Mitigating N-Nitrosamine Risks with Novel Active Material Science Innovations

Jason Pratt
Director, Material Science
Aptar CSP Technologies

Jean Daou
R&D Manager
Aptar CSP Technologies

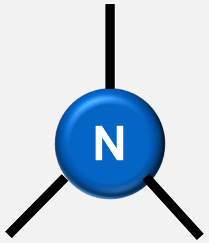
Matt Riccio
Business Development
Aptar CSP Technologies

Aptar CSP Technologies

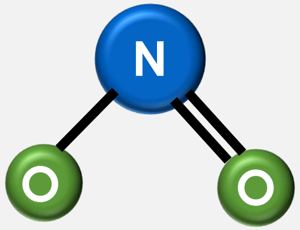
Confidential and Proprietary Property of Aptar CSP Technologies

Nitrosamines: The Basics

- Nitrosamines are a family of probable carcinogenic impurities formed by the reaction of secondary amines with other nitrosating agents
- Nitrosamines are classified as Class 1 impurities: "**known mutagenic carcinogens**"



Amines can be naturally occurring in starting materials or can result from the breakdown of other compounds during synthesis.



Nitrite sources can be introduced inadvertently or originate from specific reagents or other environmental factors.

Timeline

2018

Detection of N-nitrosodimethylamine (NDMA) in Valsartan triggers global recalls of medications

2019-2020

FDA and EMA guidance released outlining mitigation strategies to control nitrosamine impurities

2021-Today

Ongoing focus on nitrosamine control:

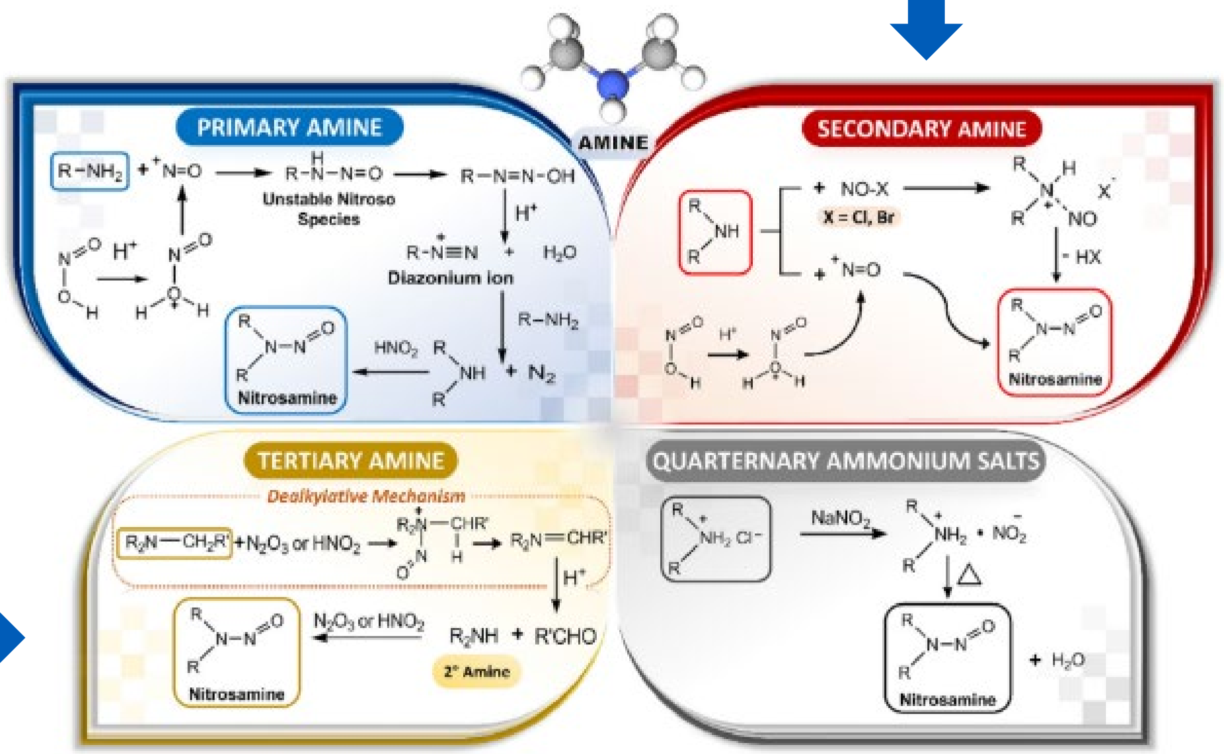
- Development of industry-wide best practices
- Continued research into potential health risks in medications
- Growing demand for innovative solutions to address nitrosamine formation in pharmaceutical packaging

In silico analysis of more than 12,000 small molecule drugs determined that **40% of API's** have the potential for the formation of N-nitrosamine impurities.*

* Joerg Schlingemann, Michael J. Burns, David J. Ponting, Carolina Martins Avila, Naiffer E. Romero, Mrunal A. Jaywant, Graham F. Smith, Ian W. Ashworth, Stephanie Simon, Christoph Saal, Andrzej Wilk, "The Landscape of Potential Small and Drug Substance Related Nitrosamines in Pharmaceuticals", Journal of Pharmaceutical Sciences (2022), doi: https://doi.org/10.1016/j.xphs.2022.11.013.

The Problem

- **Nitrosamines** are **probable carcinogens** that can form in oral dosage drug products containing nitrosating agents like nitrite
- Global regulatory requirements (incl. FDA & EMA) regarding nitrosamine impurities **mandate strict limits**
- **Increasing pressure** to comply and implement **effective strategies** to mitigate nitrosamine formation and prevent recalls



Reaction Needs:

- Secondary or tertiary amines (active ingredient, degradation product, excipient, impurity)
- Nitrosating agent (nitrite, NO_X, etc.)
- Specific environnmental conditions (low pH, T°)

FDA Recommended AI Limits

FDA website includes recommended AI limits for 251+ NDSRIs ranging from 8 ng/day to 1,500 ng/day

Potency Category	Recommended AI (ng/day)	Comments
1	26.5	Based on most potent tested nitrosamine, N-nitrosodiethylamine (NDEA).
2	100	Based on NDMA and NNK. This category shall exhibit limits no higher than these two nitrosamines.
3	400	Lower carcinogenic potency. Set to reflect a 4-fold decrease in carcinogenic potency.
4	1500	NDSRIs assigned to Category 4 may be metabolically activated through an alphahydroxylation pathway but are predicted to be of low carcinogenic potency
5	1500	NDSRIs assigned to Category 5 are not predicted to be metabolically activated via an a-hydroxylation pathway due to steric hindrance or the absence of a-hydrogens, or are predicted to form unstable species that will not react with DNA.

https://public.tableau.com/app/profile/naiffer.romero/viz/NitrosaminesRegulatoryAILimits/Dashboard1

Confidential and Proprietary Property of Aptar CSP Technologies

Regulators' Current Expectations

Stage 1: Risk Assessment

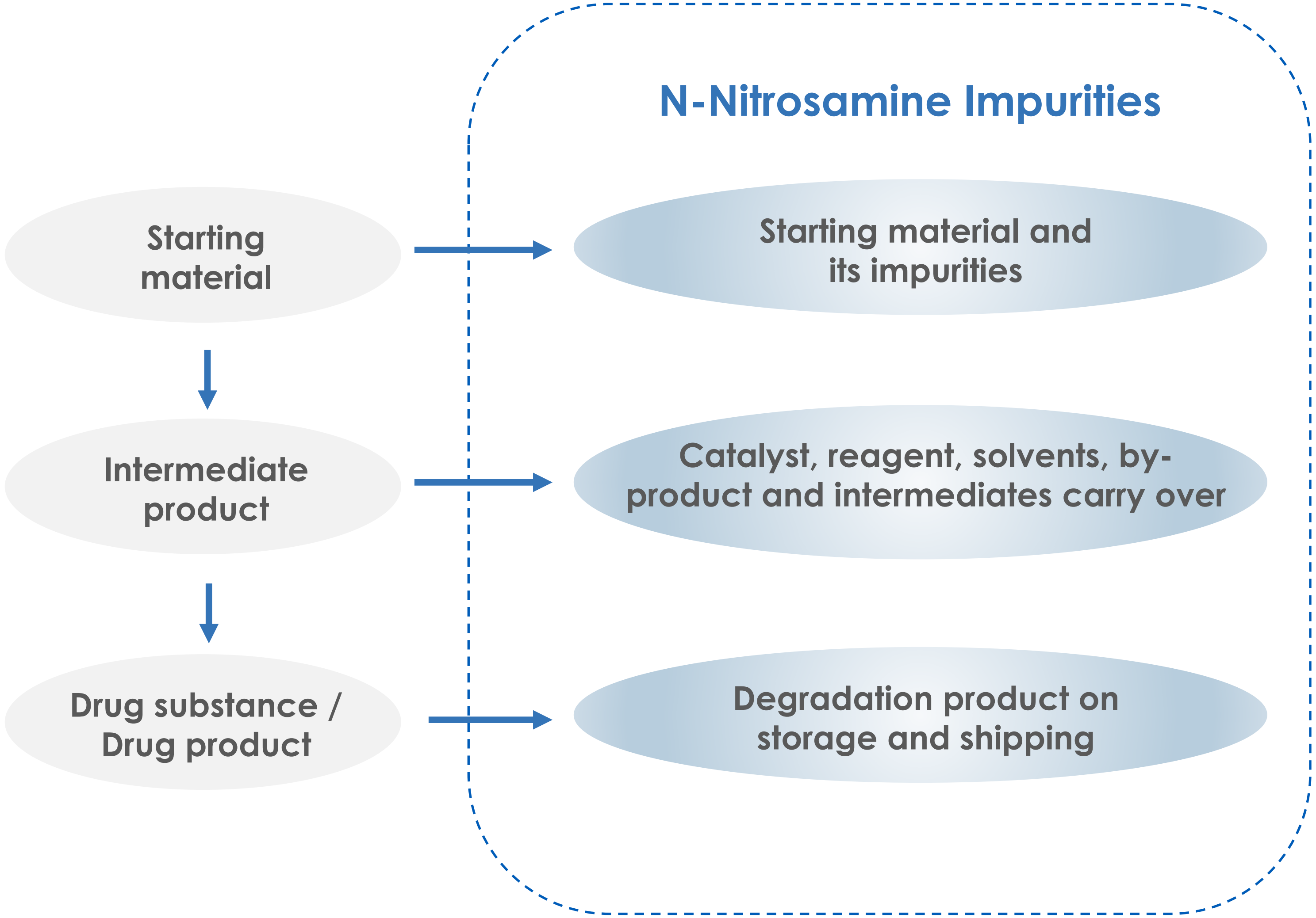
- Assess risk of nitrosamine impurities

Stage 2: Confirmatory Testing

Stage 3: Reporting and Mitigation Strategies

- Report findings of risk assessment and testing to FDA
- Report changes to prevent presence of impurities in approved and pending NDAs

> Manufacturers must ensure NDSRI's in their drug products meet the AI limits by August 2025.



Aptar CSP Technologies

Regulators' Current Expectations

Stage 1: Risk Assessment

- Assess risk of nitrosamine impurities

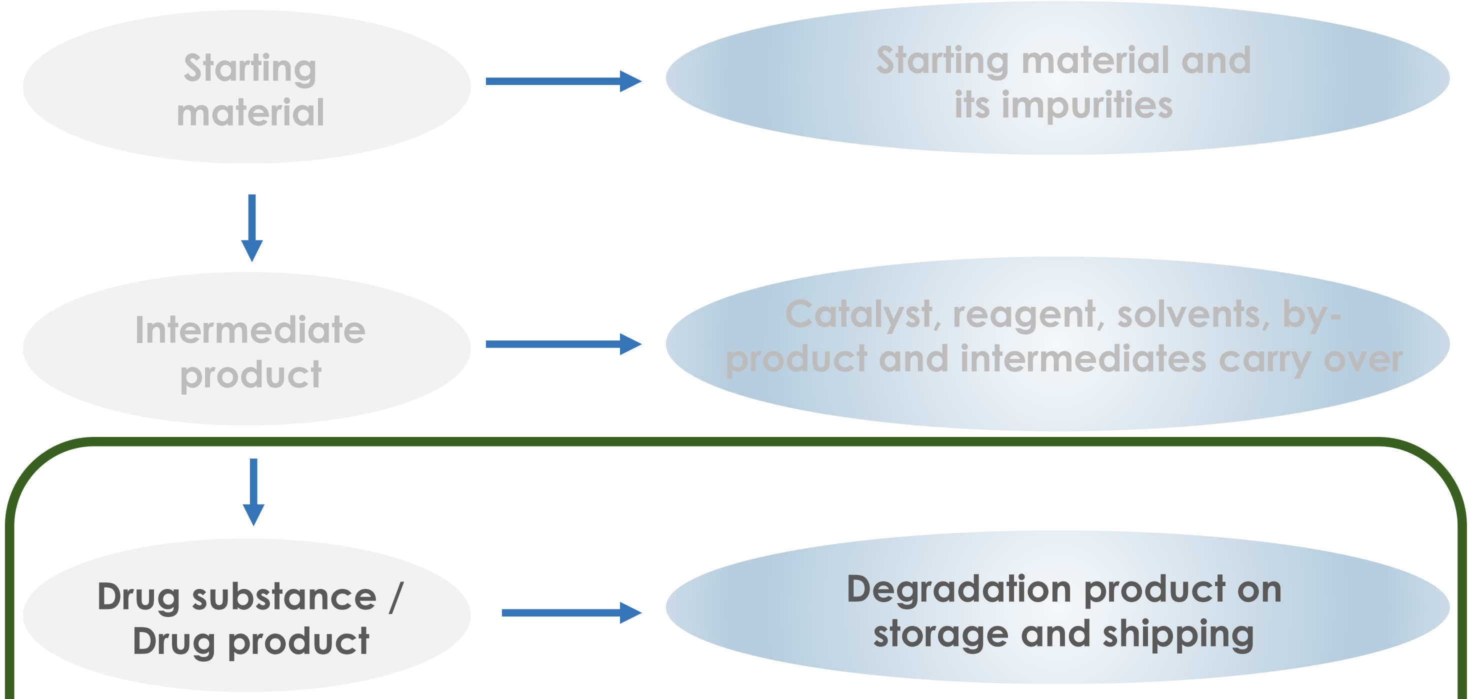
Stage 2: Confirmatory Testing

Stage 3: Reporting and Mitigation Strategies

- Report findings of risk assessment and testing to FDA
- Report changes to prevent presence of impurities in approved and pending NDAs

Manufacturers must ensure NDSRI's in their drug products meet the AI limits by August 2025.

N-Nitrosamine Impurities



CSP's solution can support Regulatory Compliance by ensuring that NDSRI impurities remain below specified limits thought out shelf life, from the packaging stage, until shipping, storage, and patient use.

Aptar CSP Technologies

The Challenge

- **Targeting all precursors**
- **Analytical limitations**
- **Balancing efficacy and safety**
- **Cost and feasibility of implementing preventive measures**
- **Evolving regulatory landscape**

Direct Costs
Assembling crisis team, removing product, investigating root cause, managing PR, etc.

Impact on **brand reputation** in industry and with consumers

Lost Sales
Retailers may pull entire line (not just recalled items); clients may reduce order volumes

Decline in **stock market** value

Litigation costs from claiming damages, prosecution by government agencies

Fines from government agencies

COSTS

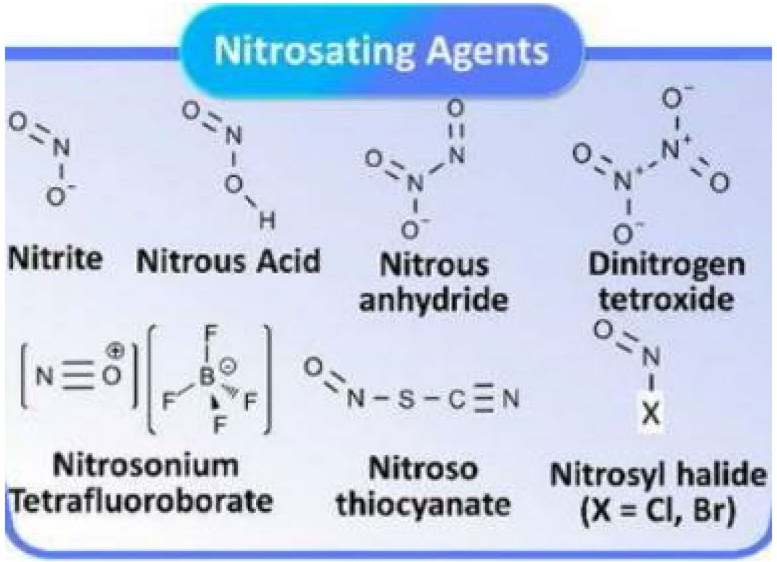
Mitigations Currently Employed

- **Starting Material Selection**
- **Process Control**
- **Scavengers**
- **Alternative Excipients**
- **Advanced Analytical Techniques**

CSP Technologies Packaging Mitigation Pathway

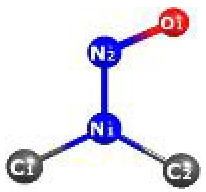
2 Strategies

Targeting Nitrosating Agents

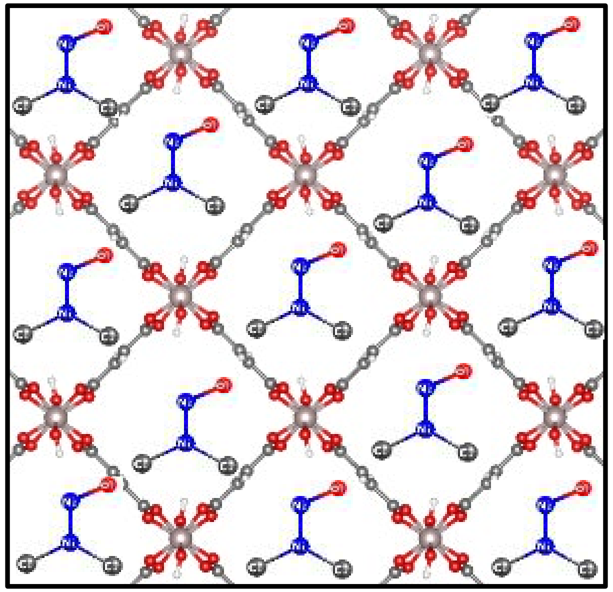


Targeting N-nitrosamine Molecules

Nitrosamines



NDMA



Porous Materials

CSP Activ-Polymer™ Platform Technology – How We Do It

1 Majority Polymer

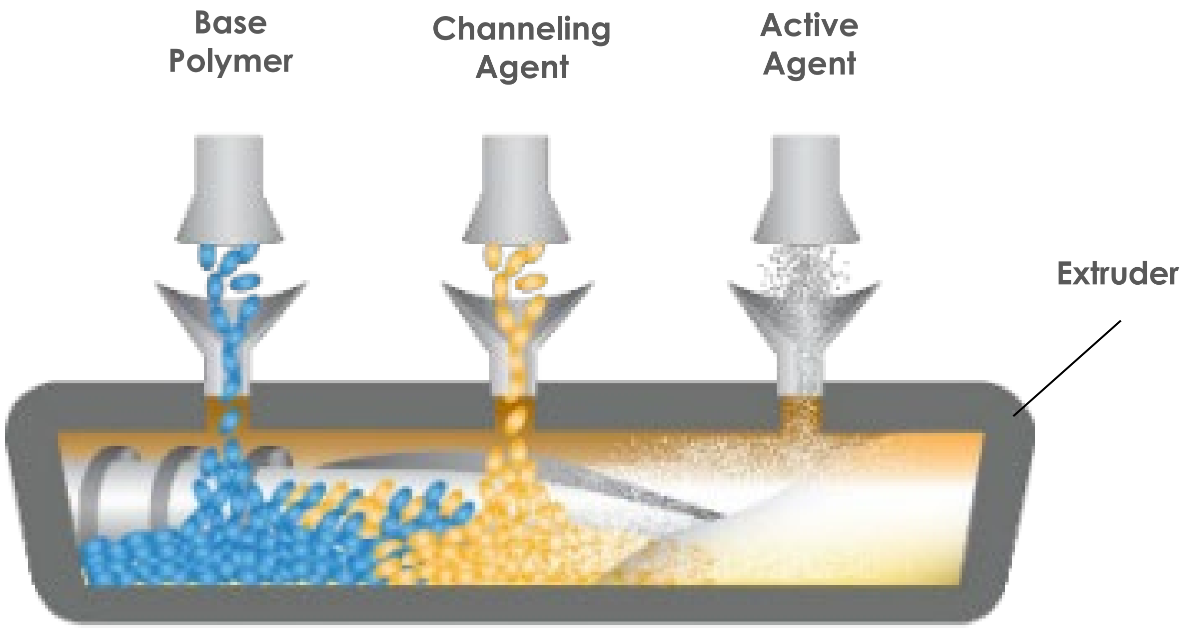
Base Structure Component

2 Particle

Mitigating Active Agent – Reacting, buffering, etc.

3 Minority Polymer/ Channeling Agent

Immiscible in majority polymer

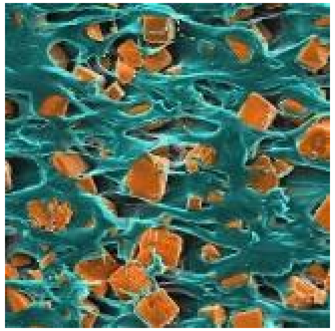


Aptar CSP Technologies

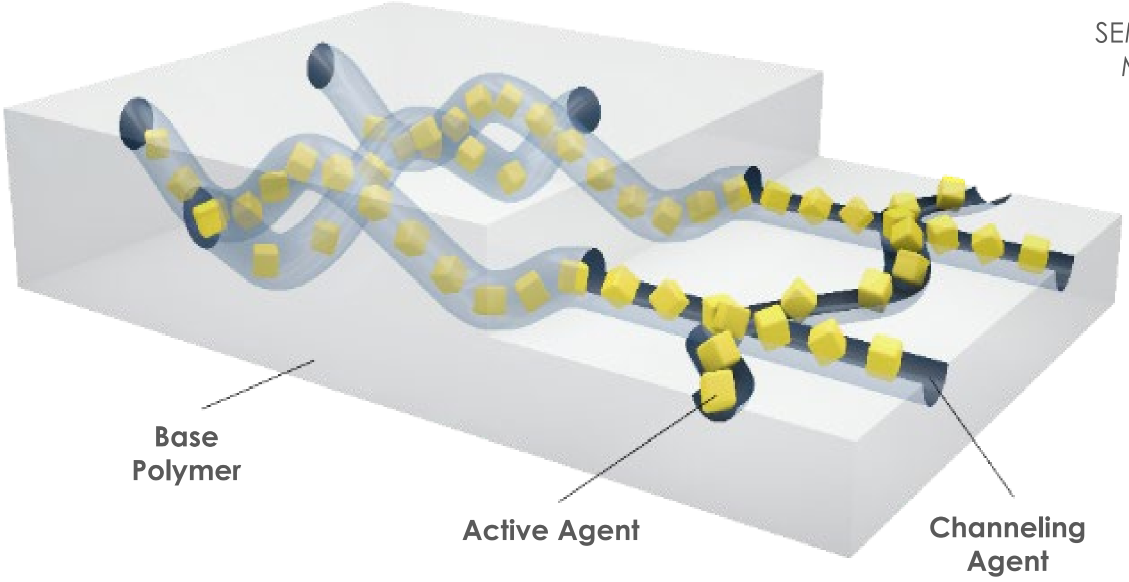
Material Science: Adding Chemistry to Polymers

HOW IT WORKS:

- Channels created within a polymer allow movement of gases
- "Active" particles are added to polymer to:
  - **Adsorb** or **Absorb**
  - **Scavenge**
  - **Release/Emit**
  - **Buffer**
  - **React**
- **Gas diffusion** is controlled through the channel composition



SEM Image Inside the Matrix of 3-Phase Activ-Polymer™ Technology



Delivery Mechanism

Activ-Polymer™ Multi-Layer Bottle Wall

COMPLEX SHAPES

STANDARD SHAPES

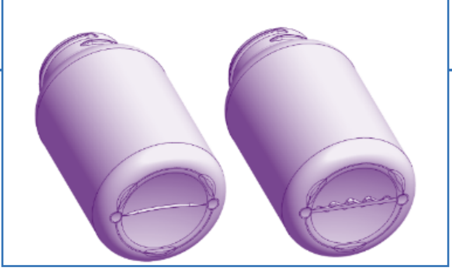
HDPE Outer Bottle Wall

Moisture Flow Direction

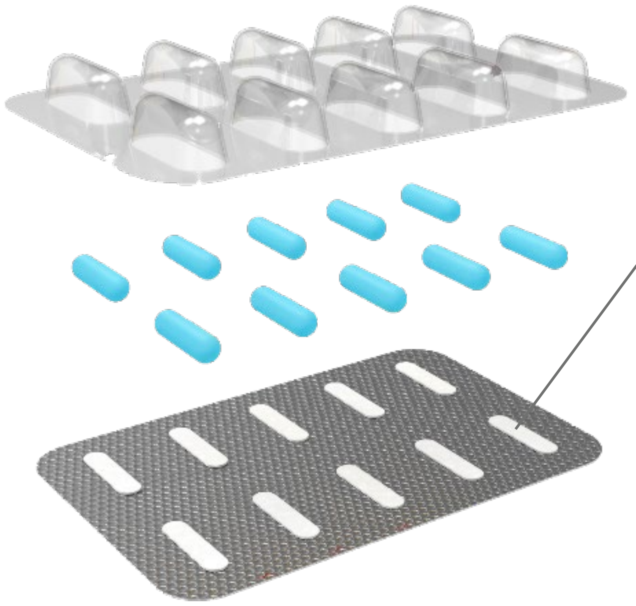
Activ-Polymer™ layer covers entire inner surface to maximize protection

HDPE Outer Bottle Wall

Moisture Flow Direction



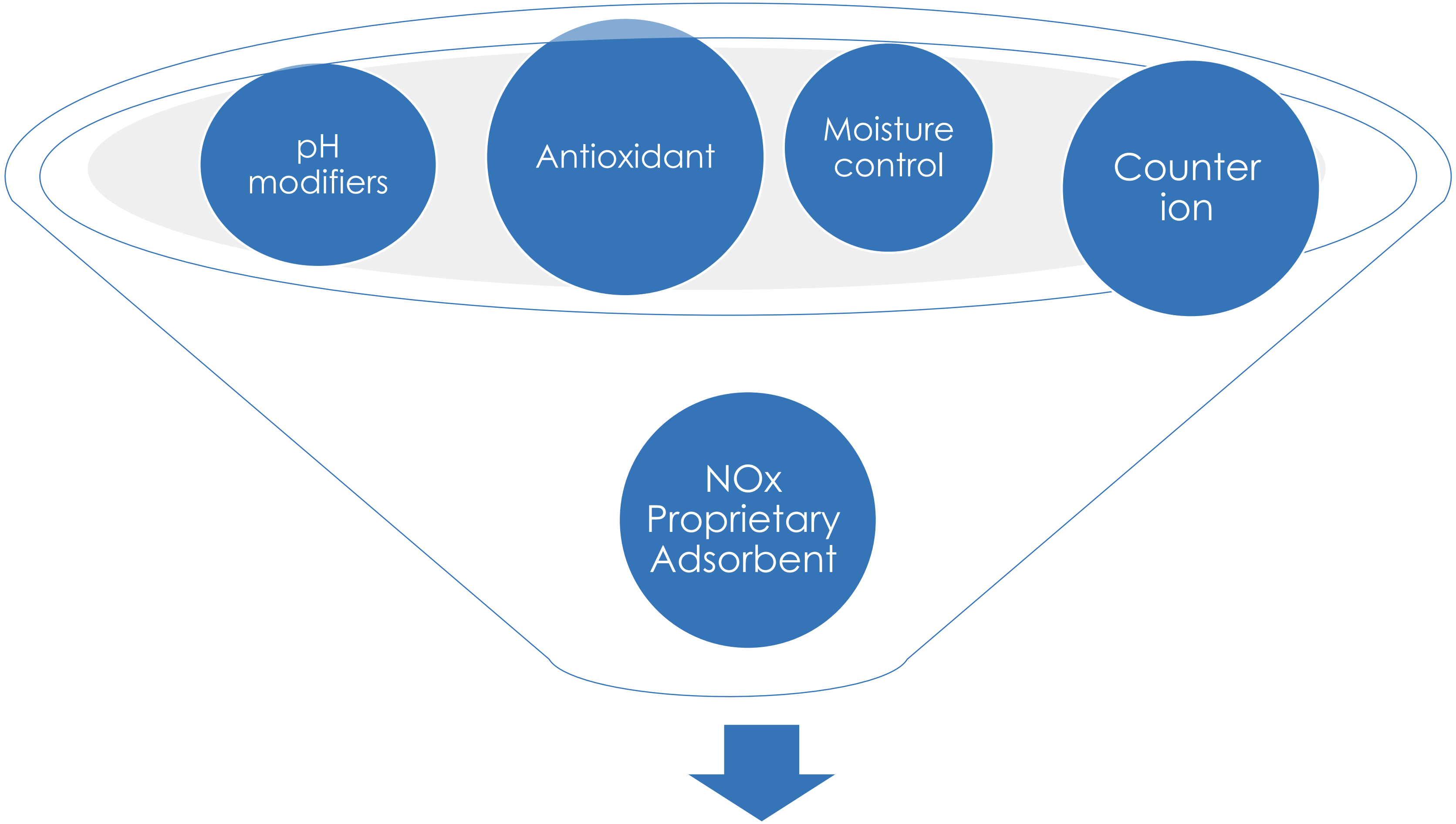
Activ-Blister™ Solutions



Activ-Film™ Material

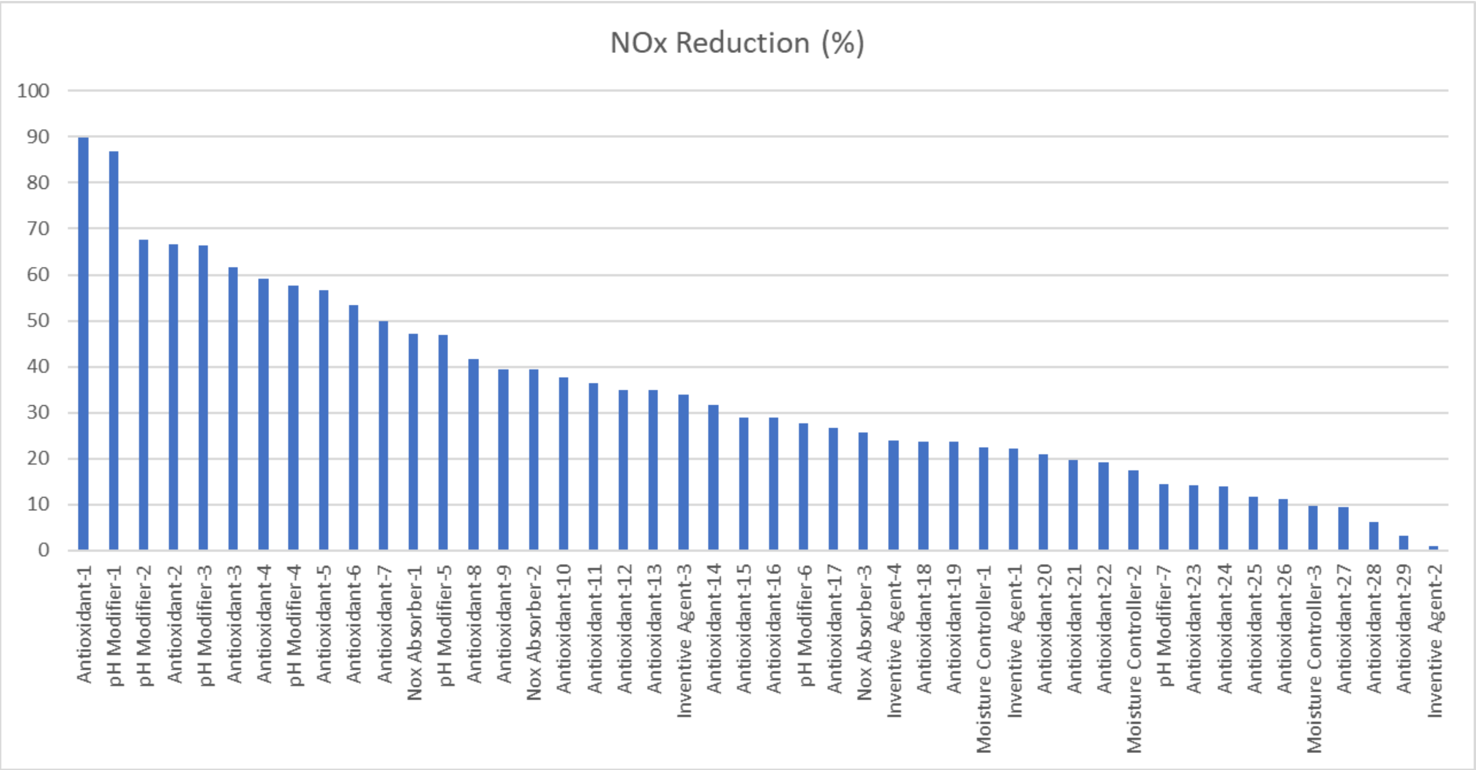
Aptar CSP Technologies

Mitigant Screening



264 active agents evaluated to test

Top 50 Materials Screened



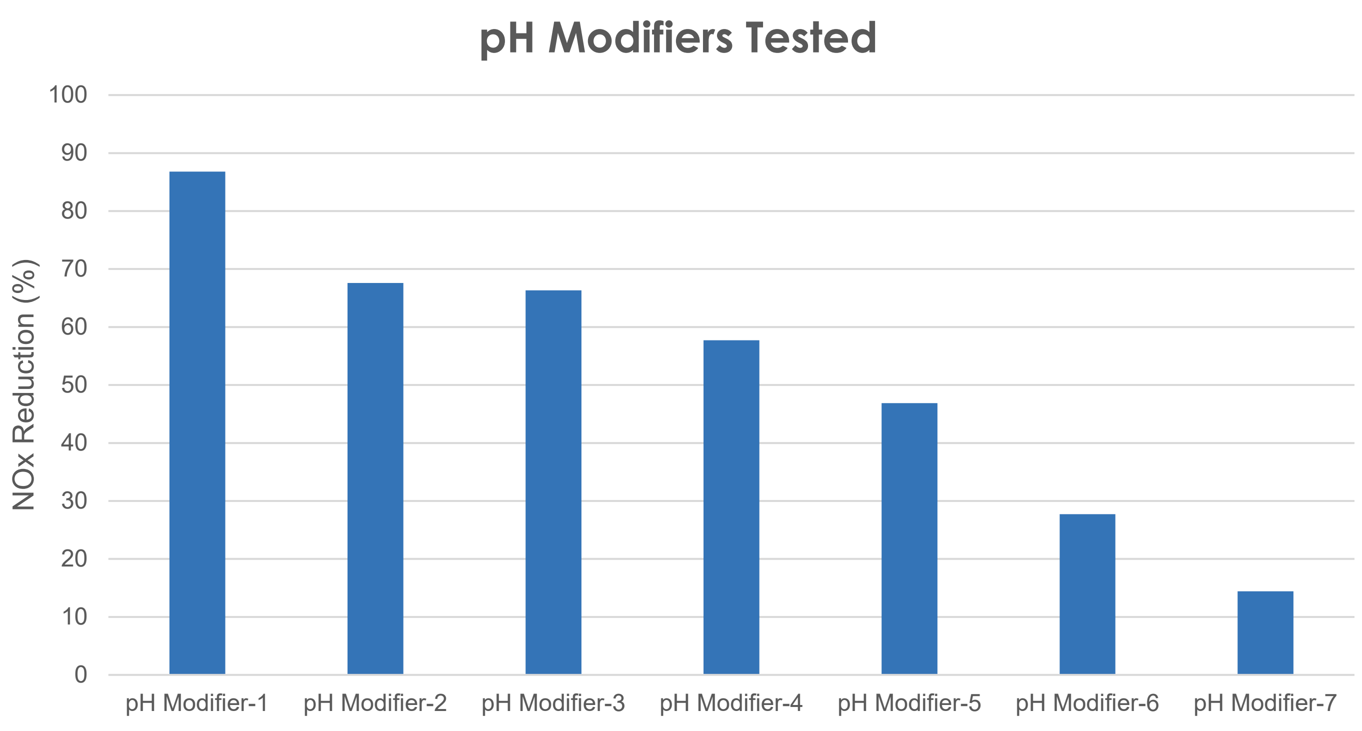
EXPERIMENTAL METHOD:

- 50 mg of active agent suspended
- 2 mL NOx providing solution
- Aged 24 hrs at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

50 active agents screened, ranging from 0-90% NOx reduction.

Aptar CSP Technologies

pH Modifiers

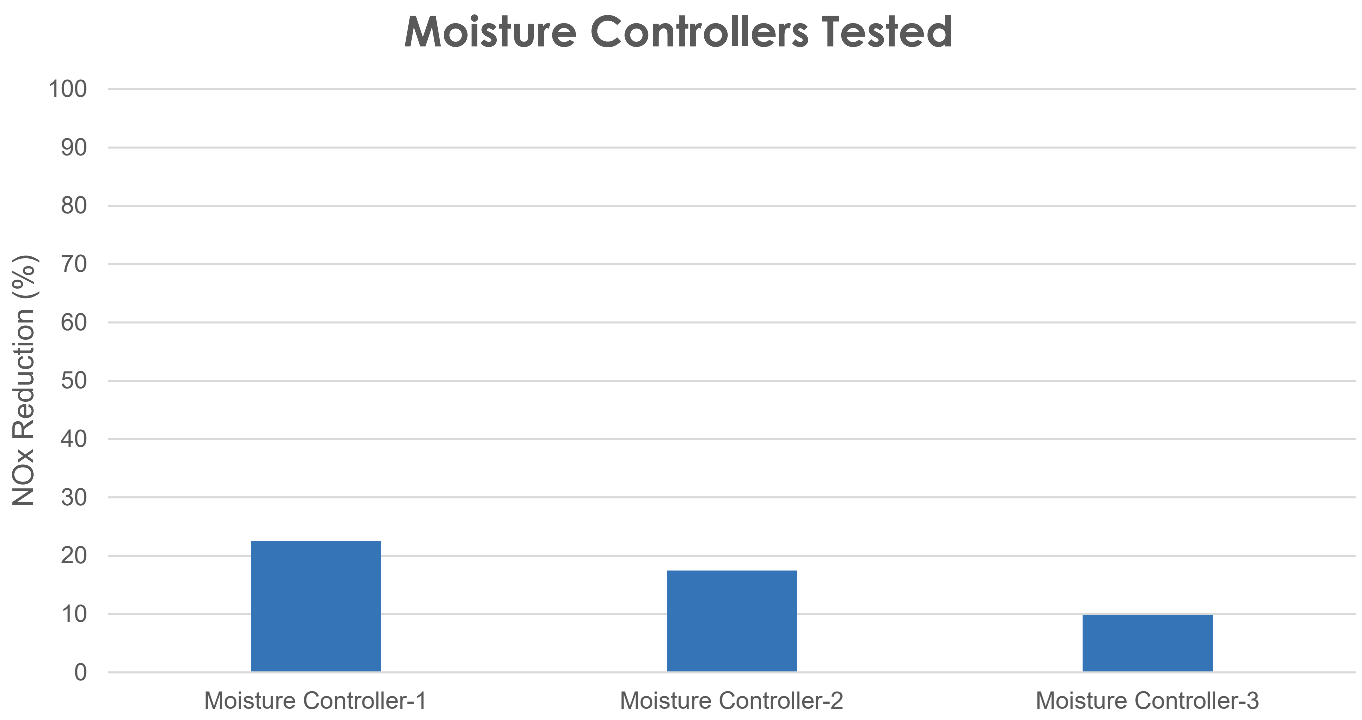


EXPERIMENTAL METHOD:

- 50 mg of active agent suspended
- 2 mL NOx providing solution
- Aged 24 hrs at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

85%-15% NOx reduction.

Moisture Control Actives

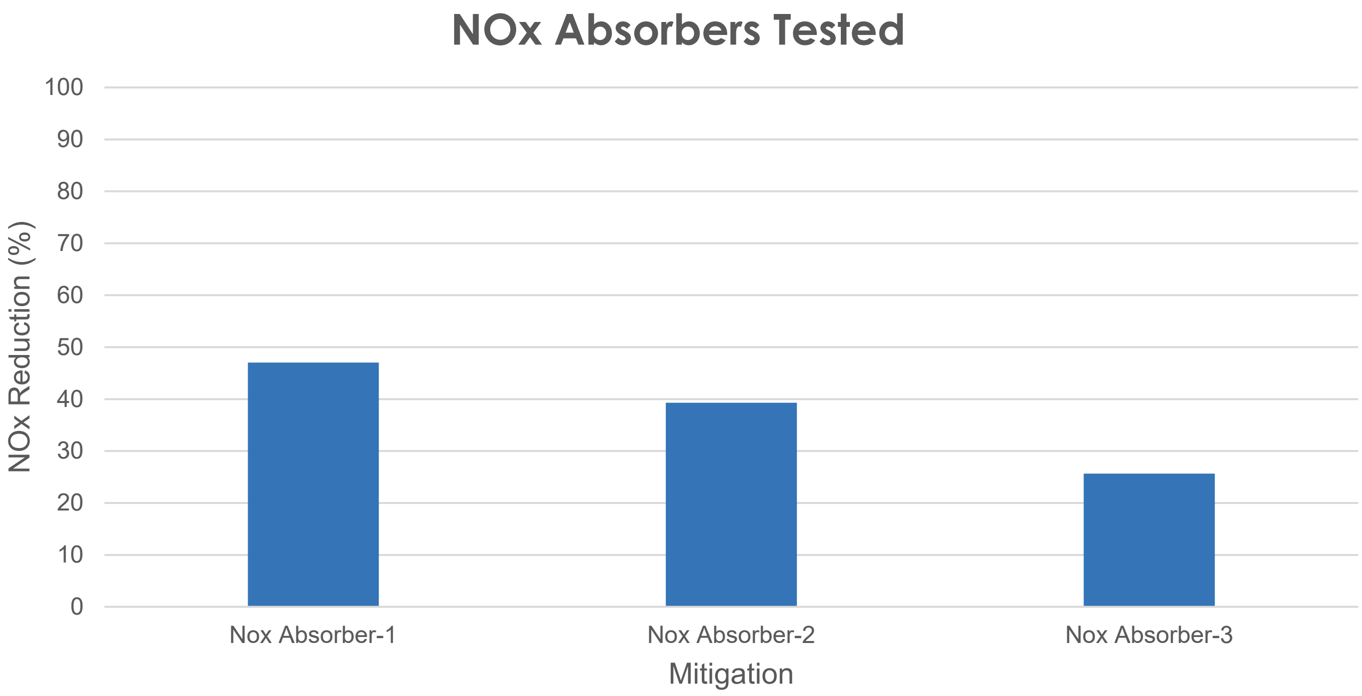


EXPERIMENTAL METHOD:

- 50 mg of active agent suspended
- 2 mL NOx providing solution
- Aged 24 hrs at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

10-25% NOx reduction

NOx Absorbers/Adsorbers & Metal Organic Frameworks (MOFs)



EXPERIMENTAL METHOD:

- 50 mg of active agent suspended
- 2 mL NOx providing solution
- Aged 24 hrs at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

45-25% NOx reduction

Aptar CSP Technologies

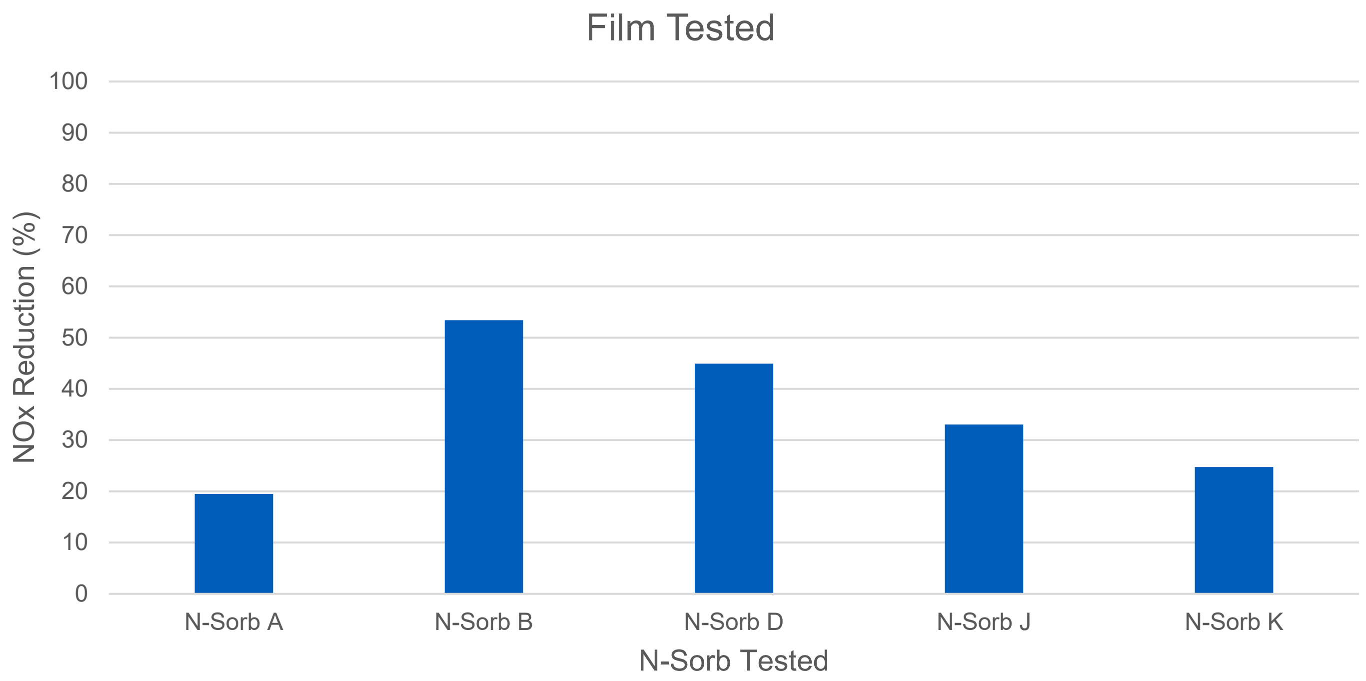
Confidential and Proprietary Property of Aptar CSP Technologies

Experimental Summary: Mitigation Solution Actives

Activ-Polymer™ Nitrosamine Mitigation Solutions	Activ-Film™ Platform	Proposed Mechanism of Action (MOA) Hypothesis
N-Sorb A	Engineered Oxygen Scavenger	Traps free radicals such as NO so that NO is not available to react with molecular oxygen and nitrogen to form NO_2 or N_2O_3 (nitrosating agents).[a]
N-Sorb B	Antioxidant	Reduces the nitrosating agent to non-nitrosating nitric oxide or via nitration reactions.[b]
		Yields dinitrosyl ascorbate.[c]
N-Sorb C	Alkaline Compound	Increases pH to create conditions less favorable to Nitrosamine formation [d]
		Reduces reactivity of nitrite ions
N-Sorb D	Modified Activated Carbon	Removal of nitrosamine precursors (nitrosating agents or amines) and nitrosamines post formation
N-Sorb E	Ionic Compund	Impacts chemical equilibrium of nitrosation reactions by altering solubility [e]
N-Sorb F	Alkaline Buffer	Acts as a buffer to impact the pH
		Increases pH to create conditions less favorable to Nitrosamine formation [d]
N-Sorb G	Antioxidant	Scavenges reactive oxygen and nitrogen species including NO radicals [a]
		Neutralizes radicals to prevent chain reactions to form nitrosamines

[a] Rapid formation of N-nitrosamines from nitrogen oxides under neutral and alkaline conditions (B C Challis, A Edwards, R R Hunma, S A Kyrtopoulos, J R Outram)
[b] Free Radical Properties, Source and Targets, Antioxidant Consumption and Health (Martemucci, Giovanni, Ciro Costagliola, Michele Mariano, Luca D'andrea, Pasquale Napolitano, and Angela Gabriella D'Alessandro)
[c] Inhibition of N-Nitrosamine Formation in Drug Products: A Model Study (Kausik K. Nandaa, Steven Tignorb, James Clancyc, Melanie J. Marotac, Leonardo R. Allainb, Suzanne M. D'Addioa)
[d] PRESERVATIVES | Permitted Preservatives – Nitrites and Nitrates (J.H. Subramanian, L.D. Kagliwal, R.S. Singhal)

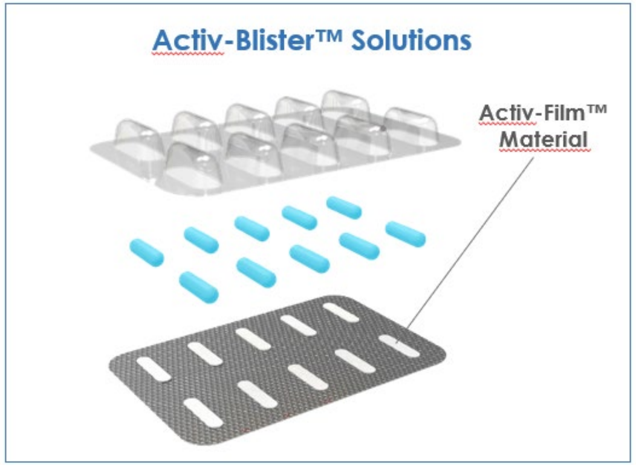
Engineered Activ-Film™ Technology



EXPERIMENTAL METHOD:

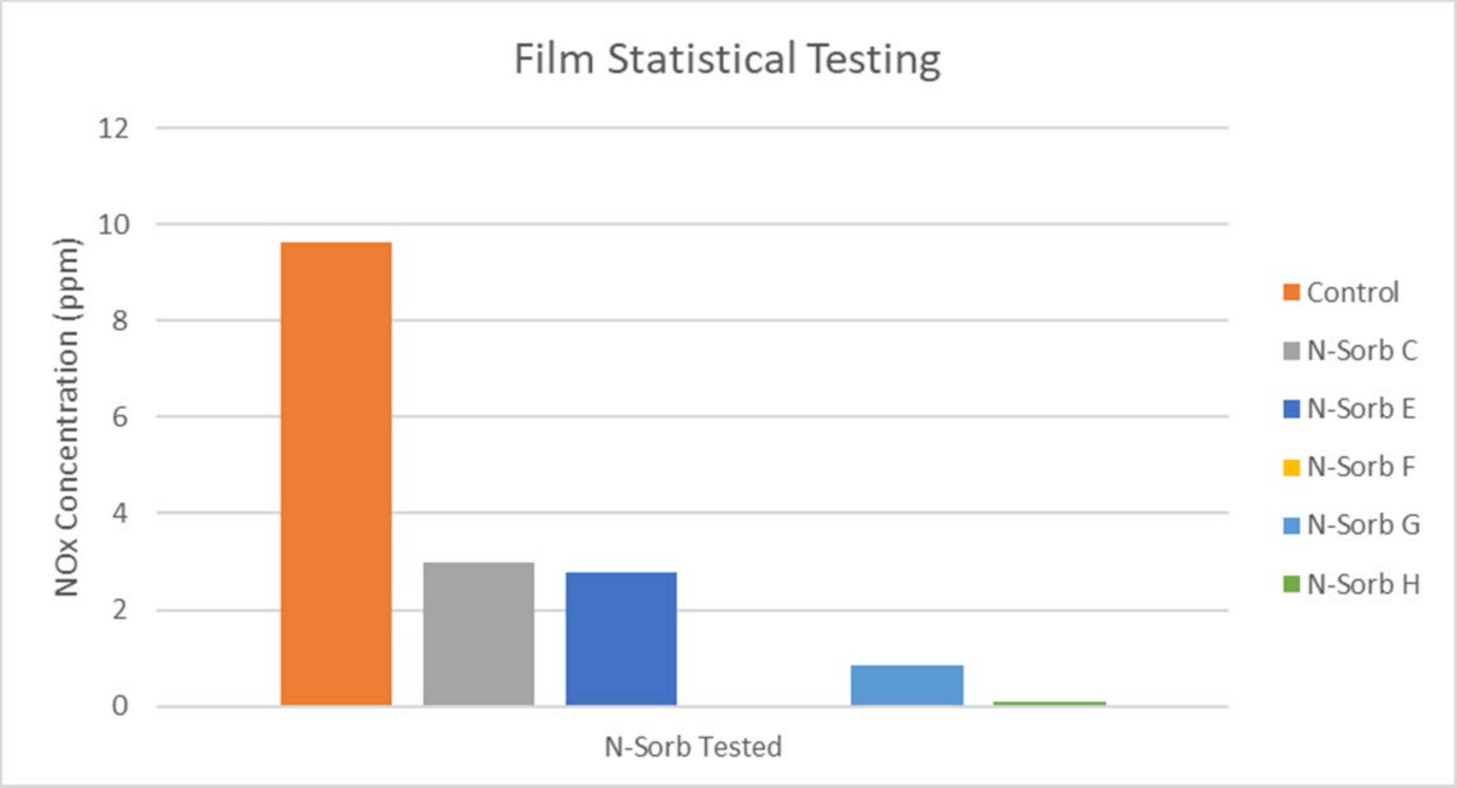
- 1 cm^2 of N-Sorb film suspended
- 2 mL NOx providing solution
- Aged 24 hrs at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

Film showed 15-55% NOx reduction



Aptar CSP Technologies

Top 5 Films Statistical Analysis

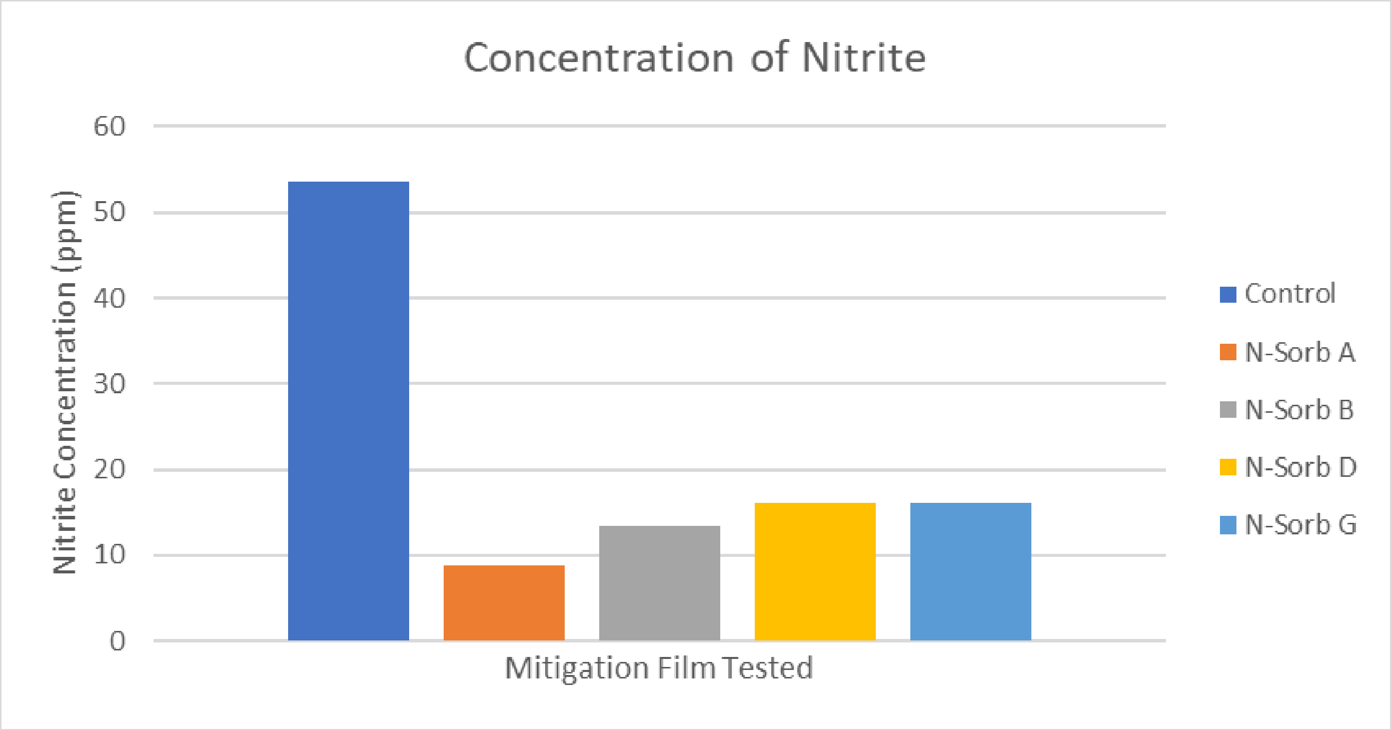


EXPERIMENTAL METHOD:

- 1 cm^2 of N-Sorb film
- N=30 all films
- 2 mL NOx providing solution
- Aged 7 days at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

Film showed max concentration of 0 – 3 ppm NOx remaining

Nitrite Adsorption in MCC* tablets



EXPERIMENTAL METHOD:

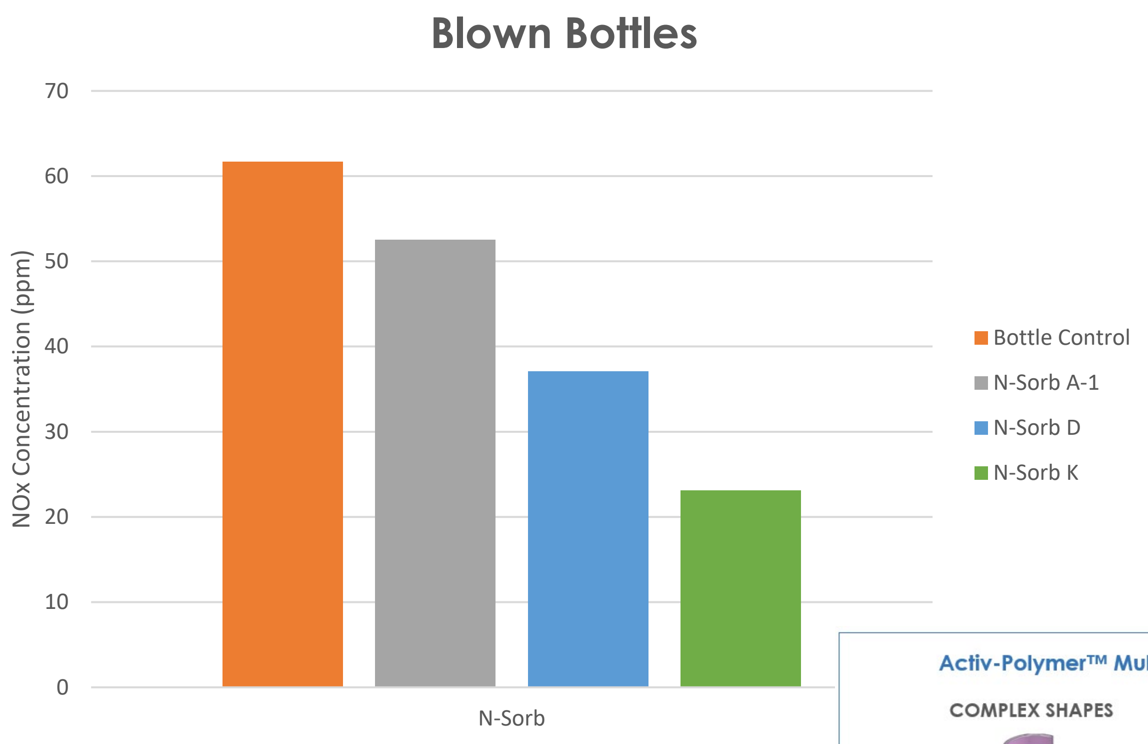
- CSP N-Sorb Film
- Film and 3 MCC placebo tablets sealed in foil bag
- Aged 6 days at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

>70% drop in concentration of Nitrite against control.

* Microcrystalline Cellulose

Nitrite Scavenger in Activ-Polymer™ Blown Bottles

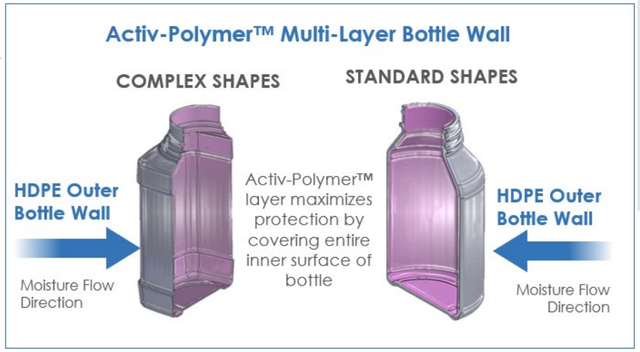
Test 1



EXPERIMENTAL METHOD:

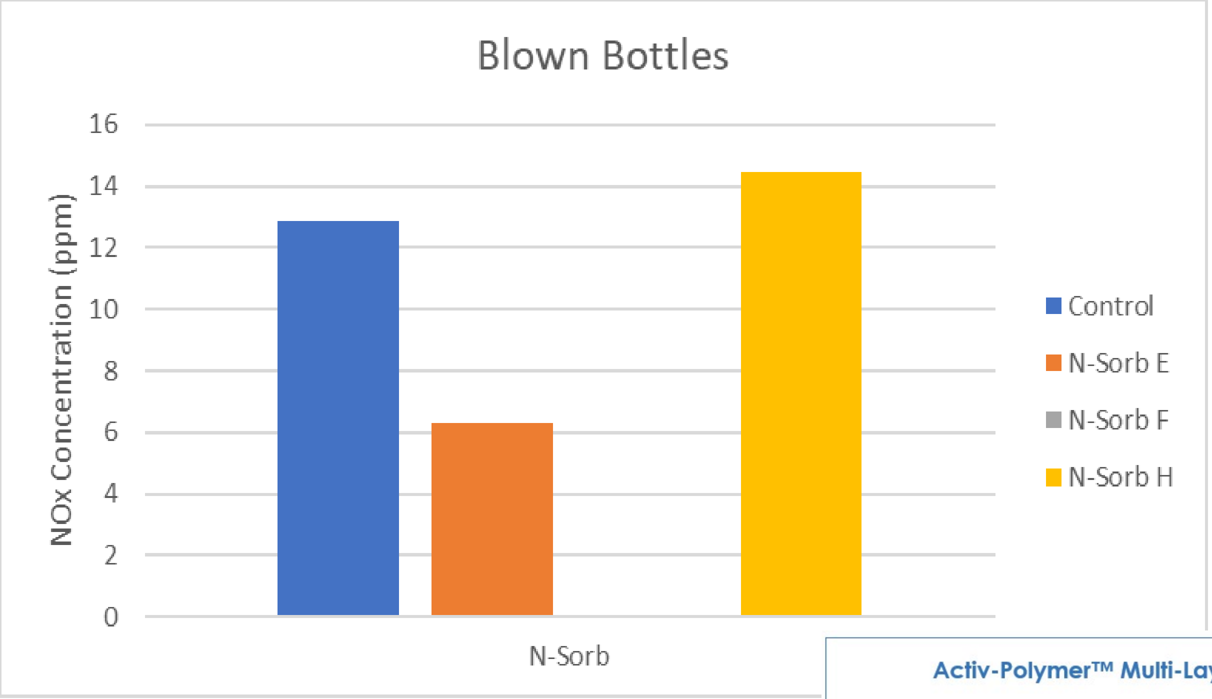
- 8.5 mL NOx providing solution placed in scintillation bottle within blown bottle
- Aged 6 days at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

N-Sorb K showed the most reduction (70%)



Nitrite Scavenger in Activ-Polymer™ Blown Bottles

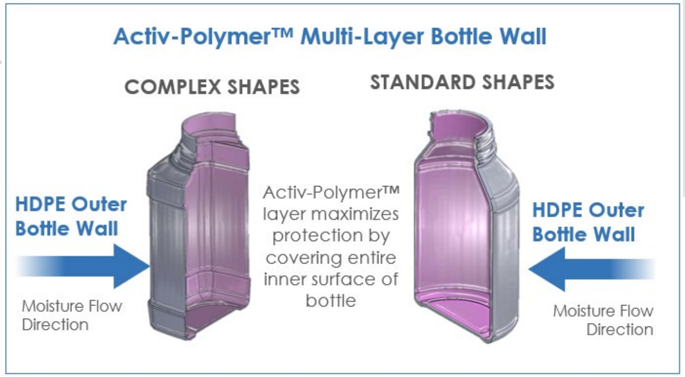
Test 2



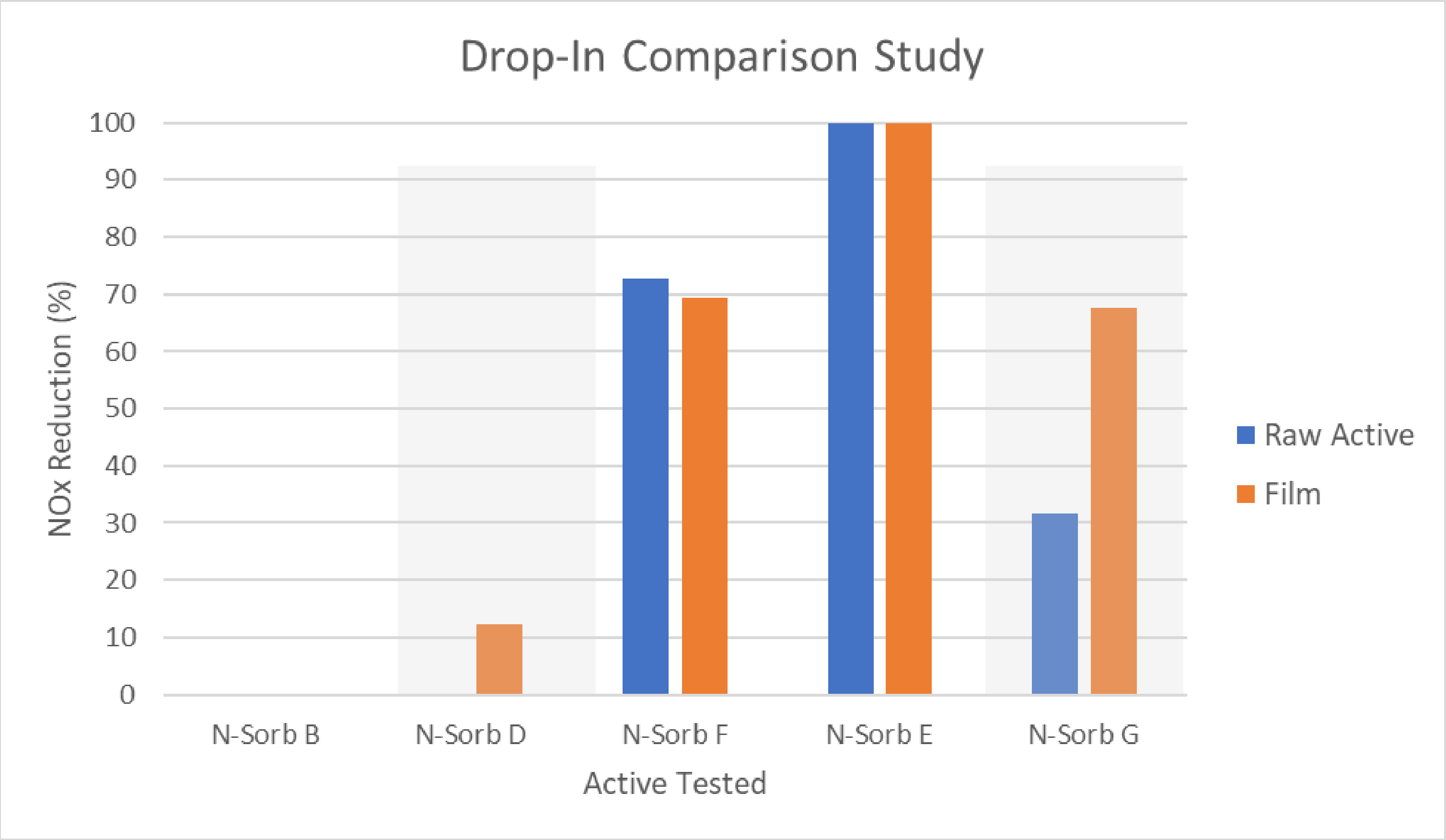
EXPERIMENTAL METHOD:

- 8.5 mL NOx providing solution placed in scintillation bottle within blown bottle
- Aged 6 days at 23°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

N-Sorb F showed 100% reduction.



Drop-In Film v. Raw Active Agent Comparison



EXPERIMENTAL METHOD:

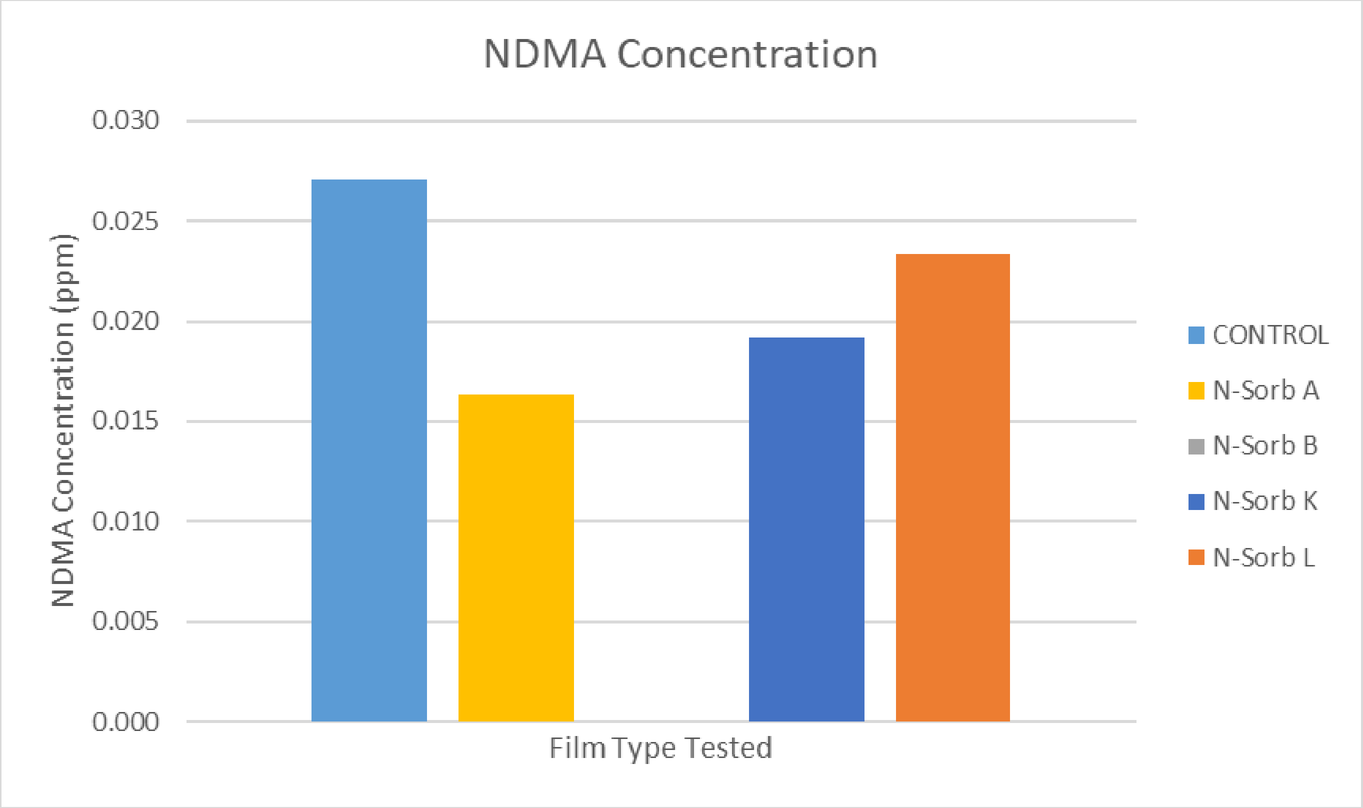
- 78 cm^2 CSP N-Sorb Film, equal mg of active agent as in film
- Placed into bottle with 7ml NOx providing solution
- Aged 6 days at 23°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

N-Sorb G and N-Sorb D saw an increase in performance when converted to film.

Aptar CSP Technologies

Confidential and Proprietary Property of Aptar CSP Technologies

Metformin (NDMA)



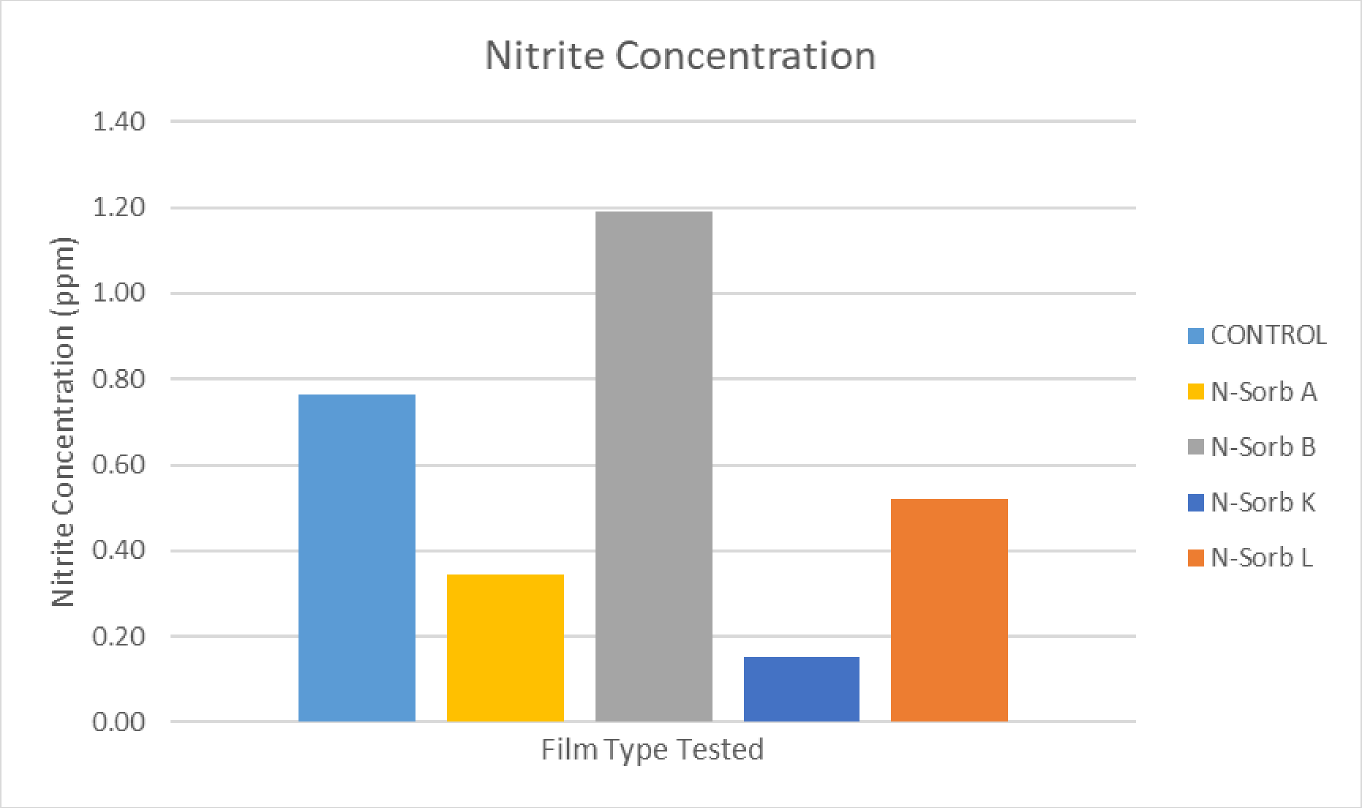
EXPERIMENTAL METHOD:

- 1 cm^2 of mitigation film
- 2mL metformin solution + 0.1 mL nitrosating agent
- Aged 24 hours
- Characterization by GC-MS Headspace with for nitrosamine concentration

N-Sorb B reduced NDMA concentration to 0 ppm.

Confidential and Proprietary Property of Aptar CSP Technologies

Metformin (Nitrite)



EXPERIMENTAL METHOD:

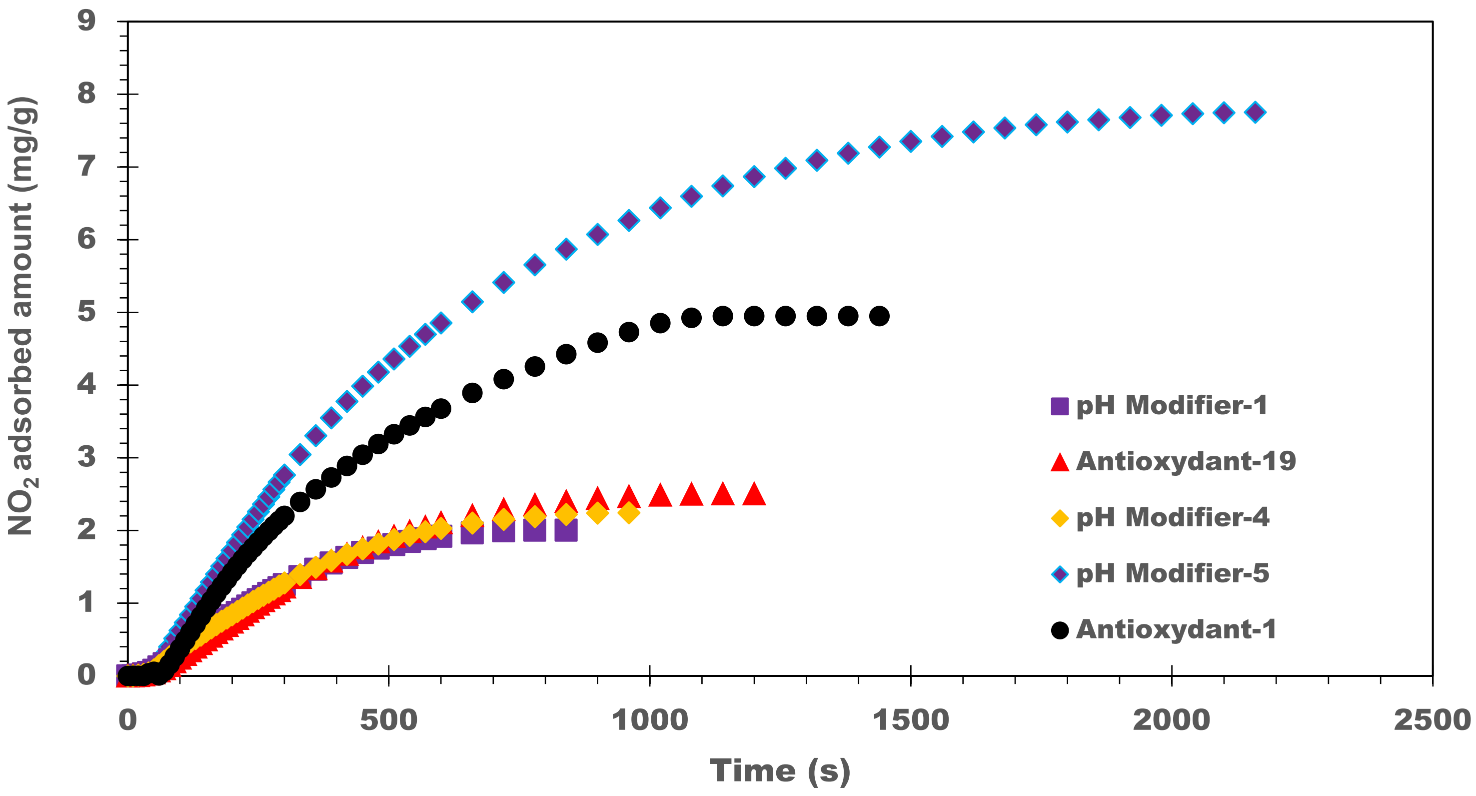
- 1 cm^2 of mitigation film
- 2mL metformin solution + 0.1 mL nitrosating agent
- Aged 24 hours
- Characterization by GC-MS Headspace with for nitrosamine concentration

N-Sorb K reduced nitrite concentration by ~0.4 ppm.

Confidential and Proprietary Property of Aptar CSP Technologies

Experimental Absorption using NO_2 Gas as probe molecule

Active Agents



EXPERIMENTAL METHOD:

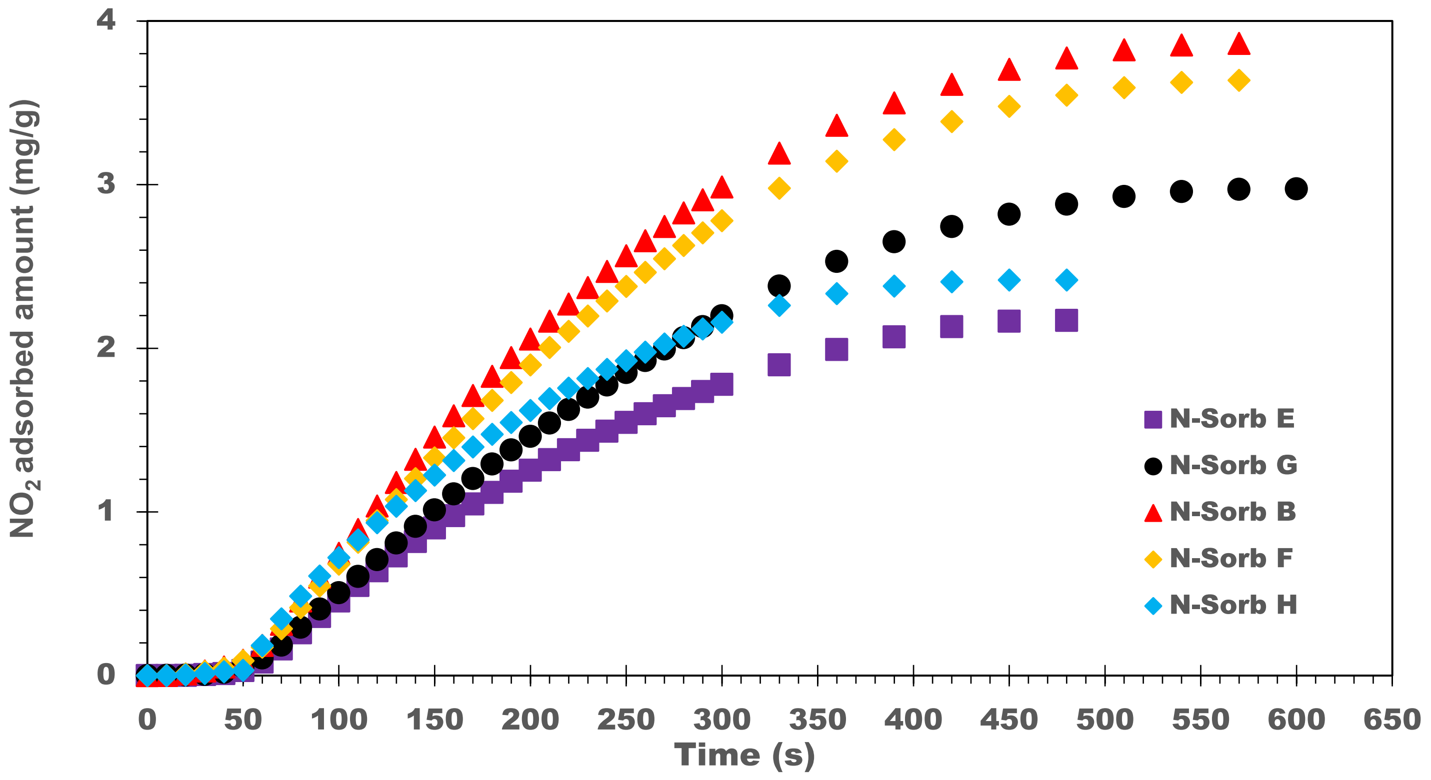
- 250 mg of sample
- 22 °C reactor bed
- ROSEMOUNT NGA 2000 detector
- 505 ppm of NO_2 through the fixed bed column of the sample

All active agents show significant absorption capacities

Aptar CSP Technologies

Experimental Absorption using NO_2 Gas as probe molecule

Films



EXPERIMENTAL METHOD:

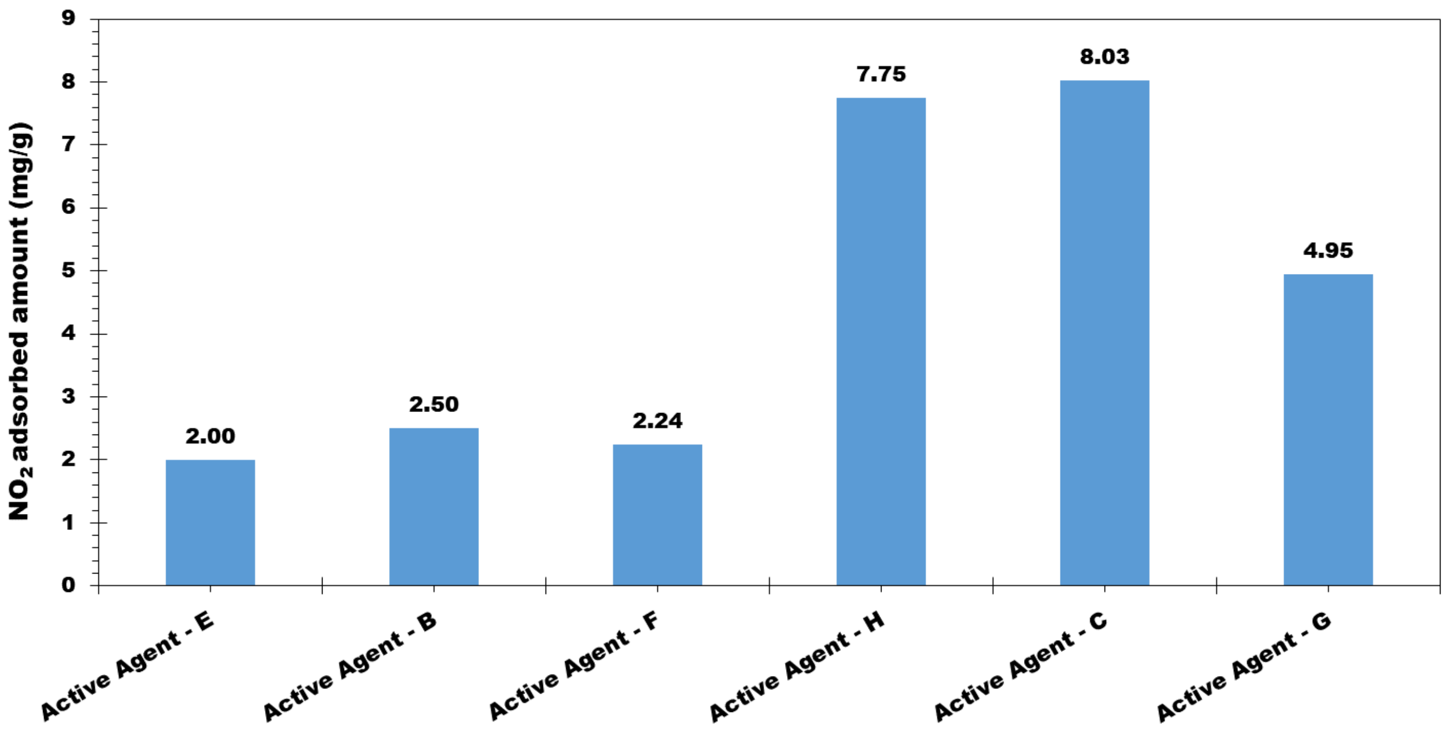
- 250 mg of sample
- 22 °C reactor bed
- ROSEMOUNT NGA 2000 detector
- 505 ppm of NO_2 through the fixed bed column of the sample

All films show significant absorption capacities

Aptar CSP Technologies

Theoretical Capacities - Utilizing NO2 Gas

Active Agents



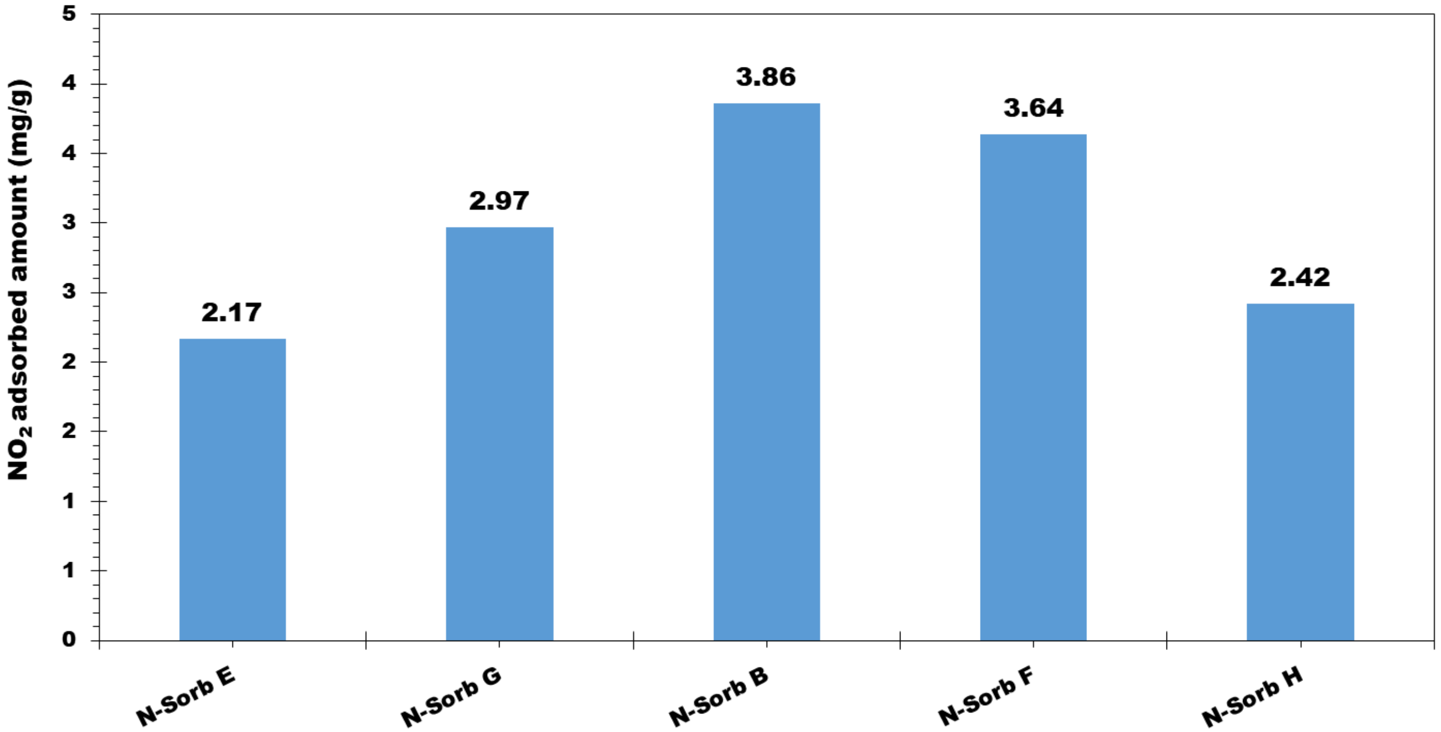
EXPERIMENTAL METHOD:

- 250 mg of sample
- 22C reactor bed
- ROSEMOUNT NGA 2000 detector
- 505 ppm of NO_2 through the fixed bed column of the sample

All active agents show significant theoretical capacity

Theoretical Capacities - Utilizing NO2 Gas

Films



EXPERIMENTAL METHOD:

- 250 mg of sample
- 22C reactor bed
- ROSEMOUNT NGA 2000 detector
- 505 ppm of NO_2 through the fixed bed column of the sample

All films show significant theoretical capacity

Aptar CSP Technologies

Closing Summary

Key Takeaways

- **+40% of API's** have potential to form Nitrosamines
- Global regulatory agencies continually update guidance with newly added nitrosamines and associated limits
- Pharma companies will be required to perform risk assessment, confirmatory testing and reporting
- Packaging mitigation solutions offer quick remediation without reformulation
- Packaging based solutions could afford the use of more and alternative active materials
- There is no "one size fits all" solution

References

US FDA

https://www.fda.gov/media/141720/download

EU / EMA

https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf

Questions ?

Aptar CSP Technologies

Confidential and Proprietary Property of Aptar CSP Technologies