FUJIFILM
Value from Innovation

Approaches and considerations for *N*-nitrosamine issues from a quality perspective

USP-MHLW/PMDA joint workshop
September 11, 2024

Yusuke Nagato
FUJIFILM Toyama Chemical Co., Ltd.

Today's topics

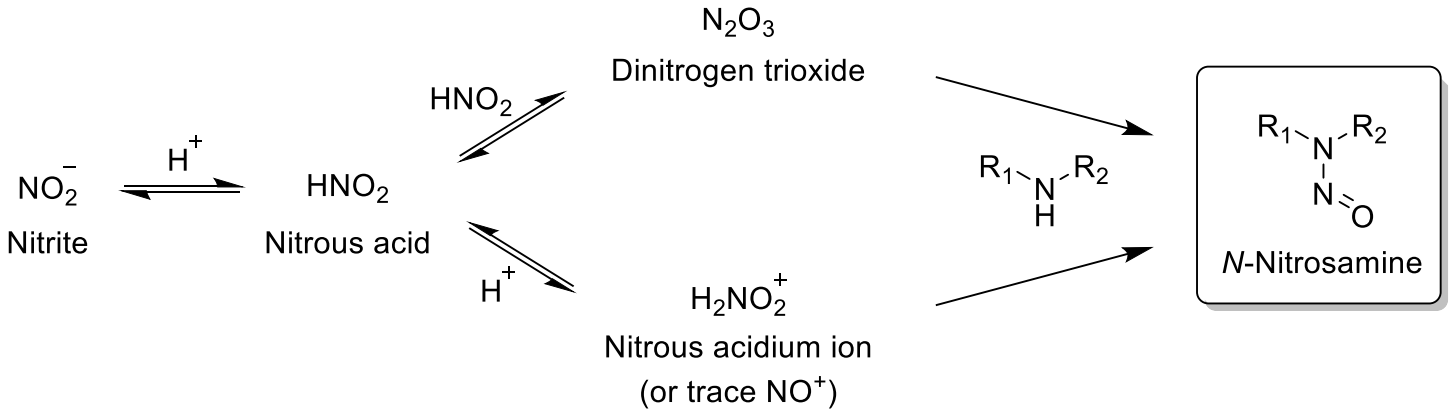
1. **Overview of *N*-nitrosamines/NDSRIs**
2. **Mitigation strategies to reduce *N*-nitrosamines/NDSRIs formation**

Disclaimer:

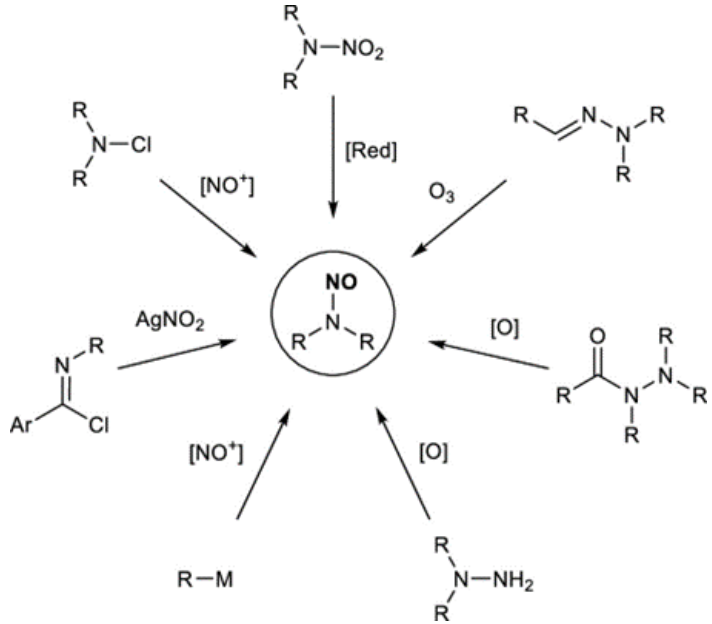
The views and opinions expressed in this presentation do not necessarily reflect the views of the company or organization to which the speaker belongs.

N-nitrosamines

- *N*-nitrosamines are known to be formed mainly by the reaction of secondary amines with nitrosating agents such as nitrous acid. It has also been reported that *N*-nitrosamines are formed by multiple reaction pathways.



Int. J. Pharm. 620 (2022) 121740

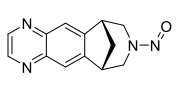


Org. Process Res. Dev. 24 (2020) 1558–1585

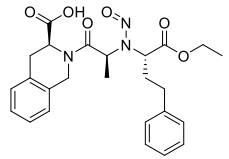
- The contamination of *N*,*N*-dimethylnitrosamine (NDMA) in valsartan in 2018 led to the discovery of contamination with *N*-nitrosamines in various pharmaceutical products, resulting in a worldwide recall of pharmaceutical products.
- *N*-nitrosamines are classified as a “cohort of concern” in the ICH M7 (R2) guideline, indicating extremely high carcinogenicity, and therefore require control at a significantly lower limit than the acceptable intake specified in ICH M7 (R2) guideline.

Nitrosamine drug substance-related impurities (NDSRIs)

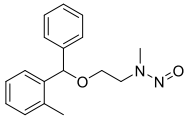
- Recalls of NDSRIs have been on the increase since the varenicline contamination case.
- NDSRIs are thought to be formed during the manufacturing process and storage of APIs and drug products.
  - Formed by the reaction of amine moieties of the API or its impurities/degradation products with nitrites contained in excipients.
  - Formed when the hydrazine moiety of the API or its impurities/degradation products is oxidized by oxygen or peroxides contained in the excipients.
  - Formed by the reaction of amine moieties of the API or its impurities/degradation products with nitrogen oxides derived from nitrocellulose contained in the blister packaging.
- Caution is required for formation of NDSRIs when the drug substance or its impurity/degradation product contains secondary or tertiary amines.



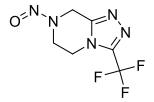
N-nitroso-varenicline



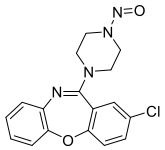
N-nitroso-quinapril



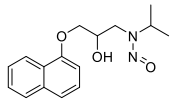
N-nitroso-orphenadrine



NTTP



N-nitroso-amoxapine



N-nitroso-propranolol

- Amines and hydrazines, the precursors of NDSRIs, may be formed by degradation of the amide or hydrazide/hydrazone moieties in the drug substance structure, respectively.
- Since toxicity data (especially carcinogenicity study data) are insufficient or nonexistent for many NDSRIs, it is necessary to establish new acceptable intakes.
- If NDSRIs are formed in excess of acceptable limits, follow-up with additional toxicity studies or change in API or drug product manufacturing methods is necessary.

Flowchart for assessing the risk of contamination with *N*-nitrosamines (based on EMA Q&As)

FUJIFILM
Value from Innovation

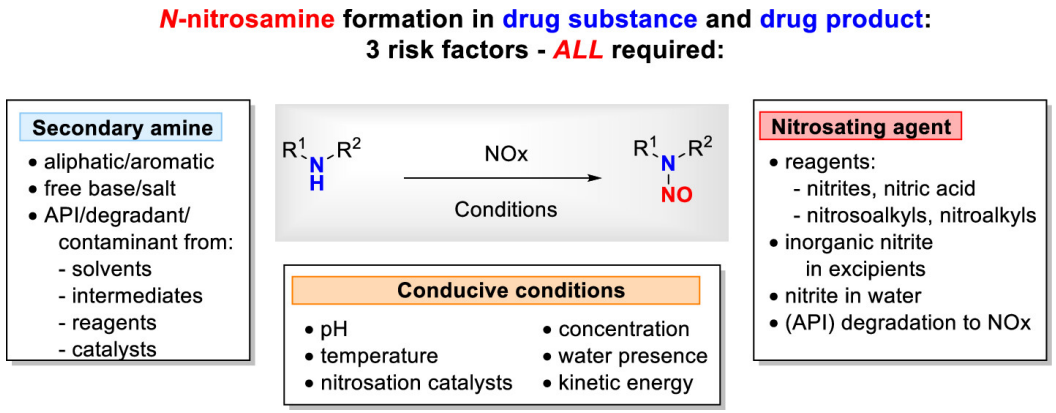
Step 1	**Investigation of API manufacturing process** ➢ Evaluation of manufacturing route for API GMP process ➢ Assessment of cross-contamination due to manufacturing facilities or contaminated raw materials	● List all raw materials (e.g., reagents, catalysts, solvents) used in the API GMP process ● Request risk assessment of raw materials to be used from suppliers using a questionnaire. ● In case of contract manufacturing, request CMO to conduct a risk assessment survey using a questionnaire.
Step 2	**Investigation of drug product manufacturing process** ➢ Evaluation of drug product manufacturing process (incl. primary packaging process) ➢ Assessment of cross-contamination due to manufacturing facilities or contaminated raw materials	● List all raw materials (e.g., excipients, solvents) and packaging materials used in the formulation process ● Request risk assessment of raw materials and packaging materials to be used from suppliers using a questionnaire. ● In case of contract manufacturing, request CMO to conduct a risk assessment survey using a questionnaire.
Step 3	**Investigation of degradation product** ➢ Evaluation of degradation processes of API, starting material, etc. ➢ Evaluation by stability study or stress testing	● Evaluation of results of stability tests (long-term storage tests and accelerated tests) ● Caution is required when reactive functional groups (e.g. nitro groups) or nitrogen-containing functional groups are contained in the molecule. ● Knowledge of degradation pathways is useful for risk assessment
Step 4	**Risk assessment for the presence of *N*-nitrosamines** ➢ Prioritization of drugs to be risk-assessed ➢ Risk assessment based on quality risk management (ICH Q9)	● Prioritize drugs in consideration of maximum daily dosage, duration of treatment, indications, number of patients treated ● Identify root causes of contamination using manufacturing information and questionnaire results ● Conduct risk analysis and risk assessment for the identified root causes of contamination
Step 5	**Hazard assessment of identified *N*-nitrosamines** ➢ Toxicity assessment of identified *N*-nitrosamines ➢ Calculation of acceptable limit for identified *N*-nitrosamines	● If carcinogenicity study data are available, acceptable limits is calculated according to ICH M7 (R2) guideline ● In the absence of carcinogenicity data, acceptable limits are calculated using CPCA or read-across approach ● Follow-up with Enhanced Ames test (EAT) or *in vivo mutation* assay available
Step 6	**Confirmatory testing** ➢ Conducting confirmatory testing using trace analysis for drugs with identified contamination risk ➢ Develop appropriate control strategies	● If the amount of contamination is less than 10% of the acceptable limit, it is considered a negligible risk and no further action is required. ● Promptly report to regulatory authorities if found to exceed the acceptable limit ● Develop appropriate control strategies for identified *N*-nitrosamines in the API or drug product
Step 7	**Risk Mitigation** ➢ Implementation of risk reduction measures ➢ Timely submission of appropriate variations in accordance with the guidance	● Consider changing manufacturing methods or suppliers to reduce the risk of *N*-nitrosamines contamination. ● If *N*-nitrosamines cannot be controlled below acceptable limits, consider conducting additional toxicity testing. ● During the CAPA implementation period (up to 3 years), adjustment factors can be used to compensate for the set acceptable intake.

Differences in regulations for each region when *N*-nitrosamines are detected

Detected *N*-nitrosamine level	EMA	FDA	MHLW
Exceeds the Acceptable limit	• The MAH/Applicant should submit forthwith an (interim) investigation report including (preliminary) root cause, risk mitigating plan and benefit/risk assessment. • The competent authorities will then assess the impact on the benefit/risk balance and the consequent need for any action to be taken. • The less-than lifetime (LTL) concept or the use of interim limits may be considered by the lead authority and NCAs on a temporary basis in order to inform market actions and at the same time ensure availability of medicines.	• If API or drug product batches with unacceptable levels of nitrosamine impurities are already in distribution, manufacturers should contact FDA so the Agency can determine the regulatory action. • If NDSRIs are detected in the drug product at objectionable levels, FDA encourages applicants to develop control strategies and/or design approaches to reduce NDSRIs to acceptable levels.	• Items that are found to be contaminated with nitrosamines exceeding the limit shall be promptly reported to the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, the Ministry of Health, Labour and Welfare. • Items that are found to be contaminated with nitrosamines exceeding the limit shall be subject to risk reduction measures such as setting an acceptance criteria or changing the manufacturing process to reduce the amount of nitrosamines.
Below the Acceptable limit	• When a nitrosamine is identified after Step 2 confirmatory testing, a limit will usually need to be included in the specifications of the finished product and the product must comply if tested. • If the source of a nitrosamine impurity is identified in the active substance manufacturing process, control options 1 to 3 as stated in ICH M7(R2) guideline could be used to demonstrate that the nitrosamine will not be present above the acceptable limit based on AI in the finished product. • Only if the amount of nitrosamine present is consistently below 10% of the acceptable limit based on AI in the API or in the finished product, then a test for the nitrosamine could be omitted from the specification. • Only if levels of a single nitrosamine are consistently below 30% of the acceptable limit based on AI in the API or the finished product, skip-testing according to the ICH Q6A definition could be acceptable.	• If a nitrosamine impurity is detected above the LOQ, the manufacturer should develop a strategy to ensure that the nitrosamine level remains within the AI limit. • Manufacturers should develop an appropriate control strategy, which should include specification limits, to ensure that the nitrosamine level reliably remains well below the AI limit in the API or drug product. • Given existing uncertainties regarding nitrosamine impurities and their presence in drugs, testing of each batch on release should be conducted. • Alternate approaches (e.g., upstream test of an intermediate) should be supported by sufficient process understanding and evidence of adequate statistical control and should be submitted to FDA in a supplement prior to implementation.	• If the analytical results are below the acceptable limit, there is no need to report to the MHLW, but a report on the analytical results should be documented and kept for an appropriate period of time.

EMA and FDA guidance states that risk reduction measures should be implemented when *N*-nitrosamines are detected in pharmaceutical products.

Mitigation strategies to reduce *N*-nitrosamines/NDSRIs formation



Org Process Dev. Rev. 27 (2023) 1736–1750

- In most common pathways to formation of *N*-nitrosamines, three factors are all required.
  1. Presence of a nitrosatable amine
  2. Presence of a nitrosating agent
  3. Conditions conductive to *N*-nitrosamine formation
- Removing one of three factors is sufficient to mitigate the risk of *N*-nitrosamine formation

Mitigating the risk in API manufacturing processes	Mitigating the risk in drug product manufacturing processes
• Change in reagents/solvents or materials used ➢ Avoiding the use of solvents that can be sources of amines (e.g., DMF, DMAc, NMP) ➢ Avoiding the use of amine bases (e.g., Et_3N, iPr_2NEt) ➢ Use of purified water ➢ Change in packaging materials • Change in manufacturing method ➢ Change of reaction conditions (e.g., avoidance of nitrosating agents, change of pH) ➢ Change of synthetic route (e.g., reduce risk of coexistence of nitrosating agent and amine source) ➢ Avoidance of quenching with $NaNO_2$ or change of quench method/order ➢ Addition of purification process ➢ Change in drying conditions • Change of API form (e.g., salt type, crystal polymorphism, particle size)	• Reduce the nitrite content of excipients ➢ Changing to another excipient supplier ➢ Replacement for an excipient that contains high levels of nitrite with one containing lower levels ➢ Implementation of purification process ➢ Changing drying conditions • Change in manufacturing method ➢ Modification of manufacturing process parameters ➢ Changes in high-risk unit operations (e.g., fluidized bed drying, wet granulation) ➢ Adjustment of moisture content in the formulation ➢ Addition of nitrite scavenger ➢ pH adjustment by addition of inorganic base (e.g., Na_2CO_3) • Change in packaging materials (e.g., blister packaging containing nitrocellulose)

Papers and documents related to mitigation strategy

ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Editors' Choice
Open Access
This article is licensed under CC-BY-NC-ND 4.0
pubs.acs.org/OPRD
Review

Formation of *N*-Nitrosamine Drug Substance Related Impurities in Medicines: A Regulatory Perspective on Risk Factors and Mitigation Strategies

Răzvan C. Cioc, Ciarán Joyce, Monika Mayr, and Robert N. Bream*

Cite This: *Org. Process Res. Dev.* 2023, 27, 1736−1750 Read Online

Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products

Share Post LinkedIn Email Print

ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
pubs.acs.org/OPRD
Article

Strategy to Assess and Control Nitrosamine Formation in API during Storage: A Sitagliptin Case Study

Laura Badia, Helena Camps, Isabel Lloveras, Norbert Handler, Helmut Buschmann, Jordi Valls, and Michal Poznik*

Cite This: *Org. Process Res. Dev.* 2024, 28, 3182−3196 Read Online

N-nitrosamine risk assessments for oral dosage forms: Nitrite content in the microcrystalline cellulose (MCC) produced by Asahi Kasei Corporation.

Takako Koyamatsu, Shohei Mikami, Obata Kenji, Julia Shmyrova
Asahi Kasei Europe GmbH, Fringsstrasse 17, 40221 Düsseldorf, Germany; julia.shmyrova@asahi-kasei.eu

International Journal of Pharmaceutics 620 (2022) 121740
Contents lists available at ScienceDirect
International Journal of Pharmaceutics
journal homepage: www.elsevier.com/locate/ijpharm

Avoiding N-nitrosodimethylamine formation in metformin pharmaceuticals by limiting dimethylamine and nitrite

Joerg Schlingemann [a], Celine Boucley [a], Sebastian Hickert [a], Laura Bourasseau [a], Matt Walker [b], Caroline Celdran [a], Thibaut Chemarin [a], Celine Pegues [a], Matthias Fritzsche [a], Judith Keitel [a], Anja Goettsche [a], Maic Seegel [a], Stefan Leicht [a], Brunhilde Guessregen [a], Philipp Reifenberg [a], Stephanie Wetzel [a], Tim Müller [a], Fanny Schooren [a], Tobias Schuster [a], Mike Liebhold [a], Annette Kirsch [a], Phillip Krueger [a], Christoph Saal [a,*], Bruno Mouton [a], Sandra Masanes [a]

[a] Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
[b] Chemical Development, Pharmaceutical Technology and Development, Operations, AstraZeneca, Macclesfield, UK

Journal of Pharmaceutical Sciences 112 (2023) 1255−1267
Contents lists available at ScienceDirect
Journal of Pharmaceutical Sciences
journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

N-Nitrosamine Formation in Pharmaceutical Solid Drug Products: Experimental Observations

Check for updates

Justin Moser[a,*], Ian W. Ashworth[b], Laurence Harris[c], Michael C. Hillier[d], Kausik K. Nanda[e], Garry Scrivens[c]

[a] Pharmaceutical Sciences & Clinical Supplies, Merck & Co., Inc., West Point, PA, United States
[b] Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, United Kingdom
[c] Pfizer R&D UK Limited, Discovery Park, Ramsgate Road, Sandwich, CT13 9NJ, United Kingdom
[d] Operations Science & Technology, API Products, Abbvie Inc. North Chicago, IL, United States
[e] Discovery Pharmaceutical Sciences, Merck & Co., Inc., West Point, PA, United States

Journal of Pharmaceutical Sciences 112 (2023) 1794−1800
Contents lists available at ScienceDirect
Journal of Pharmaceutical Sciences
journal homepage: www.jpharmsci.org

Review

N-nitrosamine Mitigation with Nitrite Scavengers in Oral Pharmaceutical Drug Products

Check for updates

Anne-Cécile V. Bayne[a,*], Zdravka Misic[b], René T. Stemmler[b], Marc Wittner[b], Margarita Frerichs[b], Julia K. Bird[c], Ahmed Besheer[b]

[a] DSM Nutritional Products, 6480 Dobbin Road, Columbia, MD, United States of America
[b] DSM Nutritional Products Ltd., P.O. Box 2676, 4002, Basel, Switzerland
[c] Bird Scientific Writing, Wassenaar, 2242, the Netherlands

Journal of Pharmaceutical Sciences 110 (2021) 3773−3775
Contents lists available at ScienceDirect
Journal of Pharmaceutical Sciences
journal homepage: www.jpharmsci.org

Rapid Communication

Inhibition of *N*-Nitrosamine Formation in Drug Products: A Model Study

Check for updates

Kausik K. Nanda[a,*], Steven Tignor[b], James Clancy[c], Melanie J. Marota[c], Leonardo R. Allain[b], Suzanne M. D'Addio[a]

[a] Discovery Pharmaceutical Sciences, MRL, Merck & Co., Inc., West Point, PA 19486, USA
[b] Analytical Sciences, MRL, Merck & Co., Inc., Rahway, NJ 07065, USA
[c] Oral Formulation Sciences, MRL, Merck & Co., Inc., Rahway, NJ 07065, USA

processes
MDPI
Article

Assessment of a Diverse Array of Nitrite Scavengers in Solution and Solid State: A Study of Inhibitory Effect on the Formation of Alkyl-Aryl and Dialkyl *N*-Nitrosamine Derivatives

Miha Homšak [1,†], Marko Trampuž [1,†], Klemen Naveršnik [1], Zoran Kitanovski [1], Mateja Žnidarič [1], Markus Kiefer [2] and Zdenko Časar [1,3,*]

1 Sandoz Development Center Slovenia, Lek Pharmaceuticals d.d., Kolodvorska cesta 27, 1234 Mengeš, Slovenia
2 Global Manufacturing Science & Technology, Novartis Technical Operations, Fabrikstrasse 2, Novartis AG, 4056 Basel, Switzerland
3 Faculty of Pharmacy, University of Ljubljana, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia
* Correspondence: zdenko.casar@sandoz.com or zdenko.casar@ffa.uni-lj.si; Tel.: +386-1-5802079
† These authors contributed equally to this work.

Journal of Pharmaceutical Sciences 112 (2023) 3075−3087
Contents lists available at ScienceDirect
Journal of Pharmaceutical Sciences
journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

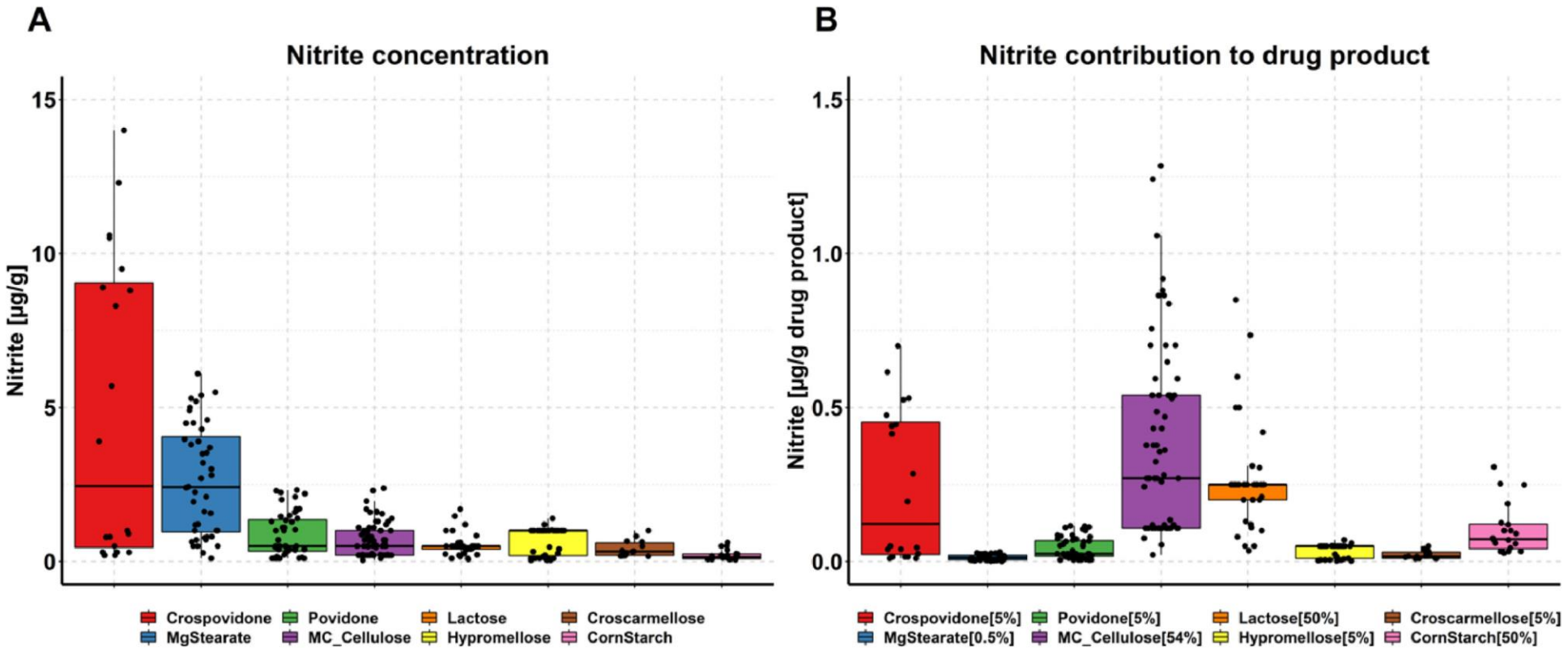
Bumetanide as a Model NDSRI Substrate: *N*-nitrosobumetanide Impurity Formation and its Inhibition in Bumetanide Tablets

Check for updates

Diaa Shakleya[a,*], Bethel Asmelash[b], Alaadin Alayoubi[a], Nicolas Abrigo[a], Adil Mohammad[a], Jiang Wang[a], Jinhui Zhang[a], Jingyue Yang[a], Tim Andres Marzan[a], David Li[a], Maha Shaklah[a], Fahd M. Alsharif[a], Saaniya Desai[a], Patrick J. Faustino[a], Muhammad Ashraf[a], Thomas O'Connor[a], Matthew Vera[b], Andre Raw[b], Vilayat A. Sayeed[b], David Keire[a]

[a] Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Office of Testing and Research, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA.
[b] Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Office of lifecycle Drug product, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

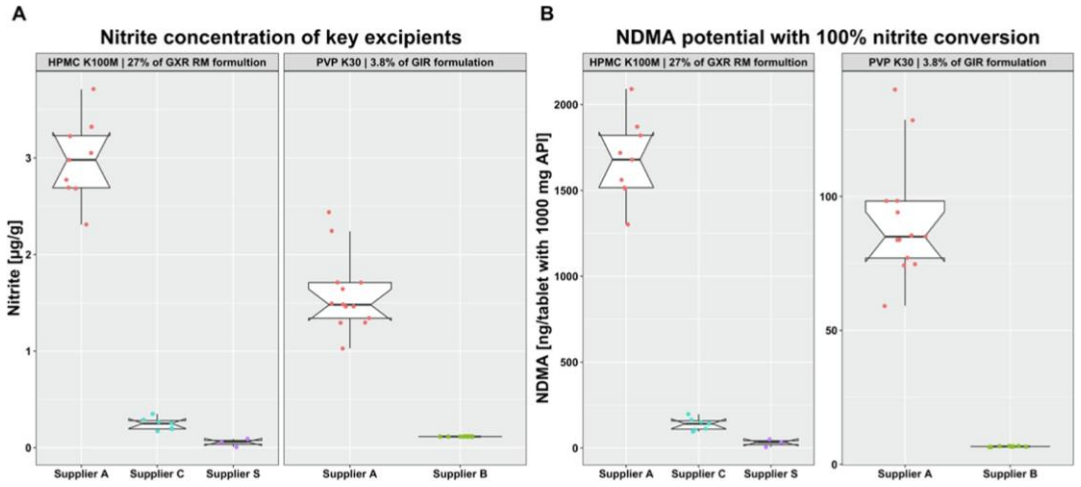
The amount of nitrite in excipients

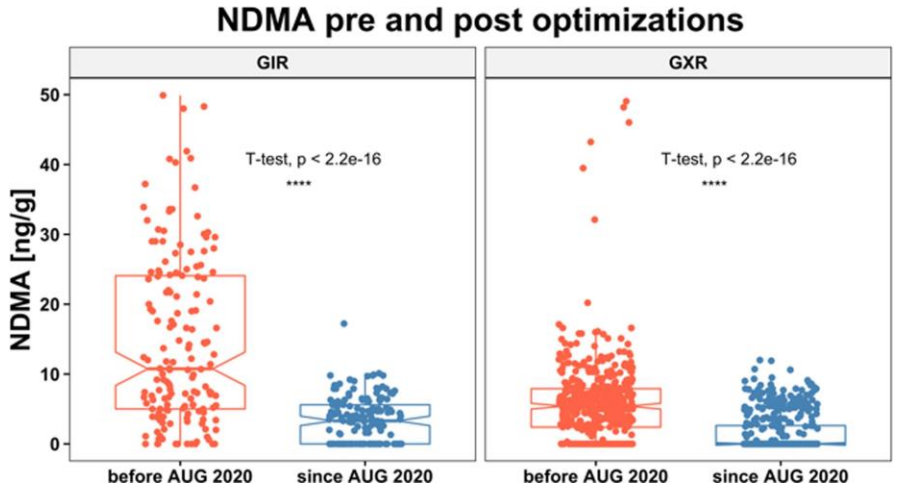


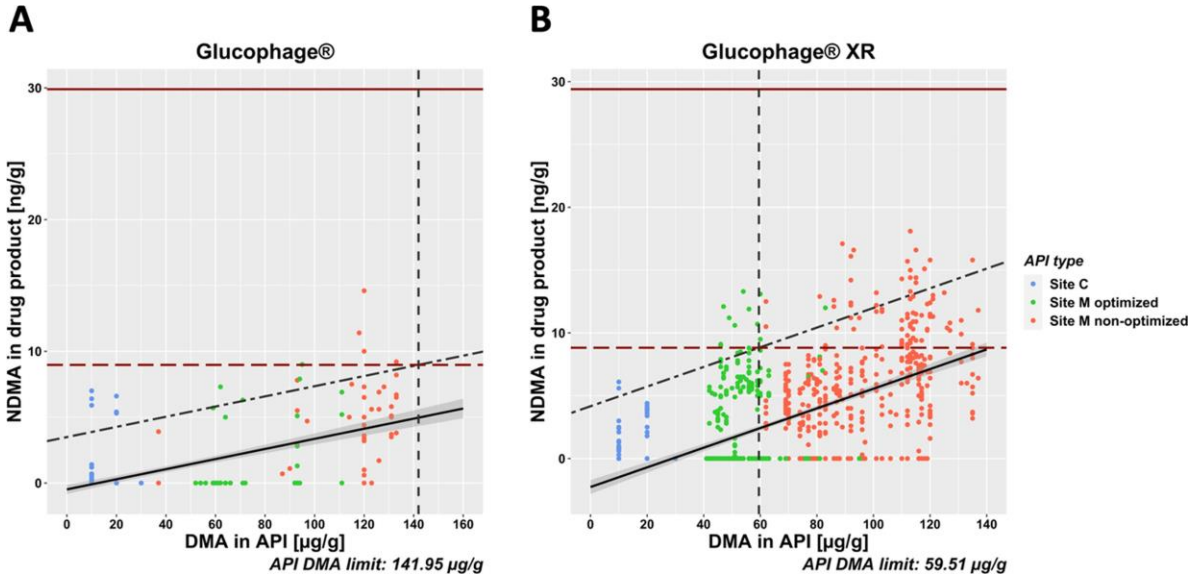
- The amount of nitrite in excipients varies from manufacturer to manufacturer or batch to batch.
- There are currently no regulatory requirements for limiting the amount of nitrite in excipients.
- With some exceptions, such as crospovidone and magnesium stearate, the amount of nitrite in most excipients is approximately 1-2 ppm or less.
- In general, excipients with higher nitrite concentrations tend to have a lower percentage of the total formulation and consequently a lower percentage of the total nitrite content in the formulation.

J. Pharm. Sci. 112 (2023) 1615–1624

Control of *N*-nitrosamine formation by limiting nitrite and amine impurities



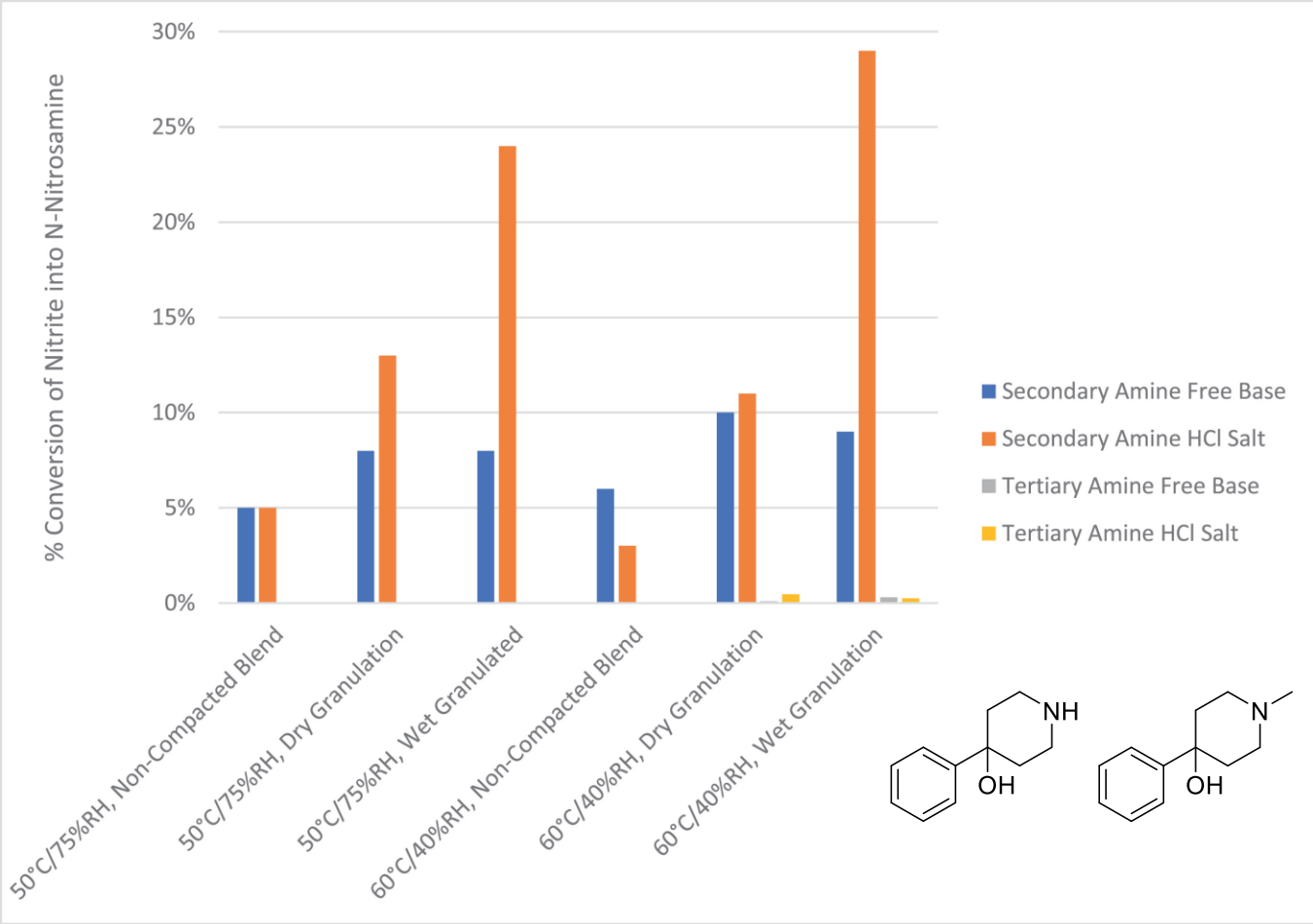




- In 2020, Metformin pharmaceuticals were found to be contaminated with NDMA above the acceptable limit and a product recall was conducted.
- Reduction of nitrite from excipients is an effective means to reduce NDMA in the drug product.
- Limiting residual dimethylamine in the API has proven to be another important factor for NDMA control as dimethylamine leads to formation of NDMA in the drug products.
- By implementing the above measures, it was possible to control NDMA in Metformin pharmaceuticals below 30% of the acceptable limit.

Int. J. Pharm. 620 (2022) 121740

The Effect of different manufacturing conditions on the formation of *N*-Nitrosamines

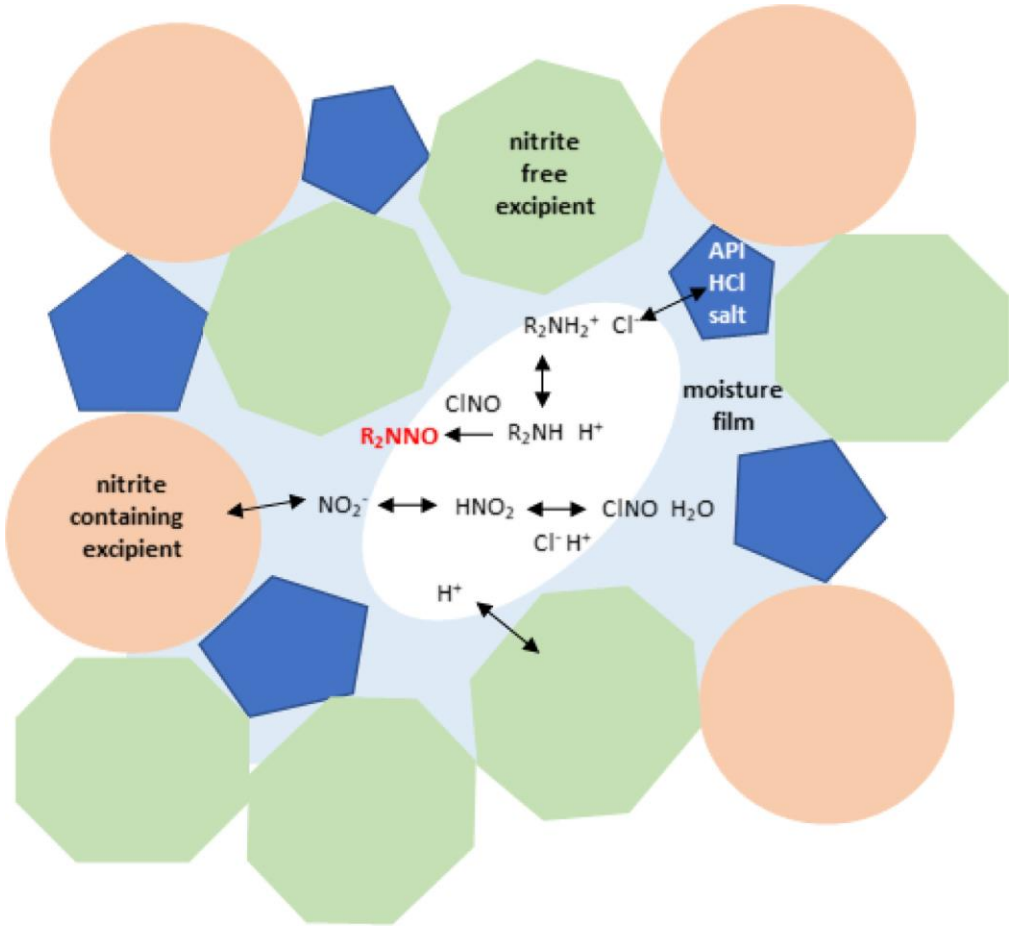


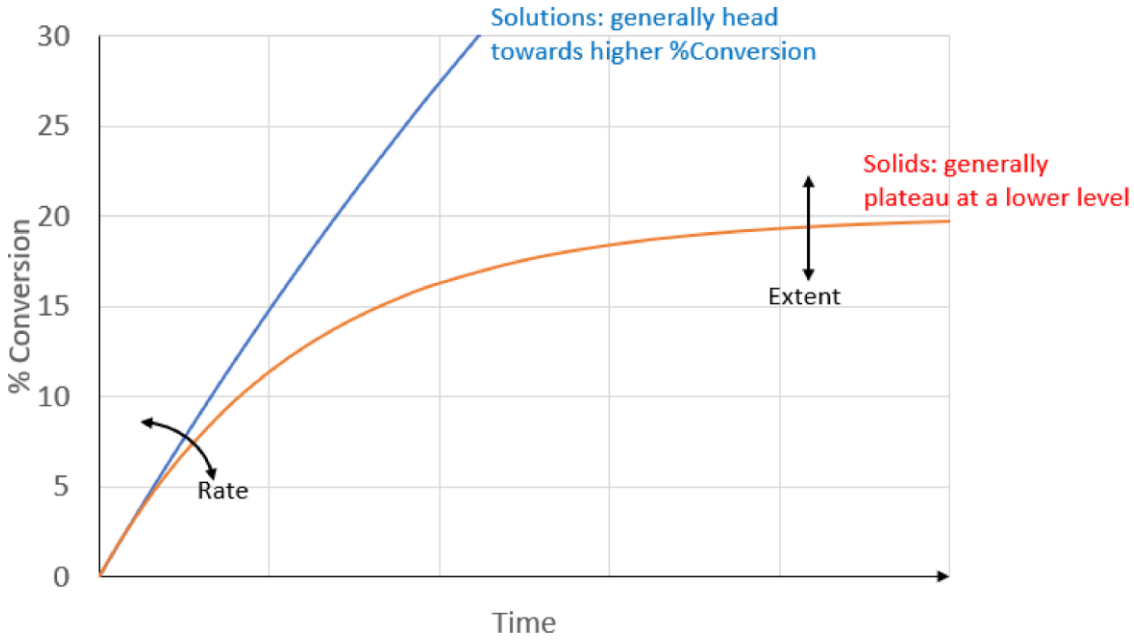
- The effects of different manufacturing methods or storage conditions of solid dosage forms on the formation of *N*-nitrosamines were studied.
- There was little difference in the formation rate of *N*-nitrosamines of secondary amines (free form) due to differences in manufacturing methods.
- On the other hand, in the case of secondary amine (hydrochloride salt), the formation rate of *N*-nitrosamine in wet granulation was very high compared to other manufacturing methods.
- The above results suggest that nitrosation of secondary amines is accelerated by the presence of acid and water in the formulation process.
- When tertiary amines were used, little *N*-nitrosamine was formed regardless of the API form, formulation manufacturing method, or storage conditions.

The presence of water was suggested to increase the risk of *N*-nitrosamine formation during the manufacturing process and storage.

J. Pharm. Sci. 112 (2023) 1255–1267

Effect of water on *N*-nitrosamine formation



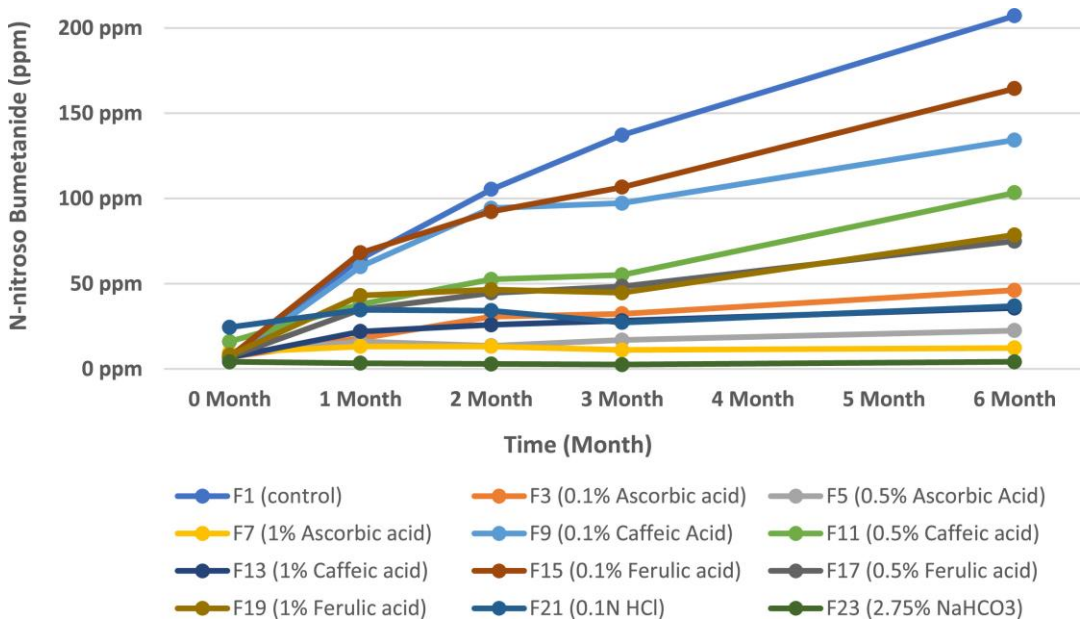


- In the formulation manufacturing process, water is thought to solubilize the API (amine component) and nitrite, thereby promoting uniform dispersion and accelerating the reaction between the API and nitrite.
- Partial solubilization of the API may change the physicochemical properties of the API, such as amorphization, change in morphology and particle size, and increase in surface area, which may accelerate the nitrosation reaction in the solid phase.
- The saturated solution layer concept allows for a water film to bridge the contacts between multiple solid particles and establish a solution that contains either or both vulnerable amine and nitrite extracted from the excipients, thus enabling nitrosation.
- Nitrosation in solids is considered to be plateaued when the concentration of amine or nitrite decreases as the reaction proceeds, since only the reactants on the surface of the solid particles are considered to be available for the reaction.

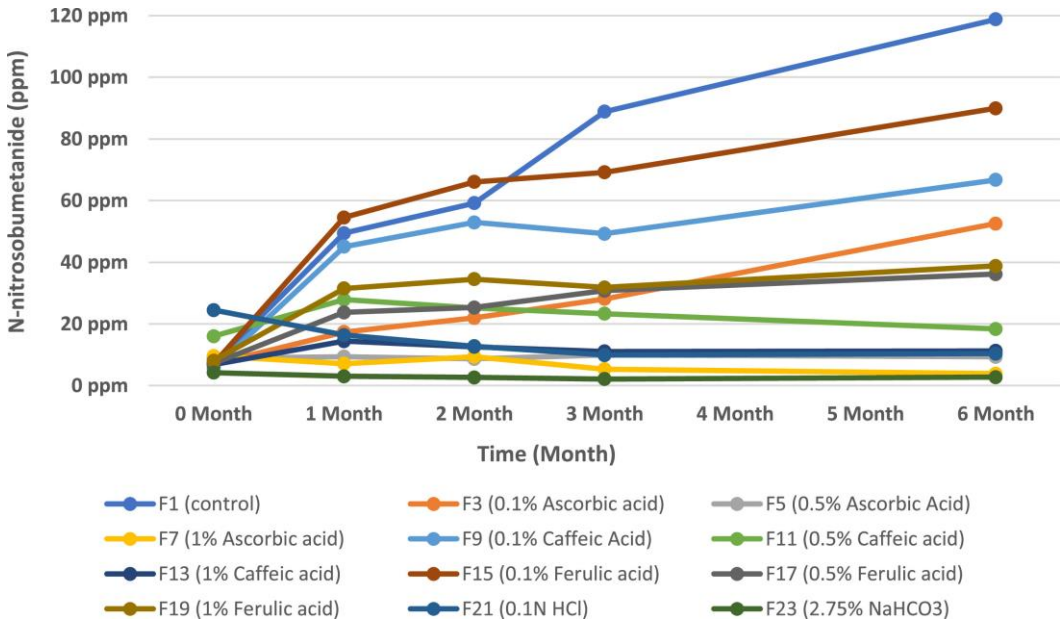
J. Pharm. Sci. 112 (2023) 1255–1267

Inhibition of *N*-nitroso-bumetanide in Bumetanide Tablets

Long Term Condition (25 ºC/60% RH)



Accelerated Condition (40 ºC/75% RH)



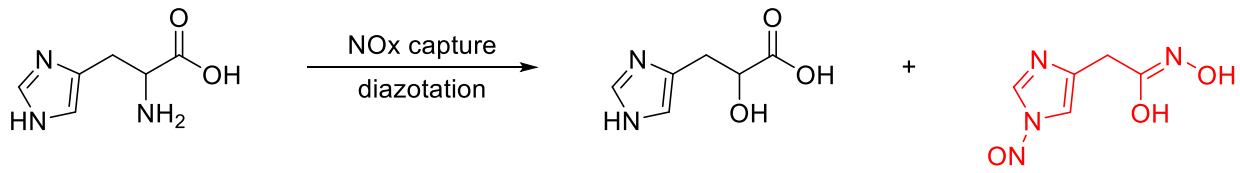
- The role of different inhibitors (antioxidants) and pH modifiers in tablet formulations were evaluated using bumetanide as a model drug to mitigate the formation of *N*-nitroso-bumetanide.
- Antioxidants and pH modifiers showed effective mitigation of *N*-nitroso-bumetanide formation in tablets prepared by wet granulation and stored at long-term and accelerated conditions.
- The highest inhibition of *N*-nitroso-bumetanide formation among the antioxidants was observed with ascorbic acid followed by caffeic acid, and then ferulic acid.
- The increase in antioxidant concentration improved the *N*-nitroso-bumetanide mitigation.
- The alkali modifier (sodium bicarbonate) had the most effective inhibition of *N*-nitroso-bumetanide formation.

J. Pharm. Sci. 112 (2023) 3075–3087

Challenges in implementing mitigation strategies for drug product manufacturing

- Reduce the nitrite content of excipients
  - ✓ Increase of manufacturing costs
  - ✓ The amount of nitrite in excipients varies from manufacturer to manufacturer or batch to batch
  - ✓ Need for additional nitrite specification of excipients
  - ✓ Necessary to ascertain the extent to which the level of nitrite in the excipient affects the level of *N*-nitrosamines produced in the drug product

- Change in manufacturing method of drug product
  - ✓ Increase of manufacturing costs
  - ✓ Stability of drug product employing new manufacturing methods needs to be confirmed (e.g., color stability)
  - ✓ The nitrite scavenger should selectively react with nitrite or nitrite-derived species and not interact with API
  - ✓ Formulation conditions may need to be adjusted due to additives
  - ✓ In vitro or in vivo bioequivalence bridging studies may be needed
  - ✓ Toxicity evaluation of the additive itself or byproducts of the scavenging reaction



Histidine

NIAH (mutagenic)

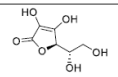
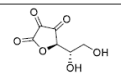
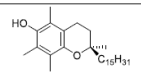
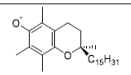
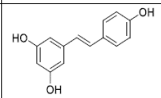
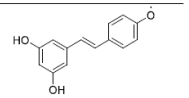
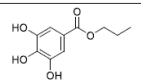
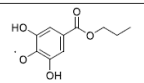
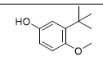
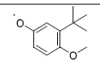
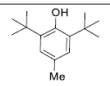
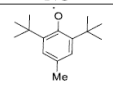
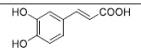
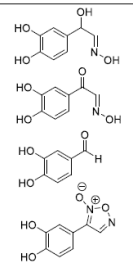
J. Agric. Food Chem. 41 (1993) 1090–1093

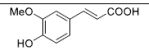
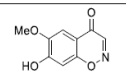
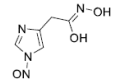
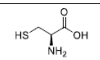
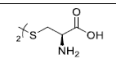
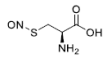
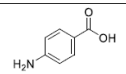
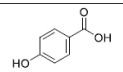
Conclusion

- All three risk factors are necessary for the formation of *N*-nitrosamines:
  - ✓ Presence of a nitrosatable (vulnerable) amines
  - ✓ Presence of a nitrosating agent
  - ✓ Conditions conductive to *N*-nitrosamine formation
- If any one of these risk factors can be eliminated, the risk of *N*-nitrosamines formation can be sufficiently mitigated.
- If the root causes of *N*-nitrosamines are understood and proven to be effective, setting nitrite specifications for specific excipients is a reasonable approach.
- The presence of water may increase the risk of *N*-nitrosamine formation in solid dosage forms during the manufacturing process or storage.
- When incorporating a nitrite scavenger or pH modifier in the formulation to control *N*-nitrosamine formation, the manufacturing conditions, drug stability, and safety effects should be carefully considered.
- When implementing a mitigating strategy, it is important to understand the root cause of *N*-nitrosamines formation and implement essential reduction measures accordingly.

Appendix

List of reported nitrite scavengers

No	Name	Structure	NDSRI formation inhibition mechanism	By-products
1[55]	ascorbic acid (ascorbate)		redox (antioxidant)	 NO
2[73]	α-tocopherol		redox (antioxidant)	 NO
3[74]	maltol		redox (antioxidant)	 NO
4[75]	resveratrol		redox (antioxidant)	 NO
5[76]	propyl gallate		redox (antioxidant)	 NO
6[77]	BHA		redox (antioxidant)	 NO
7[77]	BHT		redox (antioxidant)	 NO
8[60]	caffeic acid		NOx capture and redox	

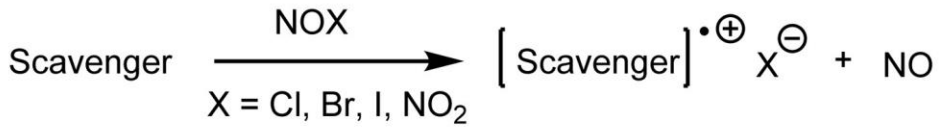
No	Name	Structure	NDSRI formation inhibition mechanism	By-products
9[59]	ferulic acid		NOx capture	
10[78]	α-aminoacids (glycine, lysine, histidine*)		NOx capture (diazotation)	N_2  
11[78,79]	L-cysteine		redox (antioxidant) or NOx capture	 NO 
12[80]	*p*-aminobenzoic acid (PABA)		NOx capture (diazotation)	 N_2
13[65]	urea		NOx capture (diazotation)	N_2, CO_2
14[65]	sodium sulfite	$NaHSO_3$	redox (antioxidant)	NO, $NaHSO_4$
15[64,81]	ammonium chloride	NH_4Cl	NOx capture (diazotation)	N_2
16[36]	sodium carbonate	Na_2CO_3	pH modulator	$NaHCO_3$

- Two main categories of additives were identified as additives to inhibit the formation of NDSRI in the drug product.
  - ✓ Nitrite scavengers (e.g., antioxidants, amino acids)
  - ✓ pH modulators (inorganic bases)
- Natural antioxidants such as ascorbic acid and polyphenol reduce nitrite (NO_2^-) to nitric oxide (NO).
- NOx is captured by C-nucleophiles such as ferulic acid, caffeic acid or tocopherol.
- NOx reacts with primary amines such as amino acids to form diazonium salt, which is captured by an adjacent nucleophile (e.g., water).
- Maintaining a basic pH in the formulation process with a basic additive (e.g., Na_2CO_3) may reduce NDSRI formation.

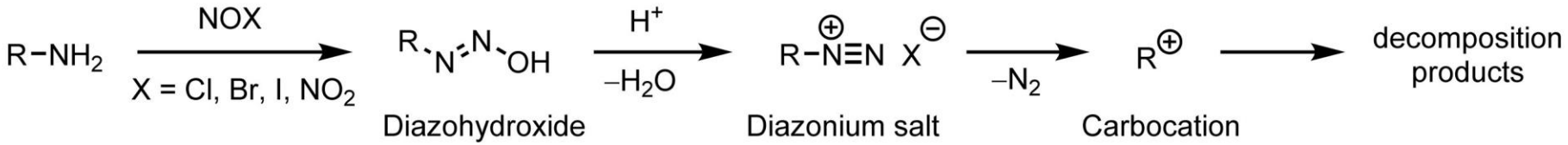
Org Process Dev. Rev. 27 (2023) 1736–1750

Proposed mechanisms of the main scavenging pathways of nitrosating agents

1) Redox Pathway



2) Diazotization of Primary Amines



3) Nitration of Phenolic Scavengers

e.g. Chlorogenic Acid