

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

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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 CSP Technologies' 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 instability.^{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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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.

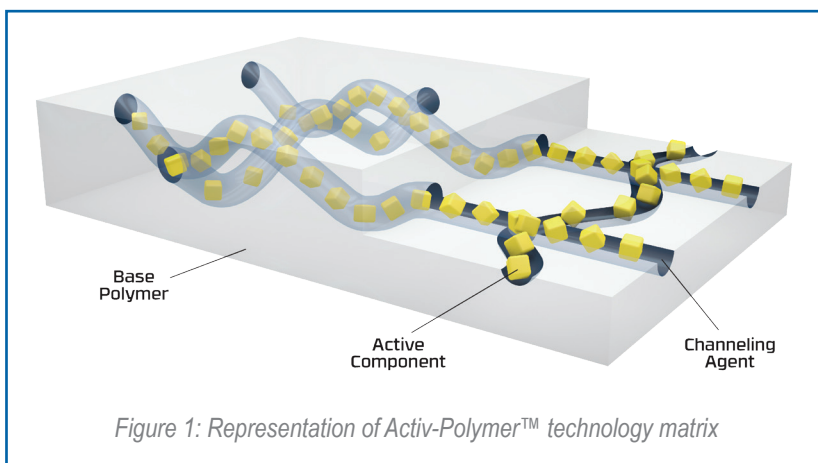
Recent advances in active material science have enabled the development of innovative solutions to address nitrosamine risks in pharmaceutical manufacturing. One such breakthrough is Aptar CSP Technologies' N-Sorb Nitrosamine Mitigation Solution. For this study, N-Sorb technology was designed to reduce 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 CSP'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 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.



(b) Packaging Preparation & Testing Conditions

For this study, 300g 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 cm² N-Sorb film was used per container.

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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.

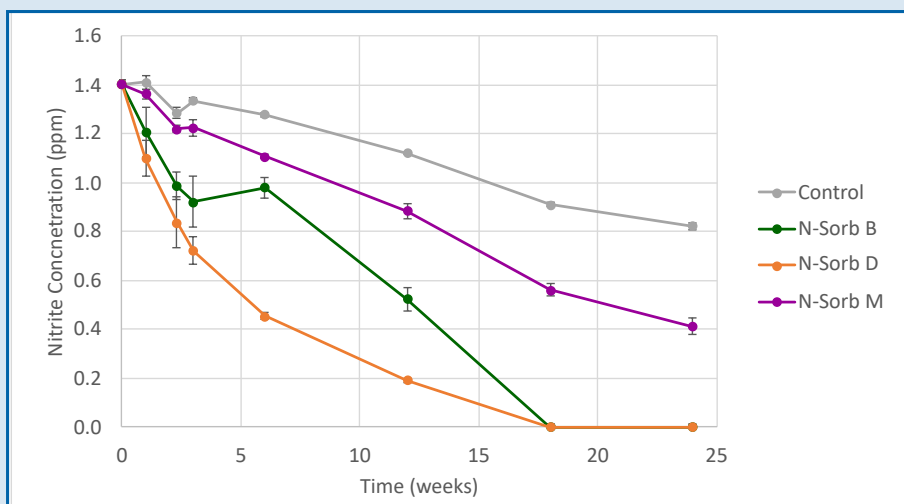


Figure 3: Reduction of nitrite concentration in MCC samples sealed in the pail with three different N-Sorb films compared to control sample (in the absence of N-Sorb film).

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Conclusion

Aptar CSP'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.

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