PHARMA SOLUTIONS
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Nitrosamine-free pharmaceuticals

Discover the benefits of ascorbic acid and alpha-tocopherol

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The nitrosamine crisis

N-nitroso compounds (NOC) – or more specifically nitrosamines – are chemical contaminants, commonly found in the air, water, soil, foods, beverages and pharmaceuticals. They first became well-known almost 40 years ago when they were identified as being present in foods treated with sodium nitrite – like bacon, cheese, cured meats and fish. However, nitrosamines have recently become a focus in the pharmaceutical industry too following their discovery in common drug products prescribed for high blood pressure (valsartan), type 2 diabetes (metformin) and heartburn (ranitidine).

Evidence suggests that more than 90% of 300+ nitrosamines are carcinogenic – that is they can react with DNA to potentially cause mutations which increase the risk of developing cancer.[1,2] As such, some nitrosamines – depending on the compound – are classified by the ICH M7 as Cohort of Concern (CoC), which means they are considered highly potent mutagenic carcinogens and require strict control to minimize human exposure. The International Agency for Research on Cancer (IARC) also categorizes nitrosamines as 'probably carcinogenic to humans'.

The crisis in the pharmaceutical market has caused thousands of drug product recalls, significant revenue losses and reputational damage – not to mention the temporary withdrawal of treatment for many patients globally. This has made nitrosamine mitigation a critical priority for global agencies to address and an important focus for drug developers across the world.

What are N-nitrosamines?

The term 'nitrosamines' refers to a family of compounds sharing a general structure that includes a nitroso (nitrogen and oxygen) group attached to an organic group. The most common nitrosamines are N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA). Many compounds in this family have been shown to be carcinogenic to humans, though there is little cancer risk at the levels present in food and beverage products.

Navigating new regulations

The maximum acceptable intake of NDMA should not exceed 96 ng/day when taken over a lifetime – that is approximately 70 years.

While there is a very low risk that nitrosamine impurities could cause cancer at the levels found in drug products, individuals may be at increased risk if exposed to nitrosamine impurities at above acceptable levels or over long periods of time.

To protect patient health, drug manufacturers now have a legal obligation to perform a thorough risk assessment and, where necessary, implement an appropriate control strategy, which might include reformulation. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have introduced legal obligation and set stringent deadlines, by which drug manufacturers are to present their risk mitigation plans for chemical medicines and biological medicines.

Nitrosamine formation in pharmaceuticals

Nitrosamines, like NDMA and NDEA, are formed when a vulnerable amine react, forming a N-nitrosamine impurity. Consequently, nitrosamine contamination can happen across the supply chain and there are a number of possible risk factors to consider.

Sources of nitrosamine contamination include, but are not limited to:

- The use of sodium nitrite ($NaNO_2$), or other nitrosating agents, in the presence of secondary amines, tertiary amines or quaternary ammonium salts within the same or different process steps
- The use of $NaNO_2$, or other nitrosating agents, in combination with reagents, solvents and catalysts, which are susceptible to degradation to secondary or tertiary amines
- Contaminated raw materials, starting materials and intermediates provided by suppliers that use processes or raw materials which may allow nitrosamine formation
- Degradation processes of starting materials, intermediates and drug substances, including those induced by inherent reactivity in combination with carry-over of $NaNO_2$ or other nitrosating agents – this could happen during finished product formulation or storage
- The presence of nitrosamine precursors in raw materials and excipients, or even packaging
- Any contact with nitrogen oxides (NO_x) during the production and storage stages – a widely underestimated risk for nitrosamine development.

Nitrosamine formation in drug products

1. Nitrite ions transform into nitrosating agents such as N_2O_3 or NO+, especially under acidic conditions
2. Even if less likely also quaternary[5]
3. Nitrosamines are formed

Which drugs are at risk?

Any active substance or ingredient whose structure comprises secondary, tertiary amines or tertiary ammonium salts is at risk of nitrosamine formation, as are drugs where the active is stabilized by buffers containing tertiary or quaternary amines. Drug products where any excipient contains secondary or tertiary amines, or quaternary ammonium salts, are also at risk.

Mitigating nitrosamine formation: the benefits of ascorbic acid and alpha-tocopherol

The basic requirement is to keep nitrosamine burden as low as possible by optimizing the processing of drug products, but even this might not completely inhibit nitrosamines from forming.

In this case, nitrosamines that are formed during drug substance processing still need to be purged in subsequent steps or additional purification steps. Importantly, nitrosamines formed in the drug product cannot always be readily purged.

For these reasons, manufacturers may look to block nitrosamine formation wherever possible in the drug manufacturing process and final drug product as an extra safety measure. Blocking the formation of nitrosamines is critical for the long-term control of impurity contamination in pharmaceuticals.

The acceptable intake for newly emerging nitrosamine impurities according to current EU regulatory guidance is 18 ng/day[3]. US regulatory guidance states 26.5 ng/day[4].

A proven solution

An approach recommended by the FDA is the addition of specific antioxidants to formulations as nitrosamine formation inhibitors – like ascorbic acid (vitamin C) or alpha-tocopherol (vitamin E).[4]

One study found that ascorbic acid and alpha-tocopherol demonstrated greater than 80% inhibition when spiked at 1% levels in solid oral dosage forms.[5] By blocking the formation of nitrosamine impurities, both ascorbic acid and alpha-tocopherol keep nitrosamine levels below the acceptable intake limits, making drugs safe for human use. In addition, both antioxidants bring other benefits – like acting as stabilizers in the finished drug product formulation. They can also be used at high levels without safety concerns. However, care should be taken to add only necessary amounts in order to avoid Maillard reaction with reactive substances, if present in the formulation.

1. Ascorbic acid: a well-known antioxidant that reacts with nitrosating agents such as N_2O_3 at high rates, thus disarming the agent
2. Alpha-tocopherol: can be used to replenish ascorbic acid
3. Ascorbic acid + alpha-tocopherol: combining both ingredients may offer potent antioxidant activity

Ascorbic acid and alpha-tocopherol offer developers **reliable and safe** opportunities to redesign their pharmaceuticals, or innovate new drugs, without the risk of nitrosamine contamination:

- Efficient nitrosamine inhibition
- Act as stabilizers in the finished drug formulation

Partner with DSM to address nitrosamine risk mitigation with confidence

We understand that meeting new regulatory requirements concerning nitrosamine formation in drug products can come with unique and complex challenges. This takes more than ingredients; **it takes a partner**.

As a purpose-led innovation partner in the pharmaceutical industry, DSM can help you implement a proven mitigation strategy by providing the technical guidance you need to reformulate existing products or develop new, risk-free pharmaceuticals. As well as providing customers with high-quality ascorbic acid or alpha-tocopherol excipients – and the knowledge to formulate with these ingredients – our broad experience in nitrosamine assessment is supported by strong expertise in chemistry and toxicology.

Partner with DSM

Industry leading ingredient portfolio

DSM has more than 70 years of experience in producing and securing the supply of vitamin APIs and excipients.

Regulatory insight

Our excipient production is governed by a wide range of global certification systems to support the success of your pharmaceutical solutions, including access to GMP, CEPs, DMFs and compliance with multiple pharmacopeia.

Formulation and scientific expertise

We have the formulation capabilities, scientific know-how and cutting-edge technologies you need to mitigate the risk of nitrosamines in your oral solid, semisolid, liquid or injectable formulations.

Together, we can ensure that your pharmaceutical products are fit for human use.

Learn more about our quality ingredients and expert services:

Talk to an expert

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5. Nanda et al. Inhibition of N-nitrosamine formation in drug products: a model study. J Pharm Sci., vol. 110, no. 12, pg. 3773-3775.