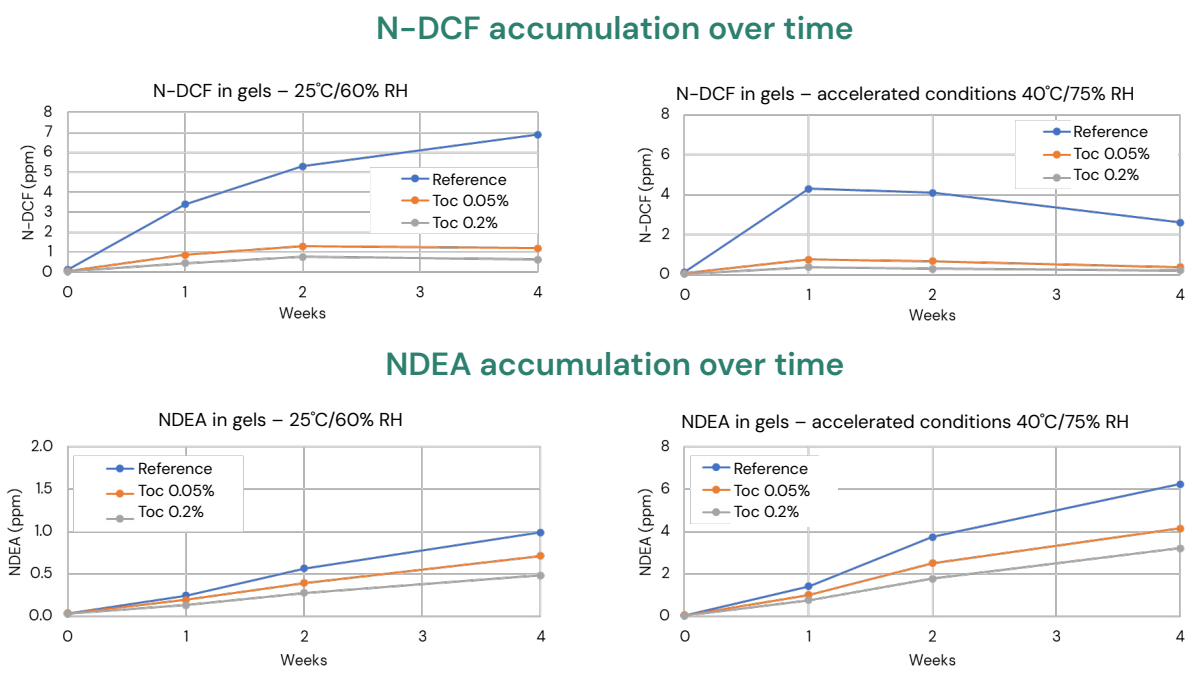

Figure 1: Alpha-tocopherol (Toc) prevents N-nitrosodiclofenac (N-DCF) impurity accumulation and reduces NDEA accumulation in 2% diclofenac sodium gels.

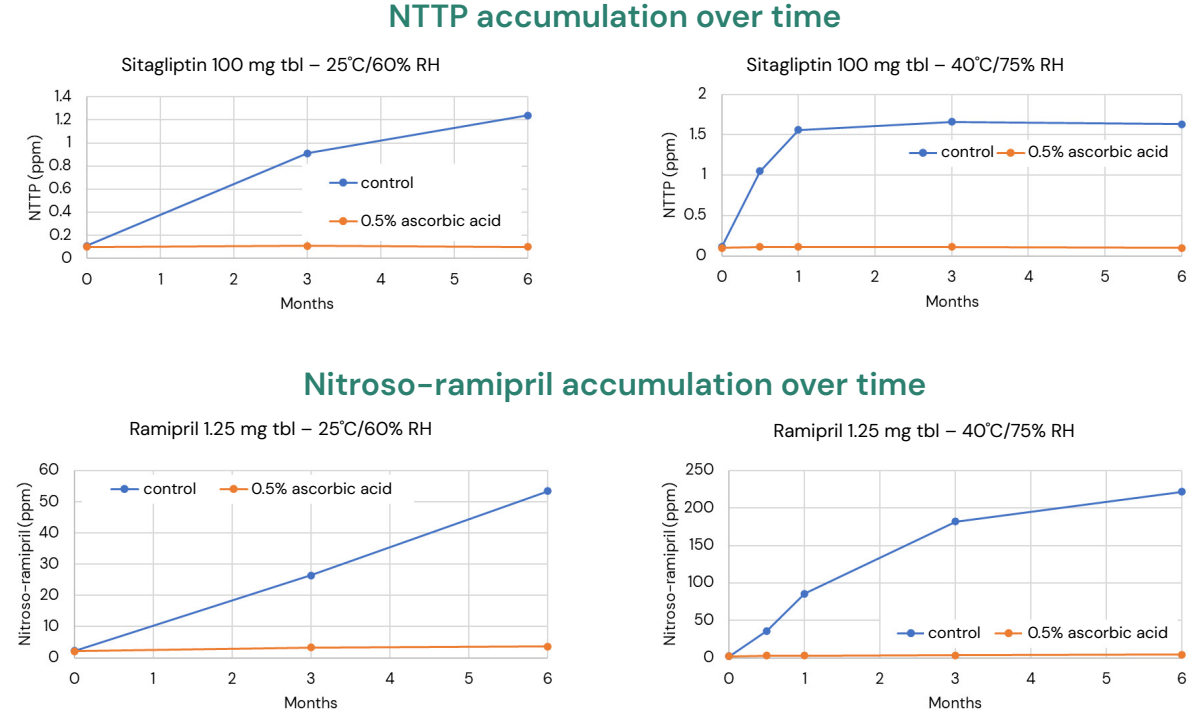

Figure 2: Ascorbic acid prevents nitrosamine accumulation in model drug formulations under stress conditions. Tablets were manufactured via wet granulation and packaged in PVC/PVDC blisters. Results were measured from composite samples prepared from 10 tablets. (NTTP: nitroso-STG-19, tbl: tablet).

Considerations for formulators

Incorporating ascorbic acid, even at concentrations lower than one percent, can play a key role in reducing the risk of nitrosamine formation in drug formulations containing sensitive APIs and residual nitrites. It is obviously crucial to evaluate the quality, purity and grade of any components added to the formulation, as these factors directly influence the safety and efficacy of the final product. Ascorbic acid can cause product discoloration through Maillard-associated reactions, which are known to contribute to this issue. Controlling conditions such as moisture, oxygen availability, pH and the storage environment can help to minimize discoloration.[10] Comprehending to excipients' compositions and their variability is essential to understand how to minimize the chance of adverse reactions. Moreover, the choice of manufacturing method plays a critical role, influencing both nitrosamine formation and the efficiency of ascorbic acid in scavenging nitrites.

A knowledgeable partner

Nitrosamine mitigation in pharmaceutical formulations is still a relatively new issue. Partnering with an experienced and knowledgeable excipient supplier and solution provider can therefore be crucial to effectively manage the risks and ensure the development of safe and compliant drug products. dsm-firmenich offers an industry-leading ingredient portfolio backed by more than 70 years of experience in producing and securing the supply of vitamin APIs and excipients. This is backed by deep regulatory knowledge and product manufacturing that is governed by a wide range of global certification systems, including access to GMP sites, CEPs and DMFs, as well as compliance with multiple pharmacopeia standards. dsm-firmenich's expertise also extends beyond supply, providing the formulation capabilities, scientific know-how and cutting-edge technologies necessary to mitigate the risk of nitrosamines in different dosage forms. By partnering with dsm-firmenich, pharmaceutical companies can confidently navigate the complexities of nitrosamine management, ensuring the safety and compliance of their drug products.

Conclusion

Monitoring and minimizing the presence of nitrosamines in drug products is critical to ensure patient safety. However, this can be challenging, as nitrosamines can form at any point during the manufacturing process. The use of a nitrite scavenger as a functional excipient has proven to be a promising approach to overcome this issue, with common scavengers – such as certain vitamins – known to inhibit nitrosation reactions. Scavengers can therefore play a crucial role in creating safe and effective drug formulations and ensuring compliance with regulatory standards. As an innovation partner in the pharmaceutical industry, dsm-firmenich provides high-quality products and technical guidance to help formulators apply the use of nitrite scavengers effectively in drug products, whether for reformulating existing medicines or creating new ones.

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