TARGETING NITROSAMINE PRECURSORS IN ORAL SOLID DOSE DRUGS WITH NOVEL ACTIVE MATERIAL SCIENCE SCAVENGER TECHNOLOGIES

A Promising Approach to Mitigating Nitrosamine Impurities

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Introduction

N-nitrosamine or Nitrosamine Drug Substance Related Impurities (NDSRI's) are a class of potentially carcinogenic compounds that have been wreaking havoc on the pharmaceutical industry, leading to product recalls and heightened regulatory scrutiny of commercialized drugs and those in development. Nitrosamines are found as impurities in various drug products, and studies show that over time, nitrosamine formation levels can grow beyond FDA daily thresholds (Figure 1), potentially putting patients at risk.

Nitrosamine	AI Limit (ng/day)[i,ii]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

Figure 1: AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

Nitrosamines are substances that can form under certain conditions through a process known as nitrosation, especially in the presence of nitrosating agents (e.g., nitrite salts, alkyl nitrites, nitrogen oxides (NOx), nitrosyl halides, nitrosonium salts and nitro compounds) along with amines or amides. Nitrosating agents can arise from the use of recycled solvents or reused catalysts from different processes or across manufacturing lines with inadequate control and inappropriate monitoring. They can also be generated from impure starting materials or intermediates in the upstream step or from carry-over of other manufacturing processes along the same production line. Another key variable in nitrosamine formation is the nitrite levels in many of the most commonly used excipients. For example, Magnesium Stearate and Microcrystalline Cellulose (MCC) can average 2,000 to 3,000 parts per billion (PPB) levels of nitrites, aiding in the reaction to form the nitrosamine.

Controlling the presence of nitrosating agents and their interaction with precursors is crucial in mitigating nitrosamine formation. This series of studies[1] explores the possibility of leveraging innovative active material science technologies to develop a novel nitrosamine mitigating solution for

IDEA IN BRIEF

THE PROBLEM

Pharma companies are facing increasing regulatory scrutiny and risk of product recalls due to N-Nitrosamine or NDSRIs in drug products. The mechanism of reaction and root cause of Nitrosamine formation is not always understood, making risk mitigation difficult.

THE CHALLENGE

Current mitigation strategies employed by pharma developers, such as changes to their formulation or manufacturing processes can be costly. Additionally, controlling the variables associated with N-Nitrosamine formation is not always certain. Additional or alternative mitigation strategies need to be considered to fully address risk.

THE SOLUTION

New innovations in active material science technologies offer an active packaging based solution that can react with NOx gases in the packaging headspace to inhibit Nitrosamine formation. Not only can these technologies stop Nitrosamine formation, but they can serve as an additional "insurance policy" by adsorbing/scavenging N-Nitrosamines post-formation, delivering a holistic risk mitigation solution.

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oral solid dosage forms. This branch of the study focuses on the role nitrites in excipients play in nitrosamine formation. It also investigates how Aptar CSP Technologies' proprietary Activ-Polymer™ platform technology can mitigate risk associated with Microcrystalline Cellulose (MCC). The data presented will explore whether nitrite impurity levels contained in a sample lot of placebo MCC tablets can be meaningfully reduced when placed together with Aptar CSP's Activ-Film™ material in a sealed environment.

Challenge: Mitigating Nitrosamine Risks Associated with Excipients

Drug formulations typically involve a blend/granulation of their active pharmaceutical ingredients (API) with various excipients, many of which have been shown to include nitrite impurities at trace levels. According to Boetzel et al., the excipients, like fillers and diluents, have the greatest influence over the nitrite concentration of the solid dosage forms.[2] Microcrystalline Cellulose (MCC) is an extremely common diluent in oral solid dosage forms, particularly tablets and capsules, and has the highest number of results in Lhasa Limited's Nitrite in Excipients database at 0.04 to 2.4 ppm. These nitrites can form nitrosating species such as nitrous acid and various volatile nitrogen oxides (NOx), especially under moderately acidic conditions (Figure 2). For APIs at risk of nitrosamine formation, the presence of nitrosating species in the excipients used in the formulation have been shown to directly increase the rate of formation of nitrosamines.

As pharmaceutical developers seek to assess and mitigate N-nitrosamine risks in their current drug products and new APIs in development, they are employing strategies such as sourcing nitrocellulose free packaging or choosing alternate or supplemental excipients, reagents or catalysts. However, these solutions are not fail safe as they may not always be able to source low or no nitrite excipients and these strategies can result in overformulation which could potentially lead to new problems. Additionally, the mechanism of reaction and root cause of nitrosamine formation is not always understood, complicating the process of finding an adequate risk mitigation strategy. Our challenge as an active material science company is to provide pharma companies with an active packaging-based solution to prevent nitrosamine formation and/or remove nitrosamine impurities post-formation, at the point of packaging, reducing the need for formulation or manufacturing changes. The technology could be used as a primary solution or an additional measure of protection to complement other strategies used to prevent N-nitrosamine formation.

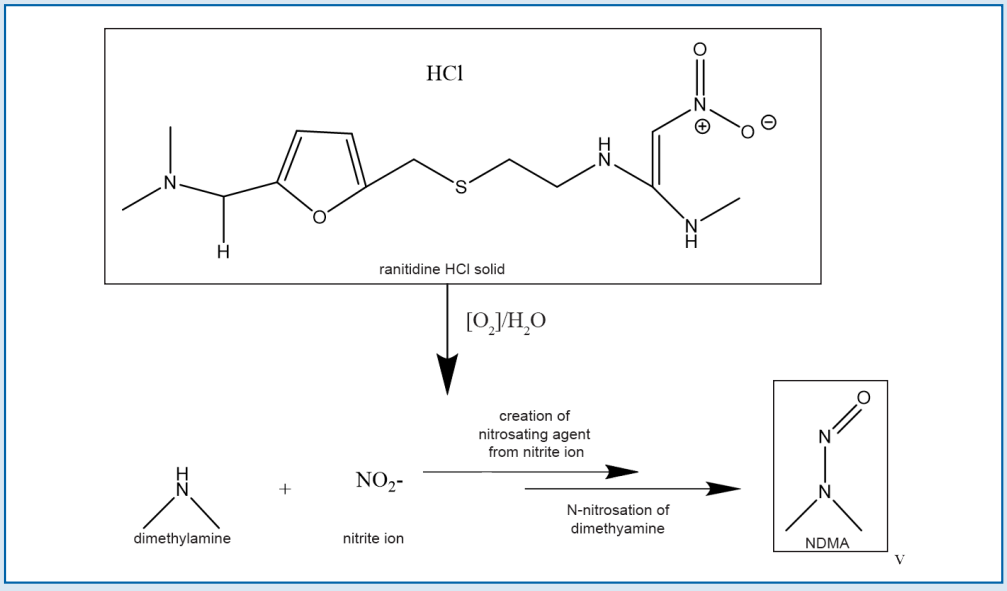

Figure 2: Chemical Pathway for NDMA Generation from Ranitidine HCl in Solid Form

Solution: Innovations in Active Material Science Technologies

Nitrites are known to form volatile, gaseous NOx components (especially through protonation under mildly acidic conditions).[3] In the absence of any additional reactions, such gases will come to an equilibrium in the environment. However, by removing the gas (NOx) from the environment, the equilibrium reaction will drive the formation of additional NOx gases, which if removed, will continue until the trace levels of nitrite are consumed.

New innovations in active material science technologies offer an active packaging based solution that can react with NOx gases in the packaging headspace to inhibit Nitrosamine formation. Leveraging 20+ years of material science expertise, Aptar CSP Technologies' 3-Phase Activ-Polymer™ platform technology is delivered in a unique formulation comprised of a base majority polymer that provides the structure, a channeling agent, and active particles (Figure 3). The channeling agent coats and distributes active particles throughout the polymer matrix and allows targeted molecules to enter through the hydrophilic channels. Those molecules migrate to the active particles, where they are adsorbed and permanently removed from the headspace.

For the purposes of this study, the technology, deployed as an Activ-Film™ material sealed together with the MCC tablets, was engineered to quickly and efficiently capture and/or react away the volatile NOx species, thus preventing the formation of nitrosamines by removal of the nitrosating agent (Figure 4). This technology is called N-Sorb (Figure 5).

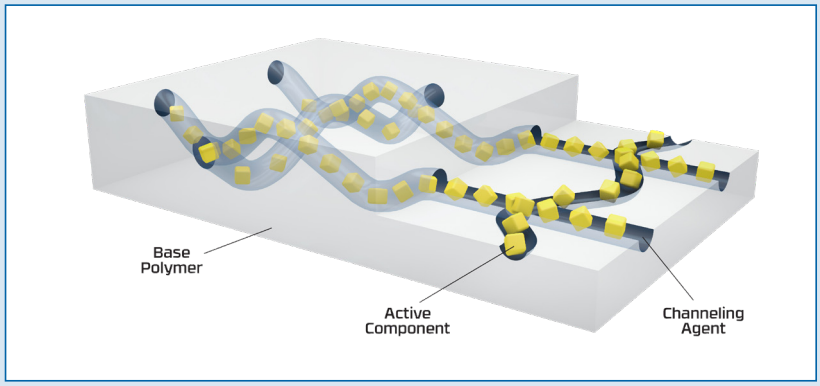

Figure 3: 3-Phase Activ-Polymer™ Technology Matrix

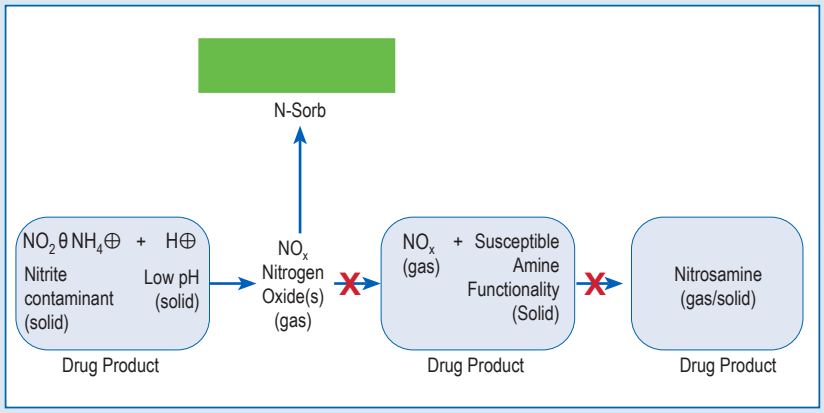

Figure 4: How N-Sorb Can Prevent Nitrosamine Formation[4]

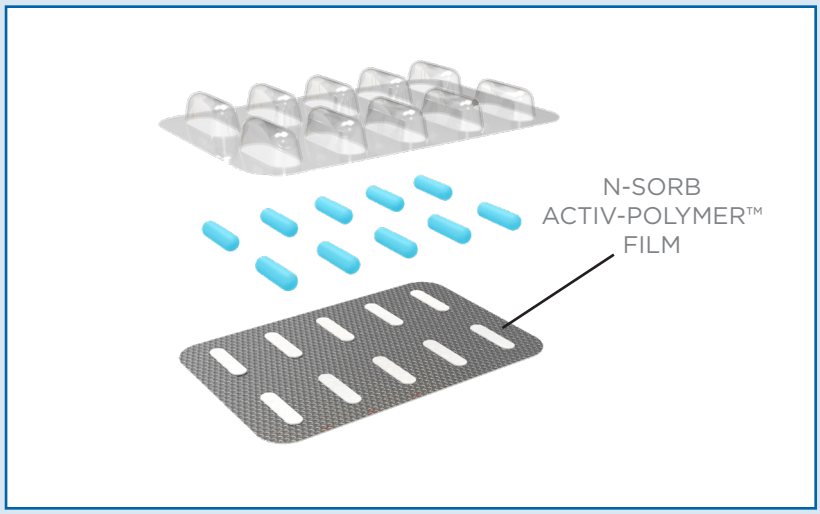

Figure 5: Example deployment of N-Sorb Activ-Polymer™ Film sealed in an Activ-Blister configuration with tablets

Data Review: N-Sorb Studies

For this study, four versions of N-Sorb mitigation films were exposed to MCC tablets in sealed foil bags during a 6-day aging period. The methodology[5] used for the experiment is based on a chemical derivative method that reacts all available nitrites directly into a measurable compound. The compound is detected and quantified utilizing a GC-MSD headspace, with a detection ranging from 5-100 ppm.

Instrumentation Specifications:

- Agilent GC 8890, Model Number G3542A
- Agilent MSD 5977, Model Number G7077C
- Agilent Headspace 8697, Model Number G4511A

All four versions of N-Sorb mitigation films significantly reduced the average levels of nitrite present in the samples compared to the controls. None of the mitigant's range of concentration overlapped or extended into the control concentration, indicating nitrite levels significantly reduced after aging. After 6 days of aging at 60°C in the oven, the samples containing the MCC and either N-Sorb 20 or N-Sorb 23 mitigation film resulted in the lowest level of nitrite concentration remaining in the headspace (Figure 6). The percent reduction of the nitrite species relative to control during the aging period can be seen in Figure 7.

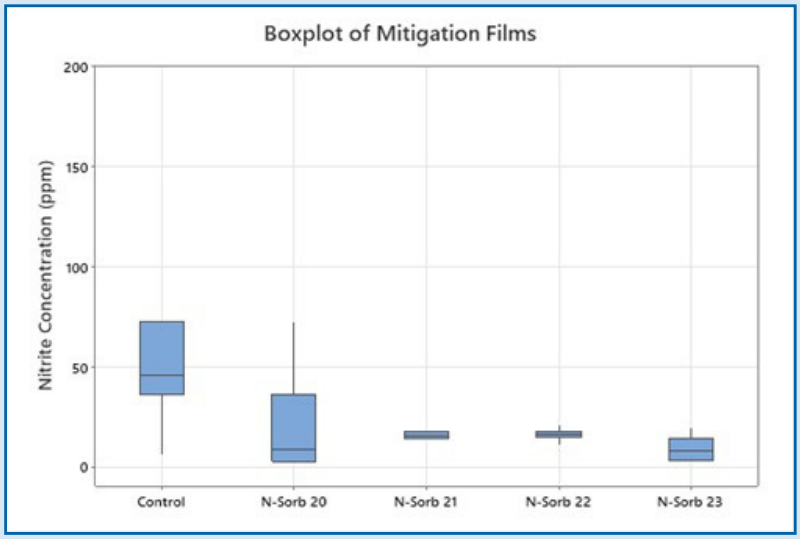

Figure 6: Nitrite Concentration (ppm) vs. N-Sorb mitigation films in the sample headspace of vials sealed with MCC tablets

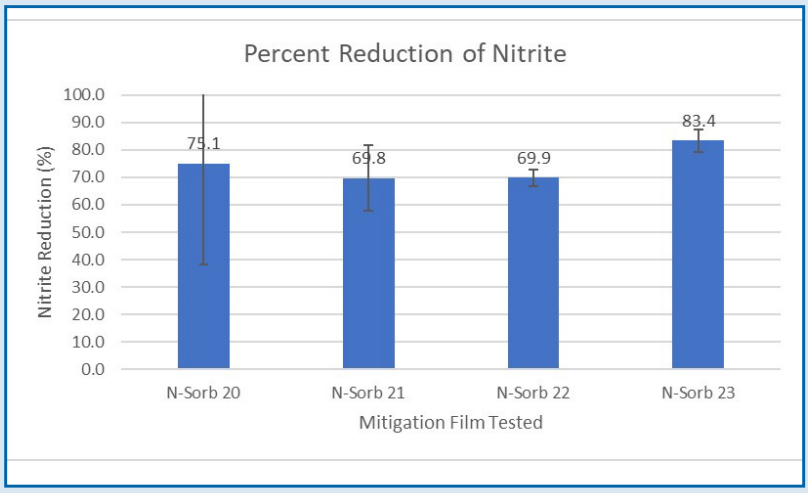

Figure 7: Percent reduction of nitrite in MCC tablets sealed with N-Sorb mitigation films when compared to control sample

Nitrite is reduced (measured in ppm) by all N-Sorb mitigation films tested with MCC tablet samples during the aging period compared to the amount measured in the control samples (Figure 7). All the mitigation films exhibited a percent reduction by ~70% or more compared to the amount measured in the control sample. MCC tablet samples exposed to N-Sorb 23 mitigation film during the test period resulted in the highest reduction of nitrite concentration along with the lowest variation of the top two mitigation film performers, as illustrated by Figures 6 and 7.

Conclusion

Aptar CSP Technologies' innovative Activ-Polymer™ platform with its N-Sorb technology offers pharmaceutical developers a promising alternative to current Nitrosamine mitigation strategies by actively removing nitrosamines in the headspace of sealed drug packaging. Key findings from this study demonstrate the potential of N-Sorb as a potent scavenger of nitrite precursors:

- **Significant nitrite reduction:** All tested N-Sorb mitigation films significantly reduced nitrite levels in the headspace compared to controls, with reductions exceeding 70% in some cases.
- **Efficient capture:** N-Sorb 23 exhibited the highest nitrite reduction and lowest variation, suggesting its efficacy in capturing and/or reacting with the volatile NOx species responsible for nitrosamine formation.
- **Post-formation mitigation potential:** The study focused on preventing nitrosamine formation, but the technology's ability to capture nitrite suggests its potential efficacy in reducing existing NDSRIs in packaged drugs.

For drug formulation and analytical scientists, N-Sorb presents a compelling solution offering several advantages:

- **Targeted intervention:** It specifically addresses the root cause of nitrosamine formation — the presence of nitrosating agents like NOx — without requiring extensive formulation changes.
- **Simplicity and ease of integration:** N-Sorb can be seamlessly integrated into existing packaging formats and processes, minimizing disruption to manufacturing workflows.
- **Flexibility and potential for broad applicability:** The modular design of Activ-Polymer™ allows for customization to suit specific drug product requirements and target various nitrosating agents beyond NOx.

While further research is warranted to fully validate the long-term effectiveness and compatibility of N-Sorb with diverse drug products, this study provides a strong foundation for its potential as a game-changer in the fight against NDSRIs. By offering a targeted, efficient, and easily implementable solution, N-Sorb can empower drug developers to ensure the safety and quality of their products while streamlining compliance with regulatory requirements.

References

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2. Boetzel R, Schlingemann et al. A Nitrite Excipient Database: A Useful Tool to Support N-Nitrosamine Risk Assessments for Drug Products. J Pharm Sci. 2023 Jun;112(6):1615-1624. doi: 10.1016/j.xphs.2022.04.016. Epub 2022 Apr 29. PMID: 35500671.
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