TECHNICAL BRIEF

NITROSATING AGENT MITIGATION STRATEGY: FROM RAW ACTIVE MATERIALS SCREENING TO THE ENGINEERING OF N-SORB SCAVENGER FILMS

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Abstract

New innovations in active material science technologies enable an active packaging-based solution that can react with nitrosating agents (NOx gases) in the packaging headspace to inhibit nitrosamine formation. Not only can these technologies stop nitrosamine formation, but they can be adjusted to serve as an additional "insurance policy" by adsorbing or scavenging N-nitrosamines post-formation, providing a holistic risk mitigation solution. Aptar CSP Technologies' innovative 3-Phase Activ-Polymer™ platform technology, deployed as N-Sorb, can be seamlessly integrated into existing packaging formats and processes to address nitrosamine risks without disrupting manufacturing workflows.

Introduction

N-nitrosamines are classified as probable human carcinogens. After N-nitrosamine contaminants were detected in pharmaceutical products in 2018, regulatory authorities set a framework for the risk assessment, testing, and mitigation of N-nitrosamines in drug products.[1-3] The FDA released a Guidance for Industry document in September 2020 in response to unexpected finding of N-nitrosamine impurities in a number of widely used pharmaceutical products.[3] The background and possible mitigation strategies were outlined in the report. The updated FDA guidance matches the EMA's three-step procedures and includes dates for drug manufacturers to complete each step for approved and pending drug applications. In addition, a document listing possible N-nitrosamine mitigation strategies specifically mentions ascorbic acid and α-tocopherol as common antioxidants that significantly inhibit N-nitrosamines in drug products.[4]

In general, N-nitrosamine formation requires the presence of three factors:

1. A nitrosating agent or precursor thereof, particularly nitrite. Nitrite does not directly nitrosate amines; however, they are precursors of nitrosating agents.
2. A vulnerable secondary or tertiary amine, which may be a moiety within the drug substance.
3. Conditions amenable for the reaction to occur, such as elevated temperatures, acidic conditions, or the presence of a liquid phase.

These three factors may not be sufficient for N-nitrosamine formation to occur, as the kinetics of N-nitrosamine formation can vary significantly, depending on the structure and environment.[5,6]

IDEA IN BRIEF

THE PROBLEM
Nitrosamines have gained attention in the pharma industry due to their discovery in some APIs and excipients. These chemical substances are often carcinogenic and can form under various conditions. Regulatory authorities (FDA, EMA) set a framework for the risk assessment, testing, and mitigation of N-nitrosamines in drug products.

THE CHALLENGE
Most N-nitrosamine mitigation research has focused on prevention of nitrosation by adding nitrosating scavengers directly in the drug formulation, which can be time consuming and costly. Nevertheless, the same principles can be applied by adding active material directly into the packaging framework, avoiding time and costs associated with drug reformulation.

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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One strategy to inhibit the formation of N-nitrosamines during the manufacture and storage of drug products involves the use of nitrosating agent scavengers. In screening studies, diverse molecules, including the antioxidant vitamins ascorbic acid and α-tocopherol, amino acids, and other antioxidants used in foods or drugs, have been tested for inclusion in drug products to mitigate N-nitrosamine formation.[7,8] The use of nitrosating agent scavengers that are currently listed as inactive ingredients in drug products by the FDA offer advantages from a regulatory perspective, and also in terms of the development time needed to establish N-nitrosamine mitigation.

Recently, as part of compound screening, 19 structurally-diverse compounds with an acceptable toxicological profile were evaluated by Homšak *et al.*[7] These included certain amino acids (L-cysteine, histidine, lysine), general antioxidants (propyl gallate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT)), ammonia-related compounds (urea, ammonium sulfate and ammonium chloride), the pyrone maltol, para-aminobenzoic acid (PABA), and vitamins with antioxidant properties (ascorbic acid, α-tocopherol). Likewise, the use of ascorbic acid and α-tocopherol to inhibit N-nitrosamine formation in pharmaceutical products has been specifically mentioned by the FDA.[4]

Ascorbic acid has a wide applicability for many nitrosating agents and is nontoxic at effective amounts in drug products.[9,10] It is particularly suited to aqueous and weakly acidic conditions and can react with N_2O_3, $H_2NO_2^+$, and NO_X, converting them to NO.[9,10] However, under aerobic conditions, NO can oxidize to NO_2 and subsequently convert back to nitrosating agents (i.e. N_2O_3 or N_2O_4). Good scavenging efficiency of redox scavengers such as ascorbic acid is thus expected under anaerobic conditions, although their efficiency is already very good in the presence of oxygen.[11]

As mentioned above, until now, most research has focused on the prevention of nitrosation by adding the nitrosating agent scavengers directly in the drug formulation. Nevertheless, the same principles can be applied by adding the active material directly into the packaging framework, avoiding time and costs associated with mitigation by drug reformulation. The work described in this paper outlines key considerations for the inclusion of Aptar CSP Technologies' innovative N-Sorb technology, which contains nitrosating agent scavengers directly inside pharmaceutical packaging. There will be a special focus on NO_X scavenging, as NO_X is a common nitrosating agent that can be found in drug packaging.

Methods

Diverse NO_X mitigant raw materials (264) were identified from literature and 52 of them were tested in screening studies, including different categories of organic and inorganic materials (antioxidants, adsorbers, pH modifiers, moisture controllers and other innovative agents, etc.) (see Figure 1).

The results of this screening were then used to formulate various mitigation films with the best active candidates. These raw active materials were then engineered for inclusion into a polymer matrix to form our innovative 3-Phase

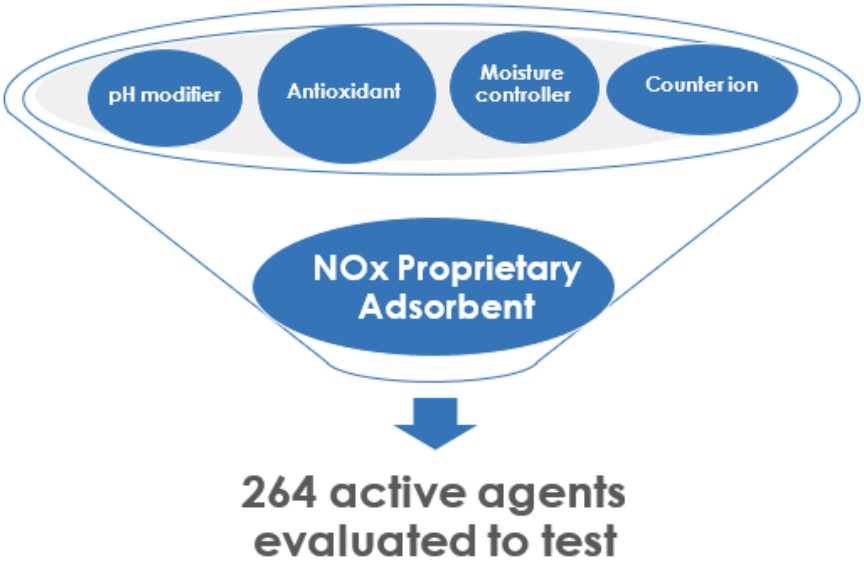

Figure 1: Illustration of the different categories of NOx scavengers identified from literature

Activ-Polymer™ (Figure 2) "N-Sorb" technology, which is able to mitigate N-nitrosamine formation by scavenging nitrosating agents. The obtained N-Sorb technology, deployed as Activ-Film™ alone (Figure 3), heat-staked films (blister packaging/Activ-Blister™), blown films, or blown bottles were tested to determine their ability to reduce nitrite and NO_X concentration to avoid or limit N-nitrosamine formation.

Mitigants (in powder or N-Sorb shaped formats) were put with a NO_X- and nitrite-provider (when needed) in a vial, blister or bottle and aged for different periods of time. The different compounds were detected and quantified using different analytical equipment such gas chromatography mass spectroscopy headspace, etc. Each active raw material and film formulation were tested 3 and 30 times respectively in order to have high confidence in the results.

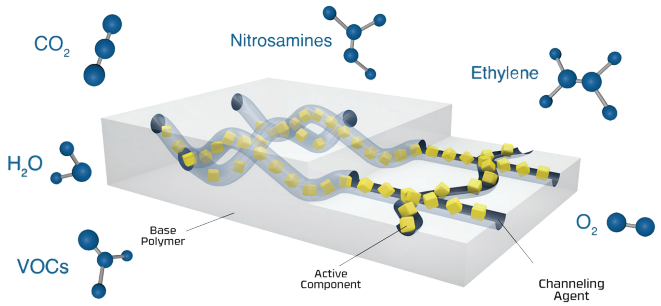

Figure 2: CSP's Activ-Polymer™ matrix employs active materials as fillers in composite materials to improve their physical and/or adsorption/absorption properties. The proprietary technology is delivered in a unique formulation comprised of a base majority polymer that provides the structure, a channeling agent, and active particles.

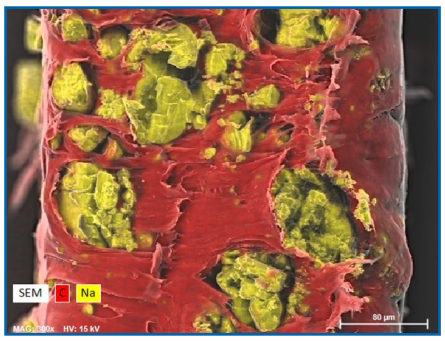

Figure 3: High-resolution Scanning Electron Microscopy image coupled with EDX analyses of a 3-Phase Activ-Polymer™ N-Sorb film.

Results & Discussion

A total of 52 active raw materials were tested. Figure 2 show the NO_X percent reduction with the best 46 mitigant raw materials after 24 h at 60°C. Of the 52 mitigants identified and tested, 10 mitigants reduced 50% or more of NO_X present in the headspace of the vials (Figure 4).

The five materials demonstrating the highest adsorption capacities were then incorporated into a specially designed Activ-Film™ material, compatible with traditional blister packaging. Each film formulation and the control were

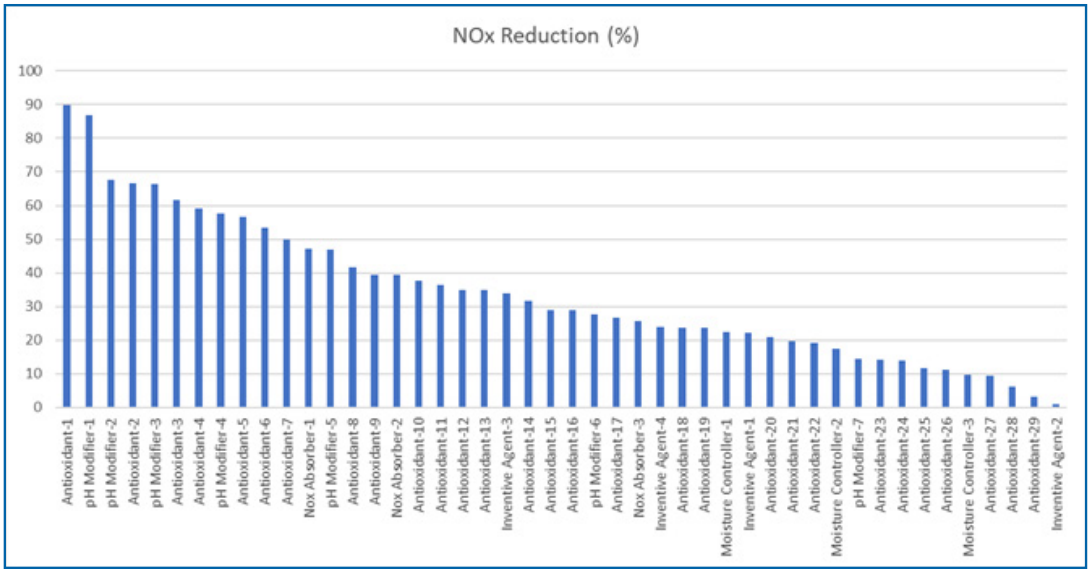

Figure 4: Percent reduction of NOx species after 1 day at 60°C

analyzed 30 times in order to have high confidence in the results so they can be used for further evaluation and determination of the best performing N-Sorb films. The controls averaged 9.63 ppm after 7 days of aging at 60°C. All 5 mitigant films reduced NO_X overall concentration dramatically, with N-Sorb F and N-Sorb H films averaging complete removal of NO_X (below than 0.1 ppm) in the headspace (Figure 5).

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.

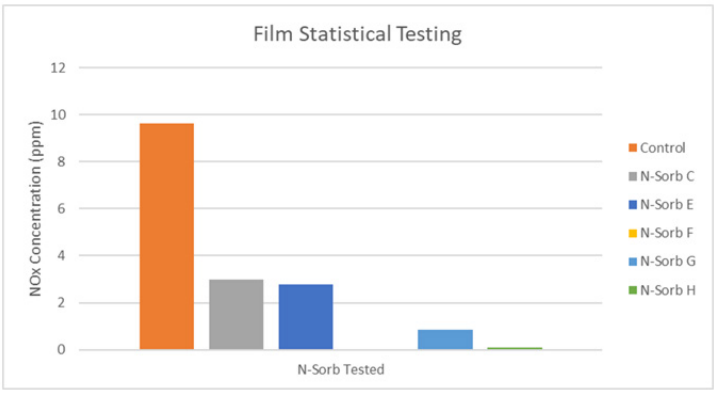

Figure 5: NOx concentration in vials after 7 days at 60°C in absence of N-Sorb film (Control) or in presence of different N-Sorb films

Conclusion

Aptar CSP Technologies' innovative 3-Phase Activ-Polymer™ platform technology, engineered as N-Sorb, offers pharmaceutical developers a promising alternative to current nitrosamine mitigation strategies (based on drug reformulation) by actively removing or decreasing nitrosamine concentration in the headspace of sealed drug packaging. The key findings from this study demonstrate the potential of N-Sorb as a potent scavenger of nitrosating agents, addressing the root cause of N-nitrosamine formation. N-Sorb can be seamlessly integrated into existing packaging formats and processes, mitigating risk while minimizing disruption to manufacturing workflows. N-Sorb is a game changer in the fight against NDSRIs.

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