Protecting Excipients Today, Preventing Nitrosamines Tomorrow: *An Active Material Science Approach*

Amanda Murph, Ivy Comer, Brian Wilson, Jason Pratt and Dr. Jean Daou
Aptar Active Material Science

Abstract

Nitrosamine contamination has emerged as a critical challenge in pharmaceutical manufacturing, primarily driven by nitrite impurities in excipients. Microcrystalline cellulose (MCC), a widely used filler in oral solid dosage forms, often contain nitrite impurities that contribute to nitrosamine formation in finished drug products. This study investigates the effectiveness of Aptar Active Material Science's N-Sorb℠ film technology for nitrite scavenging in bulk powder MCC during storage. Results demonstrated that N-Sorb℠ films reduced nitrite levels by up to 100%, effectively eliminating this impurity pathway. By addressing nitrosamine precursors at the excipient stage, N-Sorb℠ technology offers a proactive, scalable solution that aligns with evolving regulatory expectations. These findings highlight the potential of active packaging inserts as a proactive safeguard for pharmaceutical quality.

Keywords: N-nitrosamines, nitrite scavenging, MCC, impurities, packaging, N-Sorb℠ films, 3-Phase Activ-Polymer™ technology

Introduction

Nitrosamine contamination has become one of the most significant challenges in pharmaceutical manufacturing over the past decade. Regulatory agencies worldwide, including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have issued stringent guidance to mitigate nitrosamine impurity risks in drug products.[1-3] These compounds, classified as probable human carcinogens, can form through multiple pathways during drug manufacturing and storage, with nitrite impurities in excipients serving as a significant and often underestimated driver of instablity.[1,3]

Microcrystalline cellulose (MCC) is among the most widely used excipients in oral solid dosage forms due to its compressibility, stability, and inertness. However, MCC is not immune to contamination.[4] The presence of nitrites in MCC can directly contribute to nitrosamine formation during subsequent processing steps, compromising product safety and regulatory compliance.[4,5]

IDEA IN BRIEF

THE PROBLEM

When it comes to nitrosamine mitigation, one significant and often overlooked source of nitrosamine formation is nitrite impurities in excipients such as MCC. These impurities can initiate nitrosamine formation during drug processing and storage, jeopardizing product safety and regulatory compliance.

THE CHALLENGE

Traditional mitigation strategies primarily focus on later stages of production and fail to address excipient-level contamination, leaving a critical gap in risk management. With stringent global regulatory requirements, manufacturers need a proactive, scalable solution that minimizes nitrosamine risk without disrupting existing processes.

THE SOLUTION

New innovations in active material science offer a novel excipient-level intervention. Deployed as active inserts in bulk storage containers, N-Sorb℠ films continuously scavenge and neutralize nitrite impurities in MCC during storage, reducing levels by up to 100%. This approach eliminates a primary pathway for nitrosamine formation, aligns with regulatory expectations, and provides a cost-effective, easily implemented solution that safeguards pharmaceutical quality.

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TECHNICAL BRIEF //

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Traditional nitrosamine mitigation strategies have focused primarily on reformulating active pharmaceutical ingredients (APIs), modifying synthetic routes, or introducing scavengers during drug manufacturing. While these approaches are valuable, they often overlook the contribution of excipients as precursors. Addressing nitrite contamination at the excipient stage represents a proactive strategy that can significantly reduce downstream risks. By targeting the source of nitrosamine formation before excipients enter the manufacturing line, the industry can achieve a more robust and holistic mitigation framework.

Recent advances in active material science have enabled the development of innovative solutions to address nitrosamine risks in pharmaceutical manufacturing. One such breakthrough is Aptar Active Material Science's patented N-Sorb℠ Nitrosamine Mitigation Solution. For this study, N-Sorb℠ technology was designed to reduce nitrite content in excipients during bulk storage, thereby minimizing the risk of nitrosamine formation during drug formulation.

This paper presents the rationale, methodology, and results of applying three different N-Sorb℠ film formulations to MCC excipients in bulk storage during a 24-week study. By situating N-Sorb℠ within the broader context of pharmaceutical quality and regulatory compliance, we demonstrate how excipient level interventions can complement existing strategies and strengthen the industry's defense against nitrosamine contamination.

Methods

(a) N-Sorb℠ Film Production

Leveraging Aptar Active Material Science's proprietary 3-Phase Activ-Polymer™ platform technology, three raw active materials with proven nitrite mitigation properties were incorporated into a polymer matrix to create N-Sorb℠ nitrosamine mitigation film technology. This composite structure combines a base polymer that provides the physical structure, a channeling agent for controlled diffusion, and active particles that react with and/or neutralize nitrite agents and/or their derivatives. Figure 1 illustrates the Activ-Polymer™ technology matrix, which employs active materials as fillers within a composite material to enhance adsorption/absorption properties. The formulation is designed to deliver continuous scavenging performance without compromising structural integrity.

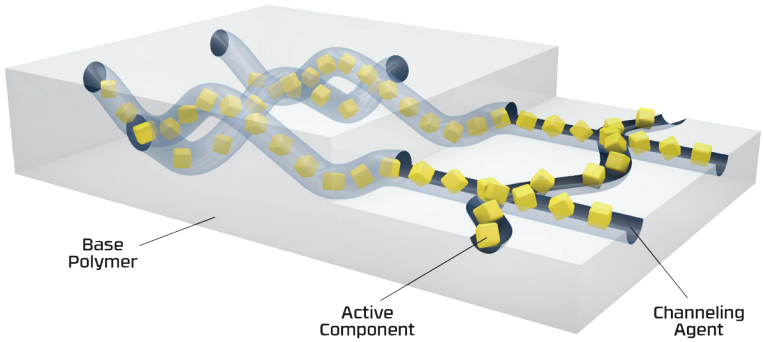

Figure 1: Representation of Activ-Polymer™ technology matrix

(b) Packaging Preparation & Testing Conditions

For this study, 300 g of microcrystalline cellulose (MCC) NF from Dupont nutrition Biosciences ApS were placed in a 0.6-gallon Lite Latch® screw-top HDPE pail lined with two 6-mil polybags. N-Sorb℠ film was positioned inside the bags in direct contact with the bulk MCC powder, along the bottom and around the sides of the pail (Figure 2). A total of 561 cm^2 N-Sorb℠ film was used per container.

The polybags were cinched closed with zip-ties to maintain containment integrity.

The pails were stored at 25°C and 60% relative humidity for a duration of 24 weeks. At each timepoint (from 0 until 24 weeks of storage) and for each of the three N-Sorb℠ films (termed N-Sorb℠ B, N-Sorb℠ M, N-Sorb℠ D) and the control, six replicates were sampled from various locations of the bulk MCC material and used to determine the nitrite content (ppm) via HPLC-UV/VIS Griess method.

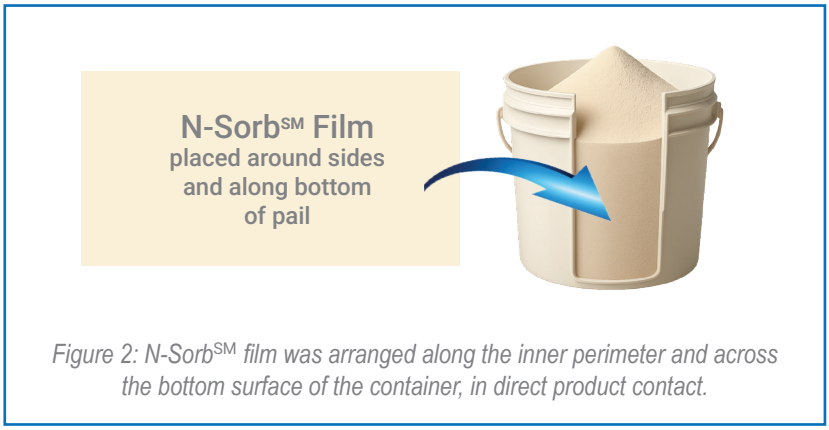

Figure 2: N-Sorb℠ film was arranged along the inner perimeter and across the bottom surface of the container, in direct product contact.

Nitrite is detected in solution using the Griess diazotization reaction, which was first described in 1858 by Peter Griess. Nitrite is detected and analyzed by the formation of a red, pink color upon treatment of a nitrite-containing sample with the Griess reagent, which consists of two components in an acidic solution: an aniline derivative and a coupling agent.[6, 7, 8] The resulting LOD/LOQ for this evaluation was determined to be 0.01 ppm.

Results

Nitrite concentration decreased significantly in MCC samples exposed to N-Sorb℠ films compared to the control. N-Sorb℠ D exhibited the fastest nitrite reduction, achieving nearly 50% nitrite reduction within 3 weeks compared to the control. MCC samples exposed to N-Sorb℠ B and N-Sorb℠ D films resulted in the removal of all the nitrite content at 18 weeks, while N-Sorb℠ M showed a 38% reduction of the nitrite level after 24 weeks. Figure 3 illustrates the comparative reduction kinetics for all three N-Sorb℠ variants versus the control.

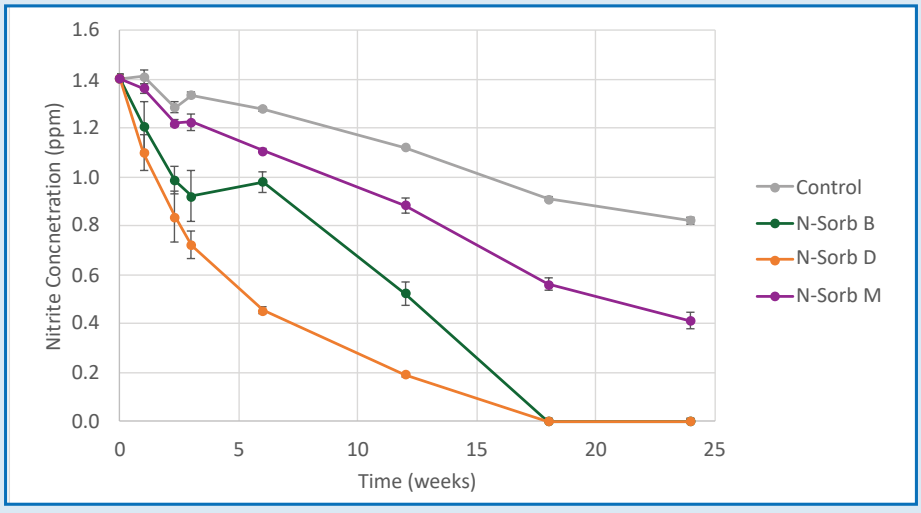

Figure 3: Reduction of nitrite concentration in MCC samples sealed in the pail with three different N-Sorb℠ films compared to control sample (in the absence of N-Sorb℠ film).

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Conclusion

Aptar Active Material Science's N-Sorb℠ technology offers an innovative and practical solution to mitigate nitrosamine risk in pharmaceutical manufacturing. Deployed as an active insert for bulk excipient storage, N-Sorb℠ films function as nitrite scavengers, continuously reducing and eliminating nitrite impurities from MCC during storage. This approach effectively neutralizes one of the primary pathways for nitrosamine formation. Implementation requires no changes to manufacturing processes, offering a cost-effective solution for large-scale adoption.

The scalability of N-Sorb℠ technology is particularly relevant for industrial settings. By integrating N-Sorb℠ films into bulk storage containers, manufacturers can protect large volumes of excipients (and potentially APIs) without altering existing manufacturing processes. This proactive strategy aligns with regulatory expectations by addressing nitrosamine risks at their origin and offers a practical, cost effective solution for industry adoption. Furthermore, the absence of regulatory concerns associated with the components of N-Sorb℠ technology provides a favorable pathway for implementation, reinforcing its potential as a compliant and forward looking innovation for pharmaceutical quality assurance.

Future studies will explore the application of N-Sorb℠ technology to other excipients and APIs, reinforcing its role in comprehensive nitrosamine risk management.

References

1. Banghale V, Ayre A: Nitrosamine Impurities in Pharmaceuticals: Regulatory Landscape and Challenges. *Pharm Sci Asia* **2024**, 51(3), 190-203.
2. Khan HS, Despres-Gnis F, Stults CLM, Mullis J, Nugara N, Sen A, Nagao L: An overview and discussion of N-nitrosamine considerations for orally inhaled drug products and relevance to other dosage forms. *AAPS PharmSciTech* **2023**, 24(1), 37.
3. U.S. Food and Drug Administration (FDA): Information about nitrosamine impurities in medications. https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications
4. Koyamatsu T, Mikami S, Kenji O, Shmyrova J: N-nitrosamine risk assessments for oral dosage forms: Nitrite content in the microcrystalline cellulose (MCC) produced by Asahi Kasei Corporation. **2023**, https://www.pharmaexcipients.com/wp-content/uploads/2023/01/N-nitrosamine-risk-assessments-for-oral-dosage-forms.pdf
5. Ashworth IW, D O, Teasdale A, Whiting M: Potential for the formation of N-nitrosamines during the manufacture of active pharmaceutical ingredients: an assessment of the risk posed by trace nitrite in water. *Org. Process Res. Dev.* **2020**, 24(9), 1629–1646.
6. Moorcroft, et.al. Detection and determination of nitrate and nitrite: a review. Talanta 54 (2001) 785-803
7. Croitoru, et.al. Nitrones are able to release nitric oxide in aqueous environment under hydroxyl free radical attack. Nitric Oxide 25 (2011) 309-315
8. Croitoru, et.al. Nitrite and nitrite can be accurately measured in samples of vegetal and animal origin using an HPLC-UV/VIS technique. J.Chrom B, 911 (2012) 154-161

For more information, contact:

NORTH AMERICA:
Brian Wilson, Ph.D.
Director, Sales & Business Development
Brian.Wilson@Aptar.com
(mobile) +1 334 752 3426

EMEA:
Christophe Chalot,
Technical Sales Manager
Christophe.Chalot@Aptar.com
(mobile) +33 6 0985 1522

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