

NITROSAMINE MITIGATION WITHOUT REFORMULATION: AN INNOVATIVE STRATEGY

Introduction

Over the next decade, NDSRIs (Nitrosamine Drug Substance Related Impurities) could easily become the sweeping issue for the pharmaceutical industry, broadly affecting drug safety, quality, profitability, and supply.

The FDA has confirmed August 1, 2025, as the deadline to conclude confirmatory testing for products with a risk of NDSRI formation and submit necessary mitigation proposals in order to comply with nitrosamine regulations. Regulatory limits, especially those concerning NDSRIs, have the industry moving quickly to define the right way to mitigate the risk of nitrosamine formation. Every drug product faces different challenges as it relates to nitrosamine risk.

For susceptible drugs, decisive action is needed to ensure compliance with US FDA and EMA regulations. To keep their drugs safe and assure success, manufacturers and applicants must have a full understanding of all risk mitigating methods and tools for controlling nitrosamine impurity formation.

The Challenge

Drug reformulation via excipient adjustment can greatly reduce nitrosamine formation in many products, but it can sometimes introduce other challenges.

Due to the bioequivalence studies required for reformulation, the path to SUPAC (Scale-Up and Post-Approval Changes) approval can be costly and time-consuming. Further, adding excipients that preferentially react with nitrite before nitrosation occurs may cause unexpected and unacceptable side reactions like product discoloration, malodor, off flavor, chemical incompatibility, new or increased degradants, and changes to bioavailability.

The Solution

A robust supplemental solution for products that can't fully benefit from traditional mitigation pathways is needed. With that goal in mind, Adare Pharma Solutions and Aptar Active Material Science partnered to study a packaging-based solution

IDEA IN BRIEF

THE PROBLEM

Pharma companies are currently working to mitigate nitrosamine risk and meet new regulatory requirements. A common approach to solve this problem is reformulation via excipient adjustment. While this approach can often reduce nitrosamine formation, it often comes with other challenges.

THE CHALLENGE

Reformulating with excipients not only requires a costly and time-consuming road to approval, but some excipients preferentially react with nitrite before nitrosation occurs, causing unexpected and unacceptable side reactions that make this approach to nitrosamine mitigation troublesome.

THE SOLUTION

New innovations in active material science technologies offer an innovative solution that can mitigate risk without reformulation of packaging change. This technology scavenges, reacts with, and/or adsorbs/absorbs nitrosamine precursors in the packaging headspace to deliver a meaningful reduction in nitrosamine formation.

to nitrosamine mitigation. Could active material science technology be applied to a drug product's primary packaging—such as bottles and blister packaging—to mitigate nitrosamine risks and potentially bypass the need for lengthy and costly reformulation?

This study utilized Aptar's proprietary 3-Phase Activ-Polymer™ platform technology, a highly engineered solution that employs active materials to improve physical and/or adsorption/absorption properties. The technology is used across the industry by global brands to protect sensitive drug products, medical devices, drug delivery systems, and probiotics. Aptar has leveraged their proven 3-Phase Activ-Polymer platform to develop a nitrosamine mitigation film, N-SorbSM.

For this proof of concept study, N-SorbSM film was added to drug product bottles to evaluate its effect on NDSRI formation. The inhibitor agent is delivered within a unique formulation composed of three elements: a base majority polymer that provides the structure (in this case, an N-SorbSM active film), a channeling agent, and active particles. The N-SorbSM films are engineered to capture and remove nitrosamine precursors from the packaging's headspace before they can form nitrosamines.

By removing nitrosating agents, such as NO_x, the N-SorbSM films deplete essential components required for nitrosamine formation, effectively limiting the process before it begins. This action acts as a first line of defense, reducing the “fuel” for nitrosamine growth by leveraging the NO_x interspecies conversion against itself.

For this study, Aptar selected six N-SorbSM nitrosamine mitigation films for testing based on the hypothesized mechanism of action for each film and previous studies on their NO_x removal.

Product Chosen & Why

Propranolol, which has been the model for multiple previous studies at Adare, including studies incorporating traditional nitrite scavengers such as antioxidants, was selected for testing. For this proof-of-concept study, the capsule shells were removed from the product, exposing the drug product beads directly. The beads have both a drug layer and a delayed release coating applied via spray drying processes.

Experimental Design

Aside from the removal of the capsule shells, the experimental system was designed using bottles comparable to those currently used in commercial packaging, thereby replicating the commercially packaged drug product in a way that facilitated a temperature and humidity stress study. At each stage of design, proof of concept was prioritized.

The bottles were filled with a quantity of beads typically packaged in capsules, and the N-SorbSM films were securely wrapped on the inside wall of these bottles. Additionally, a second set of bottles were prepared where active inhibiting agents were added in bulk within air-permeable pouches to observe the effects of N-SorbSM's activity. The amount of inhibitor added to each pouch was 5 grams, which was significantly more than the quantity within the N-SorbSM films.

Lastly, a nitrite-free humidity source was placed within each bottle before they were closed and placed into an oven for aging.

The independent headspace in each bottle is a critical design element, as the NO_x removal process occurs entirely in the gaseous phase. When a control sample, a similarly prepared bottle without any inhibiting agents, exhibited nitrosation approximately at the regulatory limit, all samples were pulled and analyzed.

The Result

Aptar's proprietary films showed significant reduction in nitrosation, reducing nitrosamine formation by as much as 28% (Figure 1). Five of the six films showed similar, if not better, performance to the bulk active inhibiting agents tested in this experiment. Similar active inhibitors were used in both arms of the study—bulk inhibitors versus inhibitors embedded in the N-SorbSM film. The N-SorbSM films generally performed better than the raw materials deployed in permeable pouches, as shown in Figure 1.

Can this technology work for your drug product?

It's important to recognize that variability should be expected when comparing the results of this study with prospective commercial material. Results will vary significantly between products, even with the same API.

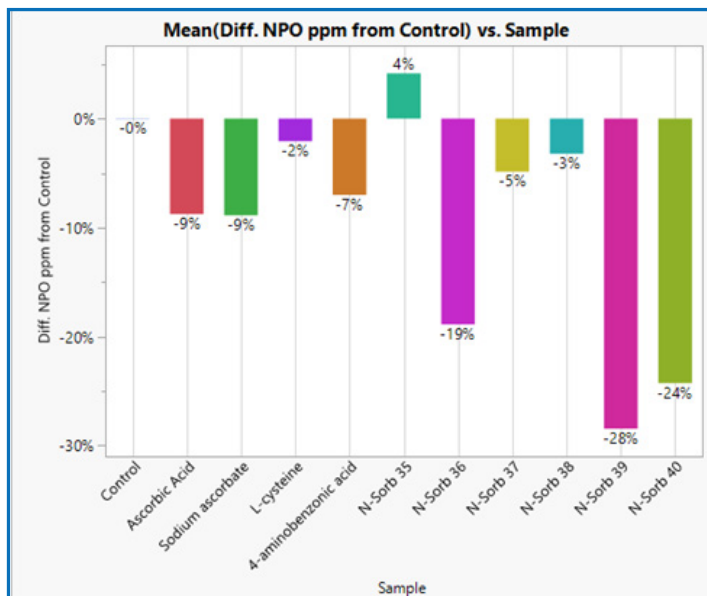


Figure 1: Reduction of Nitrosamine formation using bulk active ingredients and N-SorbSM films.

For example, there is no established correlation between the temperature and humidity conditions used in this study and true shelf life. While some generic guidelines are known and understood, none are specific for this chemical process.

More importantly, many properties specific to a drug product will directly affect the ability of the films to modulate the nitrite content immediately available to the nitrosation reaction. These properties include: proximity of nitrite to both the API and outer wall of the particles or tablets; any release coatings or capsule shells; humidity and water content; bottle vs. blister packaging; bottle headspace; and even the space between tablets or capsules, which limits air movement within the bottle.

A Promising Future

By actively removing or decreasing nitrosating agents in the headspace of sealed drug packaging, N-SorbSM technology prevents nitrosamine formation and offers pharmaceutical developers a promising replacement and/or supplement to current reformulation-based nitrosamine mitigation strategies. Active packaging intervention represents a paradigm shift in managing impurities and degradation, which could significantly enhance overall mitigation strategies. Additionally, recent FDA guidance recognizes that packaging changes represent a potential mitigation strategy.

By addressing nitrosamine concerns with active packaging, N-SorbSM technology can help accelerate drug product development and help alleviate the burden of drug shortages due to recalls.

FDA Emerging Technologies Program

N-SorbSM technology has been accepted into the US FDA's Emerging Technology Program, which helps promote the adoption of innovative approaches to pharmaceutical design and manufacturing. This is a multi-stakeholder effort that aligns with the FDA's mission to facilitate modernization in the pharmaceutical industry, reducing time and cost requirements for introducing novel solutions.

As part of this program, Aptar meets with a dedicated FDA team to discuss, identify, and resolve potential technical and regulatory issues related to the development and implementation of novel technologies prior to regulatory submission.

This collaboration empowers pharma brands to address nitrosamine mitigation challenges with innovative offerings. By offering a targeted, efficient, and easily implementable solution, N-SorbSM can enable drug developers to ensure the safety and quality of their products while streamlining compliance with regulatory requirements.

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