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TECHNICAL NEWSLETTER

SPECIAL ISSUE

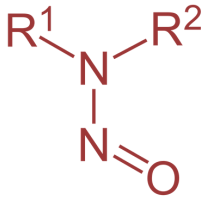
MITIGATING NITROSAMINE RISKS IN DRUG PRODUCTS: FUJI CHEMICAL OFFERS A LOW-RISK SOLUTION WITH FUJICALIN®

NEWSLETTER HIGHLIGHT

Mitigating Nitrosamine Risks in Drug Products: Fuji Chemical Offers a Low-Risk Solution with Fujicalin®

Nitrosamine impurities in drug products have been a growing concern in recent years due to their potential carcinogenic effects. ***Over 1400 products have been recalled from the market due to the presence of N-nitrosamine impurities*** beyond acceptable intake limits. Manufacturers are now reviewing each and every component of the formulation for potential nitrosamine forming chemistries.[1]

What are nitrosamines and where do they originate?



Nitrosamines, classified as probable human carcinogens, are typically formed through the acid-catalyzed reaction of a secondary or tertiary amine with a nitrosating agent such as nitrite.[2] These impurities are most commonly found in groundwater, treated water, food, beverages, and consumer products.

The detection of unacceptable levels of nitrosamine impurities in several sartan drug products in 2018 resulted in a wave of risk assessment requests from regulatory bodies worldwide. The scope of the assessment included everything from API synthesis and excipient manufacturing to process, packaging material, and beyond. This prompted the submission of risk mitigation strategies and/or reformulations by drug product manufacturers to regulatory bodies such as the US-FDA and the EMA.

"..The presence of nitrosamine impurities in drug products can pose significant risks to human health. When present in high levels over a long period of time, nitrosamines can be carcinogenic.."

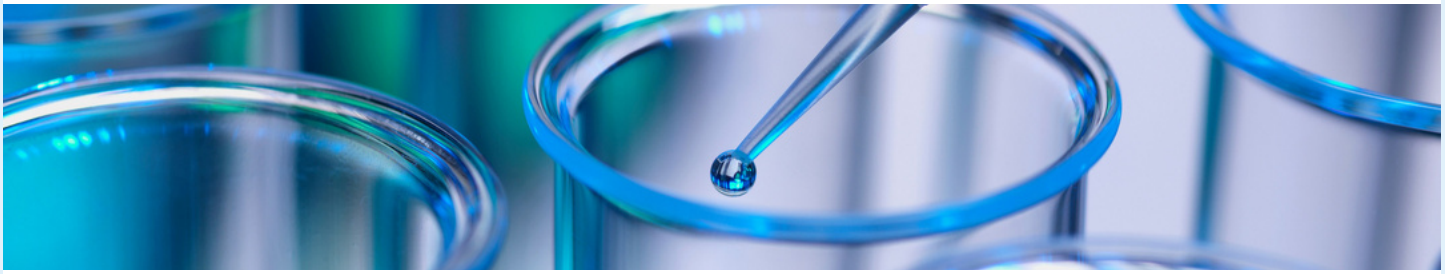
MORE ABOUT NITROSAMINES

What factors contribute to their presence in formulations?

When present at levels beyond acceptable limits over a long period of time, nitrosamines could potentially be carcinogenic. [3]However, their levels in formulations can be controlled. To understand what factors could lead to the formation of nitrosamines in formulations, it is crucial to know how they are formed: Nitrosating agents can react with amines, even in trace amounts, to form nitrosamines, particularly in the presence of an acid catalyst.

From an excipient standpoint:

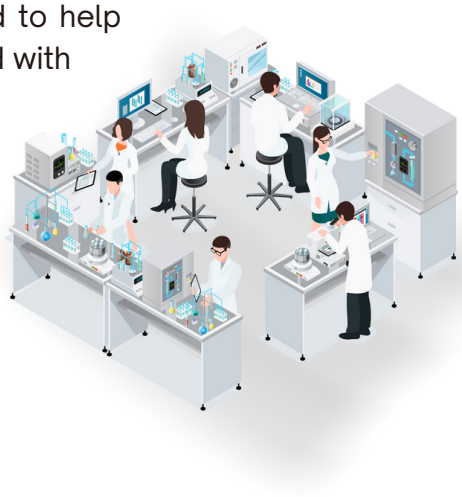
The most significant contributor to nitrosamine formation is **the presence of nitrites**. Variability in nitrite levels from one supplier to another could also be a major cause of nitrosamine variation in your drug product, particularly if it contains a secondary amine, or if it's processed using a method that results in hazardous levels of nitrosamine.



HOW CAN FUJI CHEMICAL INDUSTRIES ASSIST?

Assessing Nitrosamine Risk for Fujicalin®

Fuji Chemical Industries's nitrosamine risk assessment aligns with the latest version of the IPEC format. It is designed to help drug product manufacturers evaluate the risks associated with excipient manufacturing and potential nitrosamine formation in the final drug product.



The assessment concludes that the risk of nitrosamine presence in Fujicalin® (DCPA) is extremely low. This is because no raw materials containing amines, nitrites, or nitrosating agents have been used in the manufacturing of Fujicalin®. When tested, the water used in Fujicalin®'s manufacturing process was found to contain nitrites only to the extent of 0.004 ppm.

TESTING NITRATE AND NITRITE LEVELS IN Fujicalin®

Testing Nitrate and Nitrite Levels in Fujicalin®	
Method used: Ion chromatography	
Limit of Quantitation (Nitrate)	25 ppm
Limit of Detection (Nitrate)	2.5 ppm
Limit of Quantitation (Nitrite)	2.2 ppm
Limit of Detection (Nitrite)	0.7 ppm

Method Detail	
Operating Conditions	
Detector	Electrical Conductivity Detector
Column	With a Shodex IC IA-G guard column attached to Shodex IC I-524A
Polarity	+Range: 51.2 mS/m
Detector and column temperature	A constant temperature of about 40°C
Mobile Phase	2.5 mM phthalate eluent (pH 4.0)
Flow Rate	1.0 mL/min
Injection Volume	10µL

Method Detail

Preparation method for sample solution: Place product 5.0 g in a 200 mL conical beaker, add water 75 mL, heat to boil in an electric heat machine, place it on a previously heated stirrer, and boil gently for 15 minutes while mixing thoroughly.

After cooling, add water to make 100 mL, centrifuge (15000 rpm,20 min), and filter the supernatant liquid through an ion chromatographic disc (0.45 µm). Filter the sample solution.

Method for preparing standard solution:

Standard nitrate solution: Dilute the nitrate ion standard solution *(Fujifilm Wako Pure Chemical Industries, Ltd., 1000 mg/L)* with water to prepare a 1ppm, 10ppm, 25ppm nitric acid standard solution.

Standard nitrite solution: Dissolve sodium nitrite in water. Prepare 1ppm, 10ppm, 25ppm-nitrite reference solutions.

Measurement method: Perform the test with **10 µL** each of the sample solution and standard solution as directed under Ion Chromatography according to the following test conditions: the peak areas of nitrate and nitrite are calculated. Determine the calibration curve using the concentration of the standard solution as **x** (µg/ mL) and the peak area as **y**, and calculate the concentration (µg/ mL) from the peak area of the sample solution.

Results

Three lots of **Fujicalin®** were tested for nitrate and nitrite content using ion chromatography. Results are as shown below:

Lot Number	Nitrate ion (ppm)	Nitrite ion (ppm)
CP304511	1.2	N.D.
CP304512	N.D.	N.D.
CP304513	N.D.	N.D.

SUMMARY

The recent wave of withdrawals due to unacceptable levels of nitrosamines, specifically nitrosamine drug substance related impurities (NDSRIs), has drawn attention from the formulation development community, and has brought caution to health regulators worldwide.
Numerous consortiums and forums have recently emerged to address this issue. For instance, the FDA and the Center for Research on Complex Generics (CRCG) hosted a public workshop on June 15, 2023, titled "Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generic Products."

Fujicalin® offers a low-risk solution for manufacturers looking to mitigate these risks. Manufacturers can partner with Fuji Chemical Industries to obtain a nitrosamine risk assessment for Fujicalin® and ensure the safety of their drug products.

As a responsible manufacturer, Fuji Chemical Industries has stayed up-to-date with regulatory changes and has tested **Fujicalin®**, DCPA, for nitrate and nitrite content.
In the absence of a standardized method, Fuji Chemical Industries relies on ion chromatography, a widely accepted method. .

The extremely low levels of nitrate and nitrite in **Fujicalin®** further support the low risk of nitrosamine formation.

References:

1. Bharate SS. Critical analysis of drug product recalls due to nitrosamine impurities. Journal of Medicinal Chemistry. 2021 Mar 11;64(6):2923-36.
2. Boetzel R, Schlingemann J, Hickert S, Korn C, Kocks G, Luck B, Blom G, Harrison M, Francois M, Allain L, Wu Y. A nitrite excipient database: a useful tool to support N-nitrosamine risk assessments for drug products. Journal of Pharmaceutical Sciences. 2023 Jun 1;112(6):1615-24.
3. Brambilla G, Martelli A. Genotoxic and carcinogenic risk to humans of drug-nitrite interaction products. Mutation Research/Reviews in Mutation Research. 2007 Jan 1;635(1):17-52."

Fujicalin®

U.S Drug Master File (DMF) Number 12692

Fuji Chemical Industries

Solving Puzzles Since 1946.

Creativity and Contribution

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