TECHNICAL WHITE PAPER

Mitigating N-Nitrosamine Risks with Novel Active Material Science Innovations

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Introduction

Recent landmark discoveries of mutagenic N-nitrosamine impurities in pharmaceuticals have led to significant regulatory responses, including drug recalls and new regulatory guidances. In 2018, the highly mutagenic compound N-nitrosodimethylamine (NDMA) was discovered in several blood pressure drugs (sartans) as a manufacturing process-related impurity.[1] In 2019, regulatory authorities announced that ranitidine-containing products can form NDMA as a degradation product during storage.[2] Since then, various N-nitrosamine impurities have been detected in numerous pharmaceutical products, leading to intense regulatory review and public scrutiny.[3] In addition to product recalls, new strict, extremely low limits for N-nitrosamine impurities in pharmaceutical products were instituted by many Health Authorities (i.e., a class-specific acceptable limit of not more than 18 ng/day is now expected by many Health Authorities for N-nitroso compounds that do not have specific limits established).[4] The source of N-nitrosamine impurities can be from specific manufacturing processes, degradation in the formulation over the shelf life (e.g., from the presence of low levels of nitrite impurities in the formulation), and contamination from packaging (Figure 1).[5,6]

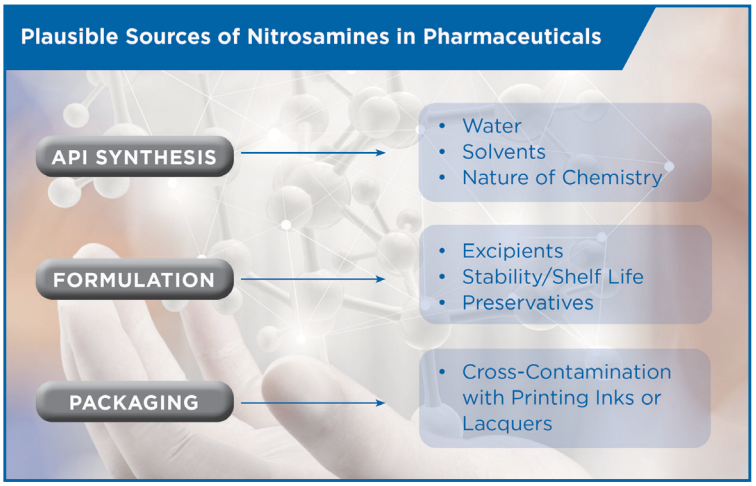

Figure 1: Potential Nitrosamine Sources in Pharmaceuticals

Drugs that are considered most susceptible to the formation of these N-nitroso impurities are secondary and tertiary amines, although other nitrogen-containing functional groups can also be at risk.[4] The extent of this risk is not limited to a few specific drugs. In silico analysis of more than 12,000 small molecule drugs determined that 40.4% of these drugs and 29.6% of the associated impurities have the potential for the formation of N-nitrosamine impurities.[4] Thus, it is clear that there is a tremendous need in the industry for effective mitigation strategies to prevent, minimize, or remove any potential N-nitrosamine impurities that

IDEA IN BRIEF

THE PROBLEM
Recent discoveries of mutagenic N-Nitrosamine impurities in pharmaceuticals have led to drug recalls and new regulatory guidance to address this risk and protect patients from these carcinogens.

THE CHALLENGE
Pharmaceutical companies need to address the source of N-Nitrosamine development and implement changes to their formulation, manufacturing processes or packaging materials.

THE SOLUTION
Active material science innovations enable active packaging based solutions that mitigate N-Nitrosamine formation and/or adsorb these molecules post-formation with minimal impact to current processes.

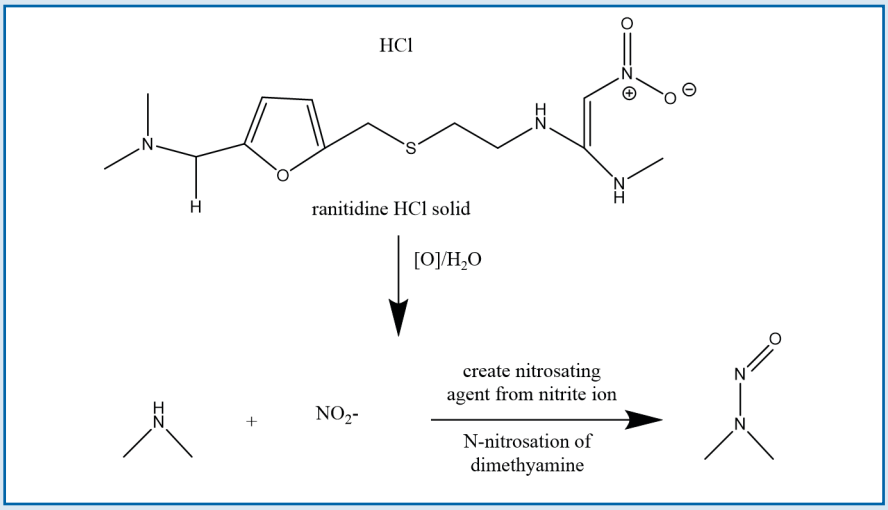

Figure 2: Chemical Pathway for NDMA Generation from Ranitidine HCl in Solid Form

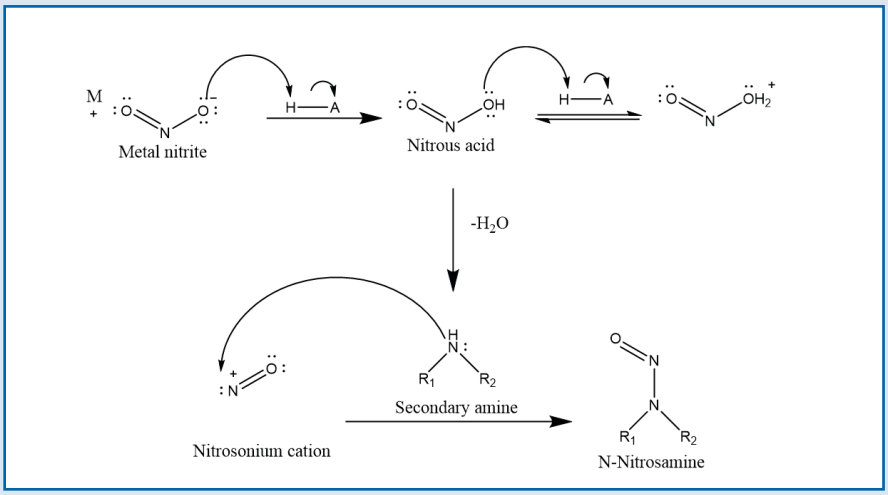

Figure 3: Suspected Pathway for NDMA Generation in Metformin ER Products

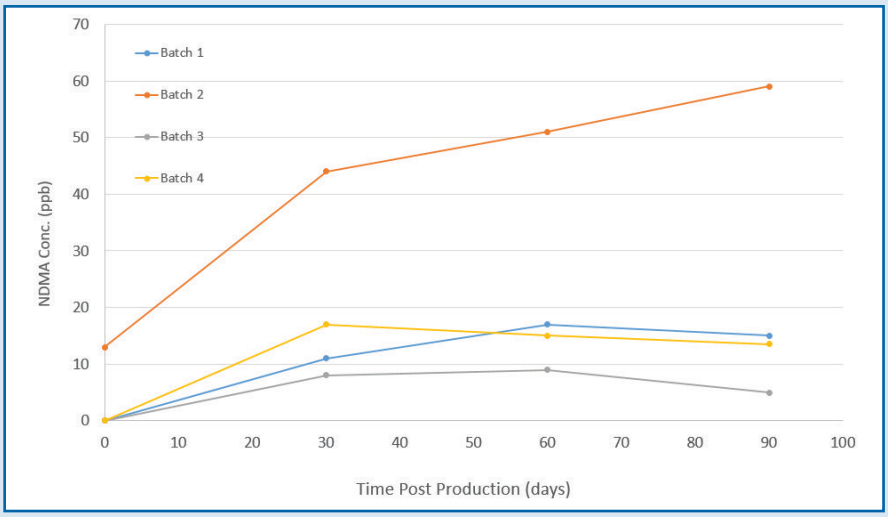

Figure 4: NDMA Concentration with Time (based on datum from Jires Et al.)

could be present or might form over the drug product's shelf-life.

The FDA recently studied multiple novel APIs due to the presence on nitrosamines above the critical limit, including NDMA in ranitidine (Zantac) and Metformin-based products, and requested the withdrawal of ranitidine HCl from the market in April 2020.[7] The agency determined, in some ranitidine-containing products, that concentrations of N-nitrosodimethylamine (NDMA) increased over time and when stored above room temperature. While it appears clear that NDMA was forming from degradation of ranitidine HCl, the mechanistic details of the pathway by which it is generated in the solid phase has not yet been firmly established. King et al. showed that the formation involves an intermolecular reaction without involvement of other impurities.[8] Harmon has postulated autoxidation as a key step in liberating both nitrite and dimethylamine from the ranitidine molecule, as shown in Figure 2.[9]

In May 2020, The FDA also recalled extended release versions (ER) of metformin from the market.[10] The agency has only found increased concentration of NDMA in ER versions of these products. Evidence of a degradation-based generation of NDMA (Figure 3) is indicated by the increased concentration as a function of time (Figure 4) as described by Jires *et al.*[11]

It should be noted that in Figure 3, there is a general need for both a metal nitrite and dimethylamine. In metformin, the presence of nitrite is understood to be from excipient contamination, while dimethylamine could be present as a manufacturing process impurity or from degradation of metformin over time.

There are a few observations to be valued in this general reaction:

- First is the need for a readily accessible secondary amine (e.g., dimethylamine);
- Second is the requirement of an acidic environment for the formation of the nitrosating agent (nitrous acid) from the metal nitrite; and
- Finally, it should be noted that moisture can be used as a driver for the formation of dimethylamine, as well as the Nitrous acid or Nitrosonium cation and subsequent N-nitrosamine.

This is just one example of the complex reactions taking place in N-nitrosamine formation. Pharma companies are attempting to mitigate this risk by controlling API synthetic reagents/conditions, incoming materials and cleaning processes, but these approaches are not a guaranteed solution since N-nitrosation can also occur in the formulated product over the shelf life. Considering a large population of drugs in development possess a secondary or tertiary amine and are exposed to similar environmental conditions as the Metformin example, all protective measures should be explored to reduce the risk of recalls and protect patients.

Regulatory Landscape

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have both taken regulatory action to address the presence of N-nitrosamines in oral drug products. Both regulatory bodies have established acceptable levels of N-nitrosamines in pharmaceuticals and have issued guidance to drug manufacturers on how to detect and prevent the presence of these impurities in their products (Figure 5).[12] Compliance with these regulations is mandatory for drug manufacturers in order to ensure the safety and efficacy of their products.

Nitrosamine	AI Limit (ng/day)[i,ii]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

Figure 5: AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

While the US FDA and European EMEA regulations for nitrosamines in oral drug products have many similarities, there are some notable differences between them. For instance, the FDA has issued guidance on the detection and prevention of N-nitrosamines in both prescription and over-the-counter (OTC) drugs, whereas the EMA has focused primarily on prescription drugs. Additionally, the acceptable levels of N-nitrosamines differ slightly between the two regulations, with the EMA setting stricter limits for certain nitrosamines than the FDA. Despite these differences, both regulatory bodies are committed to ensuring that nitrosamine impurities are minimized in oral drug products in order to protect public health.[13,14]

i The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA, NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure.
ii The conversion of AI limit into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

Challenge

With all the scrutiny from regulatory bodies about the N-nitrosamine risk and the multiple factors that can trigger N-nitrosamine formation, pharmaceutical developers must assess this risk in their current drug products as well as in new APIs in development. They need to find solutions to protect against the potential for a drug recall and the associated direct and indirect costs (i.e., lost sales, litigation costs, fines, impact to brand reputation, etc.). Today, these companies are employing strategies such as sourcing nitrocellulose free packaging or choosing alternate or supplemental excipients, reagents or catalysts, which can result in overformulation and may lead to other new problems. Pharma is searching for a more holistic solution to the N-nitrosamine problem that does not have a significant impact on drug formulation or manufacturing processes. Active packaging can serve as a primary solution or as an additional measure of protection to compliment other strategies used to prevent N-nitrosamine formation.

Solution: Active Material Science Solution Development

New innovations in active material science technologies offer an active packaging based solution that can address the N-nitrosamine challenge with no disruption to current manufacturing processes. Leveraging 20+ years of material science expertise, Aptar CSP Technologies' 3-Phase Activ-Polymer™ platform technology enables a new class of highly-engineered polymer compounds that provide premier product protection for sensitive drug products, medical devices, and drug delivery systems.

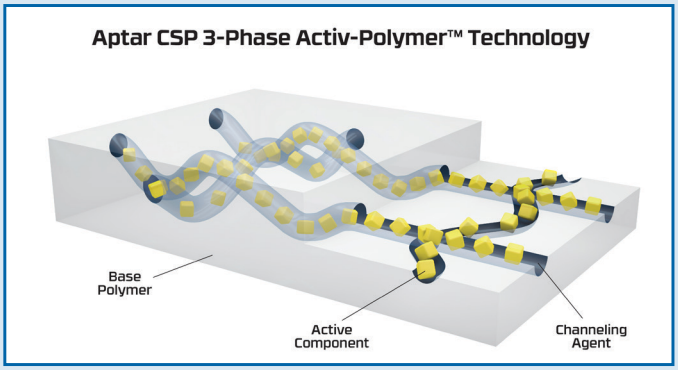

Figure 6: Aptar CSP Technologies' 3-Phase Activ-Polymer™ technology

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 6). The channeling agent coats and distributes active particles throughout the polymer matrix and allows targeted molecules to enter through the hydrophilic channels. Those molecules migrate to the active particles, where they are adsorbed and permanently removed from the headspace. The technology can be engineered to provide moisture control, gas scavenging, microbial pathogen reduction, and more. Now, Aptar CSP's developers have engineered a specific solution to inhibit N-nitrosamine formation and scavenge N-nitrosamine molecules post-formation, leveraging nanoporous materials.

The potential use of nanoporous materials in mitigating nitrosamine formation (by adsorbing any primary or secondary amine volatile units or any NOx) or by adsorbing semi-volatile nitrosamines once they are formed is vast. Due to the huge number of nitrosamines that can be formed, this merits particular attention from theoretical and experimental methods.

Nanoporous materials consist of a regular organic or inorganic framework supporting a porous structure and are separated into three subtypes: microporous materials, mesoporous materials and macroporous materials. Recently, nanoporous materials have been

recognized as promising candidates for multifunctional applications such as catalysis, ion exchange, gas storage, etc. In addition, nanoporous materials are of scientific and technological importance because of their ability to adsorb and cooperate with atoms, ions and molecules on their sizeable interior surfaces and pore space.

Aptar CSP Technologies' R&D strategies combines the advantages of interdisciplinary research, where materials and organic chemistry (synthesis, shaping and characterization of the obtained materials), thermodynamic/dynamic (adsorption, kinetics, etc.), and computational chemistry synergistically work together to focus on the most promising adsorbents (nanoporous materials) for the challenging targeted adsorption.

In this context, single component adsorption isotherms of different nitrosamines (NDMA, NDEA, NDIPA, etc.) were systematically studied in four different engineered nanoporous CSP materials (CSP-1, CSP-2, CSP-3 and CSP-4) using grand canonical Monte Carlo (GCMC) simulations at 298 K with pressure ranging from 1 ppb to 1 bar (see Figure 7).

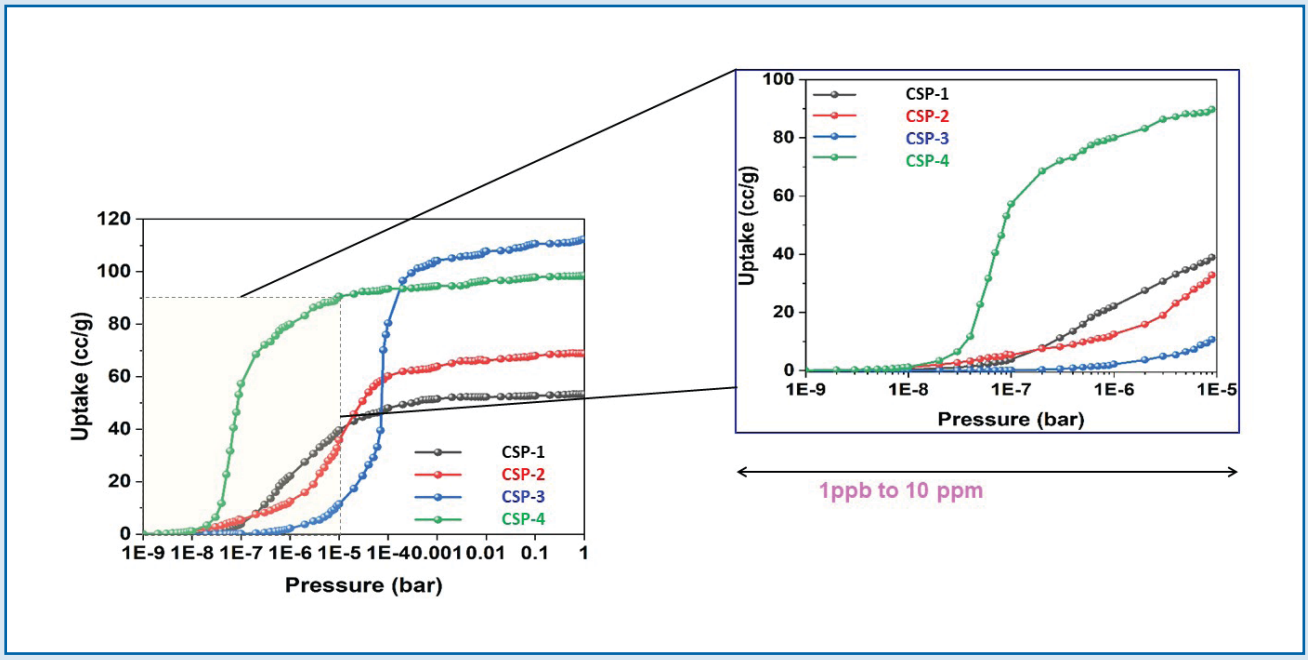

Figure 7: Single component adsorption isotherms at 298 K of NDMA nitrosamine in 4 nanoporous materials engineered at Aptar CSP Technologies

These predictions revealed that among the four studied porous samples in this example, CSP-4 showed exceptional N-nitrosamine uptake at very low pressure between 1 ppb to 10 ppm (trace levels). The simulated (i) NDMA uptake amount at 20 ppb (10 ppm) is 3.4 cc/g (91.5 cc/g); (ii) NDEA uptake amount at 20 ppb (10 ppm) is 30 cc/g (54.6 cc/g); (iii) NDIPA uptake amount at 20 ppb (10 ppm) is 3.0 cc/g (42.1 cc/g). Interestingly, these large sorption uptakes are combined with very high heats of adsorption for NDMA, NDEA, and NDIPA molecules of -75.4 kJ/mol, -84.1 kJ/mol, and -93.3 kJ/mol, respectively. This unique sorption behavior of CSP-4 originates from the structural features of this nanoporous material with a synergistic effect of (i) confined 1D channel geometry and (ii) the presence of active bridging -OH groups in the nanoporous pore wall that favors a selective capture of N-nitrosamines through strong hydrogen bond formation between

the N-nitrosamines -O atom with the CSP-4 -OH group. This multiscale modelling approach highlights that CSP-4 is one of the best sorbents to effectively adsorb N-nitrosamines at trace levels. In the future, a computational screening approach will be undertaken to explore adsorption of other N-nitrosamines and secondary amines on a series of nanoporous materils that are already known, some of which are customized with the optimal chemical, topological, and electronic features for the targeted adsorption.

As we at Aptar CSP explored these opportunities, we realized that a few of our custom absorption systems perfected for different applications may have an impact on the concentration of nitrosamines in the headspace. Thus when we evaluated them against a few of the most common nitrosamines at 5 ppm, we observed up to a 20% decrease in the headspace within 3 days (Figure 8). This is indicative of a promising trend with continuing work toward tailoring and optimizing the specific absorption system for nitrosamine applications.

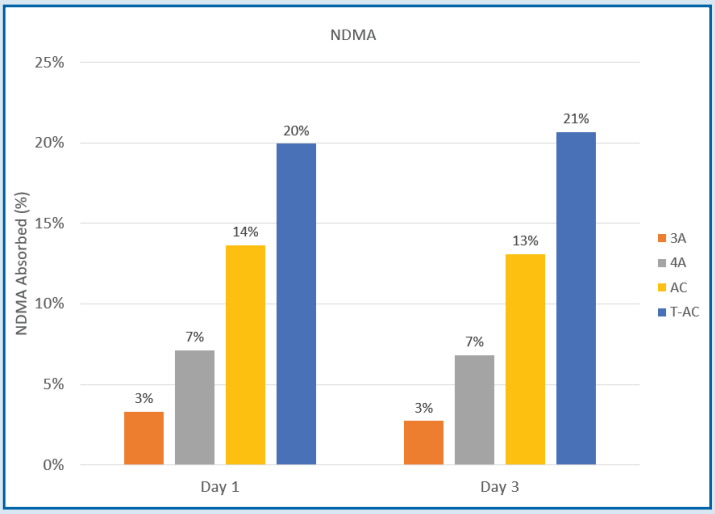

Figure 8: NDMA Concentration Reduction with Time (4 Custom Adsorption Systems)

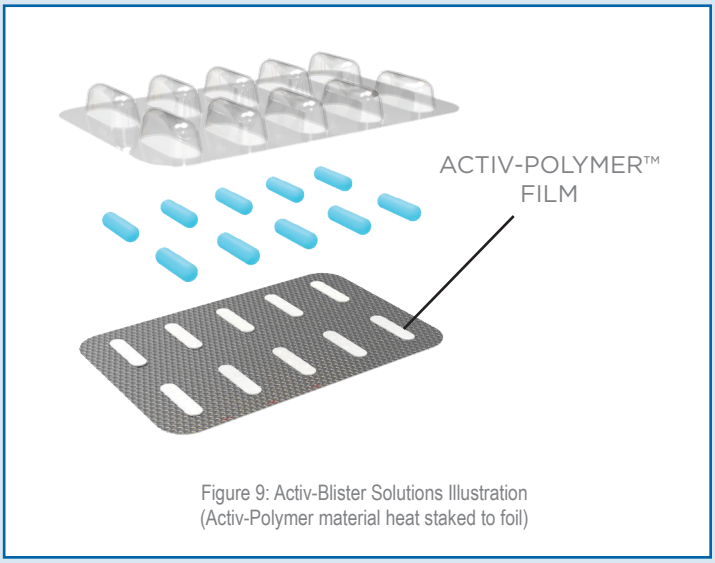

Figure 9: Activ-Blister Solutions Illustration (Activ-Polymer material heat staked to foil)

Conclusion

As we focus on the needs and pain points of the pharmaceutical developer, this technology may be a powerful tool to address the N-nitrosamine challenges they are currently facing by means of an active packaging solution. The nanoporous materials reviewed above can be engineered and deployed as bespoke formulations of Aptar CSP's Activ-Blister™ Solutions, which integrates a piece of flexible active film into traditional blister packaging designs (Figure 9). This configuration is currently used to protect highly-sensitive APIs for HIV treatment and prevention on the market today by actively controlling the internal atmosphere of individual blister cavities to improve stability and extend shelf life. As demonstrated above, today Activ-Blister™ Solutions can also be used to address the N-nitrosamine problem. The technology can be applied in line via heat staking, without the use of adhesives, and with existing blister designs, materials and equipment. Outfitted blisters can adsorb or scavenge tailored amounts of moisture and/or gasses, including N-nitrosamines, and can be produced in shapes and sizes to accommodate any tablet and capsule size.

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