Beyond the Barrier: Advancing Pharmaceutical Stability & Addressing Nitrosamine Risk with Active Blow-Molded Packaging Technology

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Packaging has always played a critical role in preserving the quality, safety, and efficacy of pharmaceutical products. Since the introduction of plastic pharmaceutical containers in the second half of the twentieth century, blow-molded bottles have become the preferred packaging format for a wide range of solid oral dosage forms. Blow-molded bottles offer design flexibility and the ability to produce lightweight containers with integrated geometries. The blow-molding process also enables the creation of seamless hollow structures that can be optimized for pharmaceutical packaging requirements while maintaining cost-effectiveness at high production volumes.

Over the past decades, the pharmaceutical industry has increasingly recognized that packaging must do more than simply contain a drug product. Modern pharmaceutical packaging is expected to actively contribute to product stability throughout the supply chain and during patient use. This requirement has become particularly important as drug formulations become more complex and experience increased sensitivity to environmental factors such as moisture, oxygen, volatile impurities, and reactive chemical species that can compromise product quality and safety over time.

More recently, the pharmaceutical industry has faced an additional, highly significant challenge: nitrosamine contamination [1-8]. Regulatory agencies worldwide have intensified scrutiny of nitrosamines because of their potential carcinogenic risk and their ability to form through complex interactions involving drug substances, excipients, manufacturing processes, and packaging environments [3, 9]. Even trace levels of reactive nitrogen-containing species can contribute to nitrosamine formation under favorable conditions. As a result, pharmaceutical manufacturers are seeking innovative approaches that not only minimize the presence of nitrosamine precursors, but also actively reduce exposure to reactive gaseous species throughout the product lifecycle.

To address these challenges, packaging technologies are evolving from passive barriers to active protective systems. For example, Aptar Active Material Science's 3-Phase Activ-Polymer™ platform serves as the engine behind a wide range of packaging-led stability and degradation solutions [10]. This advanced material platform integrates active chemistry functionalities directly into physical structures (like blow-molded bottles), creating a packaging solution capable of interacting with and controlling the internal package environment. Rather than relying solely on traditional barrier properties, the technology is designed to capture and immobilize undesirable gaseous species within the package headspace and surrounding microenvironment.
In the case of nitrosamine mitigation, the technology, which is directly integrated into the container wall, traps reactive nitrosating species in the gas phase before they can

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IDEA IN BRIEF

THE PROBLEM

Addressing nitrosamine risk is a complicated, multi-faceted challenge that often requires expensive and time consuming reformulation efforts or major changes to manufacturing processes. Pharma developers need a faster, simpler approach to mitigate this ongoing vulnerability and ensure their products meet regulatory requirements.

THE CHALLENGE

Active material science technologies designed to disrupt the chemical reactions occuring inside the drug packaging effectively prevent nitrosamine formation. However, to streamline adoption, the format in which this technology is deployed needs to align with pharma manufacturers' preferences and needs.

THE SOLUTION

N-Sorb℠ technology can be effectively deployed in a range of formats.This paper explores the efficacy of the technology when integrated into a blown-bottle format, offering pharma developers a mitigation strategy to address risk without reformulation or major changes to their packaging configuration.

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interact with the secondary or tertiary amines present in the drug product. This helps reduce degradation pathways that can compromise product quality and has the potential to significantly improve stability, mitigate the risk of nitrosamine formation, and extend the shelf life of sensitive pharmaceutical products.

The benefits of this approach extend beyond product stability. Longer shelf life can reduce waste, improve supply chain flexibility, support global distribution, and enhance product availability. Most importantly, improved protection of drug quality helps ensure that patients continue to receive medications that meet their intended safety, efficacy, and performance specifications throughout the product's lifecycle.

This white paper explores the scientific principles underlying Aptar's N-Sorb℠ nitrosamine mitigation technology when deployed as a blow-molded bottle and examines its ability to manage the nitrosamine drug substance related impurity (NDSRI) 1-nitroso-4-phenylpiperidin-4-ol, which forms from a building block of active pharmaceutical ingredient (API) "4-phenylpiperidin-4-ol". In the presence of nitrosating agents, such as nitrite or NOx species (nitrosation can also occur by non-nitrogen oxidants) originating from excipients, processing environments, or degradation pathways, the secondary amine of the piperidine ring can undergo nitrosation, leading to the formation of 1-nitroso-4-phenylpiperidin-4-ol. This API building block is a piperidine derivative frequently used as a core scaffold in medicinal chemistry. It serves as a structural base and key synthetic intermediate for developing various opioids, antifungals, and antibacterials.

Through a combination of material science, package engineering, and active environmental control, three N-Sorb℠ blow-molded pharmaceutical containers were prepared containing three different types of active materials. Results demonstrating the mitigation of 1-nitroso-4-phenylpiperidin-4-ol in N-Sorb℠ blow-molded bottles are discussed to illustrate the role of active packaging solutions in advancing pharmaceutical stability protection.

Methods

a) N-Sorb℠ blow-molded bottle production

Three different raw active materials (2 inorganics and 1 organic), previously identified through testing to mitigate nitrosamine formation by scavenging nitrosating agents, were incorporated into the 3-Phase Activ-Polymer™ technology matrix (see Table 1). This proprietary technology is comprised of a base majority polymer that provides the physical structure, a channeling agent, and active particles, as shown in Figure 1. Conversion into the blown bottle deployment method is also shown in Figure 1, where purple indicates the active N-Sorb℠ layer.

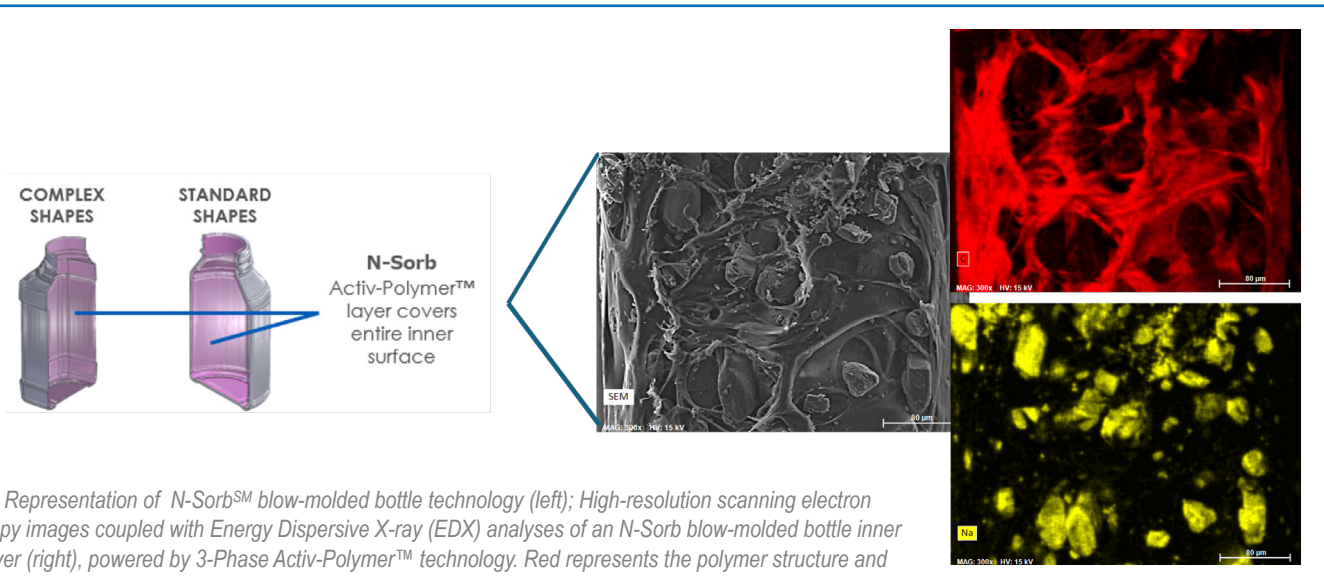

Figure 1. Representation of N-Sorb℠ blow-molded bottle technology (left); High-resolution scanning electron microscopy images coupled with Energy Dispersive X-ray (EDX) analyses of an N-Sorb blow-molded bottle inner active layer (right), powered by 3-Phase Activ-Polymer™ technology. Red represents the polymer structure and yellow the active particles within the channels of the polymer in the blow molded bottle inner active layer.

b) *Manufacturing 4-phenylpiperdin-4-ol hydrochloride tablets*

Tablets of 4-phenylpiperidin-4-ol hydrochloride were formulated in house using batches of 100 g (see composition in Table 2). These tablets were formulated to generate the nitrosamine "1-nitroso-4-phenylpiperidin-4-ol" by the nitrosation of the piperidine nitrogen (secondary amine) present in the 4-phenylpiperidin-4-ol hydrochloride (see Figure 2). While nitrosating agents can be present as native impurities in the excipients used in oral solid doses, a dedicated nitrite source was added to the formulation to ensure nitrosamine formation occurred during testing.

c) *Nitrosamine testing*

Nitrosamine evaluation was completed using an Agilent 6546 LC/QTOF/MS system. Prior to analysis, a calibration curve for 1-nitroso-4-phenylpiperidin-4-ol was established following validated LC MS methods. Solvent systems — including 0.2% formic acid in water, 100% methanol, and 50/50 acetonitrile/water — were prepared using pre-cleaned glassware and used throughout testing. After aging, samples were prepared by dissolving tablets in 50/50 acetonitrile/water, followed by sonication, centrifugation, and transfer into HPLC vials, while blanks were prepared using diluent alone. All samples and blanks were then placed on the instrument for nitrosamine analysis under previously defined parameters. The LOD and LOQ for this analyte with the established method was determined as 50 ppb and 100 ppb, respectively. For sample aging, 9 tablets were added to each blow-molded bottle, which were capped and induction sealed. The bottles were placed into accelerated aging conditions (40°C, 75% RH) for 6 months.

d) *NO_X samples preparation & testing*

Volatile NOx concentration was determined by GC-MS Headspace sampling methods adapted from solid nitrite content analysis. For comparison, blow-molded bottles without the N-Sorb℠ active technology were used as controls. For NOx generation inside the blow-molded bottles, a 4.25 mL of potassium nitrite solution (100 g/L of deionized water) and 4.25 mL of 1M of aqueous sulfuric acid solution were placed into a scintillation vial. The bottles were then immediately capped and induction sealed. After 1 week of aging at room temperature, the concentration of NOx gas formed in the headspace of each bottle was analyzed using GC-MS.

Blow-molded Bottle ID	Active
Control	n/a - Resin only
N-Sorb D	Inorganic active material 1
N-Sorb F	Inorganic active material 2
N-Sorb G	Organic active material 1

Table 1: Blow-molded bottle description

Excipient	Percentage by Mass
4-phenylpiperdin-4-ol hydrochloride	12.06
Microcrystalline cellulose	25.48
Lactose monohydrate	25.48
Calcium phosphate, dibasic	25.49
Sodium starch glycolate	4.4
Polyvinylpyrrolidone	4.4
Silicon dioxide	0.88
Magnesium stearate	0.88
Sodium stearyl fumarate	0.88
Sodium nitrite	0.05
Total	**100**

Table 2: 4-phenylpiperdin-4-ol hydrochloride tablet formation

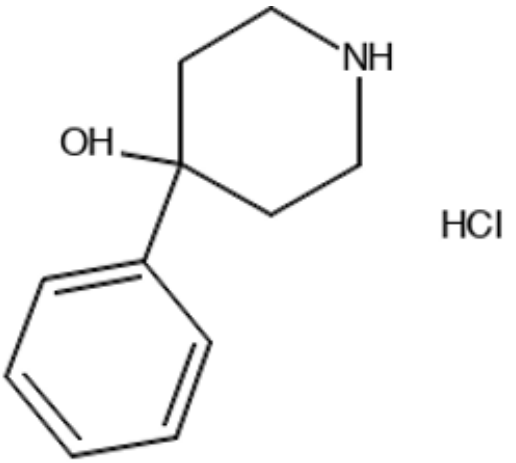

Figure 2: Representation of the chemical structure of the 4-phenylpiperdin-4-ol hydrochloride

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Results & Discussion

Figure 3 presents the concentration of 1-nitroso-4-phenylpiperidin-4-ol (hereafter referred to as 4 ol) formed in tablets stored for 1, 3, and 6 months inside the different blow-molded bottle formulations. In the control bottles, 4 ol formation showed a rapid increase for the first month of aging. Then, the rate of formation appeared to slow drastically between months 1 and 6 (almost in equilibrium). This progressive accumulation confirms that, in the absence of active mitigation, nitrosating species present in the packaging environment can drive the formation of NDSRIs over the product's shelf life.

In contrast, the three bottle formulations with integrated N-Sorb℠ active layers consistently exhibited lower 4 ol concentrations at all time points. This reduction highlights the ability of the N-Sorb℠ technology to intercept and neutralize nitrosamine precursors, thereby limiting the probability of nitrosamine formation within the drug product. Among the tested formulations, N-Sorb F delivered the strongest performance, achieving a 63% prevention in 4 ol formation after six months compared with the control. This substantial decrease demonstrates the efficiency of N-Sorb F in mitigating nitrosating species responsible for generating nitrosamines.

This study supports the proposed mechanism of action: N-Sorb℠ technology works to prevent nitrosamine formation by scavenging nitrosamine precursors (nitrosating agents, NOx, nitrites) before they can react with the amine.

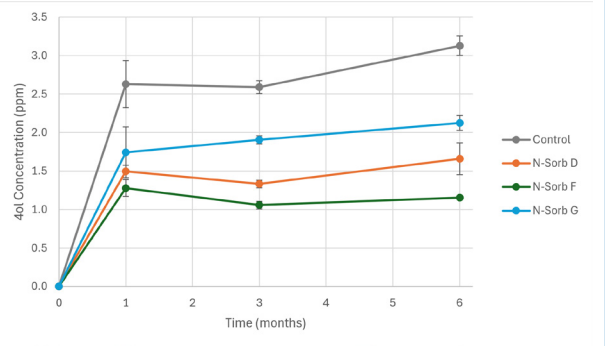

Figure 3: Nitrosamine Concentration in Formulated Tablets within N-Sorb Blown Bottles vs. Time

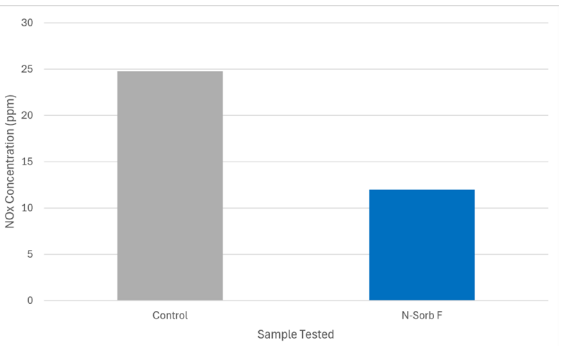

Figure 4: NOx Concentration in N-Sorb Blown Bottles vs. Control at 1 week of ambient aging

To further validate the reactivity of the N-Sorb℠ technology toward nitrosating species, an additional experiment was designed to assess the interaction of N-Sorb F with NOx. NOx is known to be one of the major nitrosating agents, attacking secondary and tertiary amines to form nitrosamine species. Figure 4 shows the NOx concentration in the different bottles. The control bottles averaged 24.77 ppm of NOx after 1 week of aging at room temperature conditions. The N-Sorb F bottle reduced the NOx concentration by 51.6%, also supporting the predicted mechanism of action above.

Conclusion

The findings presented in this paper demonstrate that blow-molded bottles incorporating N-Sorb℠ technology, provide a highly-effective mitigation strategy against nitrosating agents, and therefore nitrosamine formation in drug products, with N-Sorb F delivering the strongest results. Under accelerated storage conditions, this formulation reduced the formation of 1-nitroso-4-phenylpiperidin-4-ol by 63% after six months of aging, confirming its ability to actively scavenge and neutralize nitrosating species such as NOx and nitrites.

By targeting the root causes of nitrosamine formation — environmental and excipient derived nitrosating species — N-Sorb℠ technology provides a robust solution. This approach enables pharmaceutical manufacturers to protect patients, extend product shelf life, and avoid costly reformulation or redevelopment efforts, while maintaining compliance with evolving regulatory expectations. Together, these results position N-Sorb℠ technology as a next-generation, packaging-led solution for strengthening nitrosamine control strategies across the industry, supporting safer and more reliable drug products throughout their lifecycle.

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