AsahiKASEI

Risk Mitigation of Nitrosamine Impurities in Drug Products Containing Secondary Amine APIs Through Excipient Nitrite Control

Srinesh Naidu & Raxit Mehta

CEOLUS™
Just Pure Performance

CELPHERE™
Reliability At The Core

About Asahi Kasei

AsahiKASEI

Trade name

Asahi Kasei Corp.

Head office

Tokyo, Japan

Founding

1922

Fiscal 2024 results (consolidated)*

Net sales	¥3,037.3 billion ($20.3 billion)
Operating income	¥221.9 billion ($1.4 billion)

** ¥149per US$*

President

Koshiro Kudo

Paid-in capital*

¥103.4 billion

Employees (consolidated)*

50,352

More than 40% of the workforce based outside Japan

** As of March 31, 2025*

Head Office

MSN Group at a glance

Vision

To emerge as a globally renowned pharmaceutical company offering high-quality, affordable medicines to the world while remaining committed to social and environmental responsibilities.

Mission

To leverage our research & development capabilities for bringing affordable generics, swiftly and consistently, thereby contributing to the alleviation of life-threatening diseases and improving patients' lives.

8

USFDA approved API Manufacturing facilities

3

USFDA approved FDF Manufacturing Facilities

2000+

Scientists

$1Bn

Revenue in 2024

35%

CAGR Since 2005

Patient orientation

Sustainability

What are Nitrosamine Impurities or N-Nitroso impurities

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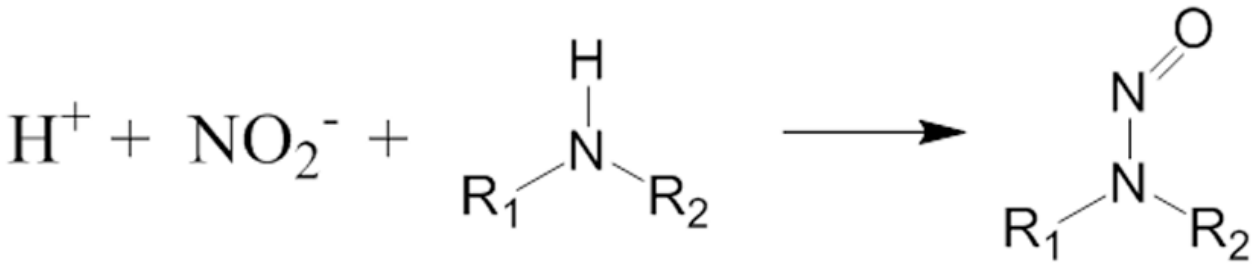
- Common contaminants in low amounts in foods, beverages, cosmetics, water, tobacco products & consumer goods.
- ICH M7- Assessment and control of DNA reactive (Mutagenic) impurities in Pharmaceuticals indicate that some structural classes like N-nitroso, display extremely high carcinogenic potency categorizing them as Cohort of Concern.
- Common N-nitroso compounds are NDMA, NDEA, NMPA, NIPEA, NDIPA, NMBA & NDBA
- Probable or possible human carcinogens and potent genotoxic agents

Formation of Nitrosamine

Nitrite ion

Secondary amine

Nitrosamine



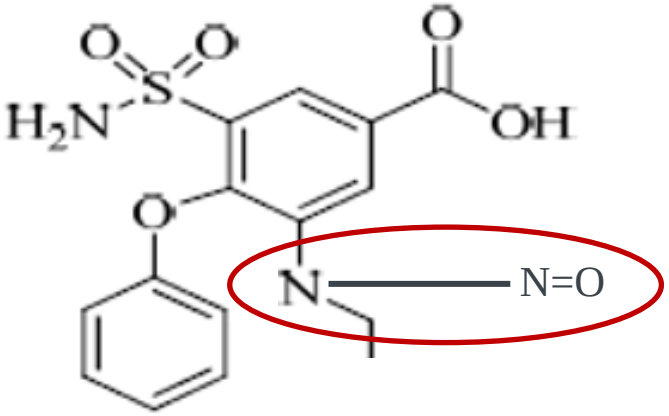
Secondary amines are more vulnerable amines compared to tertiary amine

Highlights of USP draft chapter (1469) Nitrosamine impurities

Răzvan C. Cioc, Ciarán Joyce, Monika Mayr, and Robert N. Bream. Formation of N-Nitrosamine Drug Substance Related Impurities in Medicines: A Regulatory Perspective on Risk Factors and Mitigation Strategies. Organic Process Research & Development 27 (10), 1736-1750.
Olivier Dirat, Michael W. Urquhart, Heather Akehurst, Michael J. Burns, Krista L. Dobo, James Harvey, Nadine Kuhl, Joerg Schlingemann, Paula Tomlin, Christian Wetter, Drug Substance and Drug Product Workflows for Quality Risk Management for the Presence of Nitrosamines in Medicines, Organic Process Research & Development, 2025,

Background

- Drug substance- secondary amine
- White to off white crystalline powder
- Indication- antihypertensive
- Dosage form- Tablets
- Strengths- Three (3)
- Upon filing ANDA, FDA advised to measure & develop control strategy for NDSRI

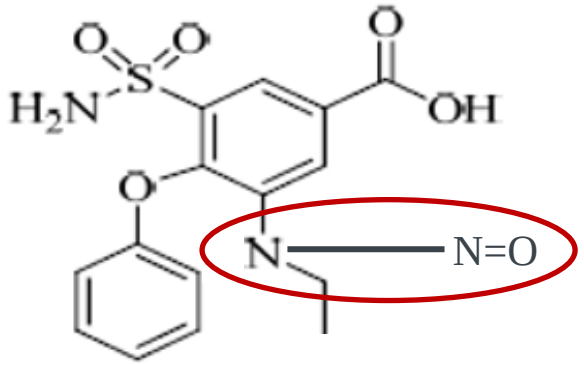


Nitrosamine Drug Substance Related Impurity (NDSRI)

NDSRI Formation

+ NO_2^-

Conducive Condition



Drug Substance with Secondary Amine

Nitrosating Agent

Nitrosamine

Challenges During ANDA Review

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The FDA has introduced control of Nitrosamines in Sep 2020 after ANDA was accepted.

The analytical results revealed that the proposed bio-equivalent formulation showed formation of nitrosamine impurity in the drug product.

However, it was essential that the proposed drug product remains stable without formation nitrosamine impurity

Therefore, it was decided to reformulate the drug product.

Nitrosamine Risk Mitigation Framework

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Identifying the Nitrosamine risk

- Analyzing the risk associated with the drug substance
- Evaluation of drug product manufacturing process
- Sources of nitrite

Managing Nitrosamine impurity in the drug product

- Nitrite and nitrosamine measurement
- Selection of suitable strategies to mitigate nitrosamine

Monitoring the nitrosamine

- Monitoring the levels of nitrosamine impurity in stability

Identifying the Risk Factors

Drug Substance Related Risk Factors

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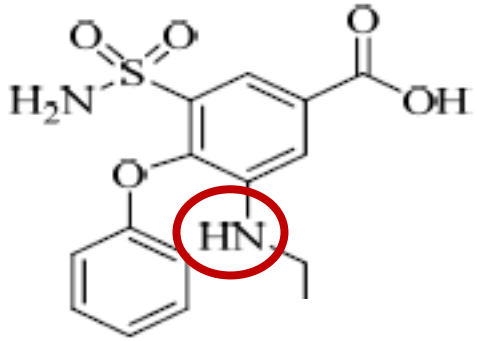
- Drug substance has a **secondary amine functional group** which is likely to react with Nitrites or Nitrates and there by form N-Nitroso impurities. (High risk)

- The drug substance **manufacturing process does not contain nitrite salts or nitrosating agents. (Low risk)**

Structural formula :



Molecular formula : $C_{17}H_{20}N_2$

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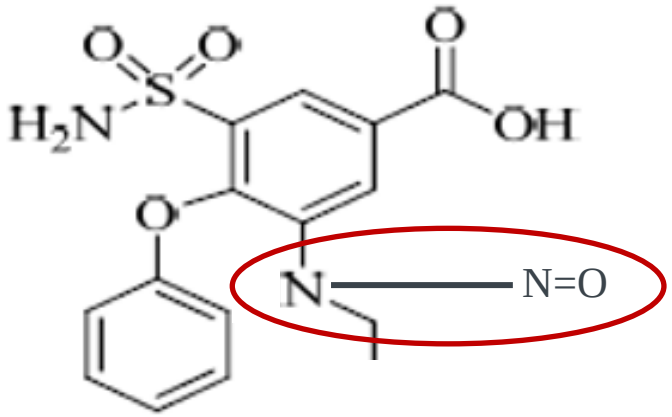
Effect of Salt Forms

- Salt forms of the drugs, such as HCl salt, are more prone to nitrosamine formation
- Risk of nitrosamine formation is 5X since HCl salt provides acidic condition favoring NDSRI formation
- **Current drug is in its base form (low risk)**

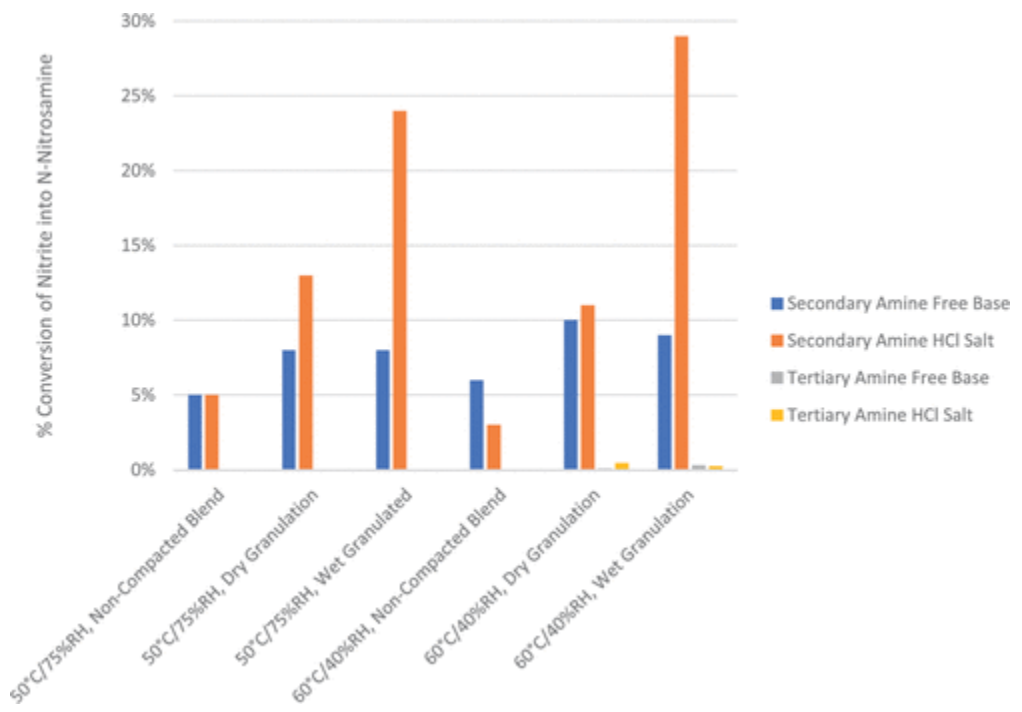
Drug Structure



Moser J, Ashworth IW, Harris L, Hillier MC, Nanda KK, Scrivens G. N-Nitrosamine Formation in Pharmaceutical Solid Drug Products: Experimental Observations. J Pharm Sci. 2023 May;112(5):1255-1267.

Drug Product Manufacturing Process

- Drug product manufacturing process significantly affect NDSRI formation
- Dry blends < direct compression < wet granulation < amorphous (EFPIA)
- DP manufacturing process: Direct compression (low risk)



Moser J, Ashworth IW, Harris L, Hillier MC, Nanda KK, Scrivens G. N-Nitrosamine Formation in Pharmaceutical Solid Drug Products: Experimental Observations. J Pharm Sci. 2023 May;112(5):1255-1267.
Workflows for Quality risk management of nitrosamine risks in medicines, EFPIA

Nitrite Levels of Different Excipients

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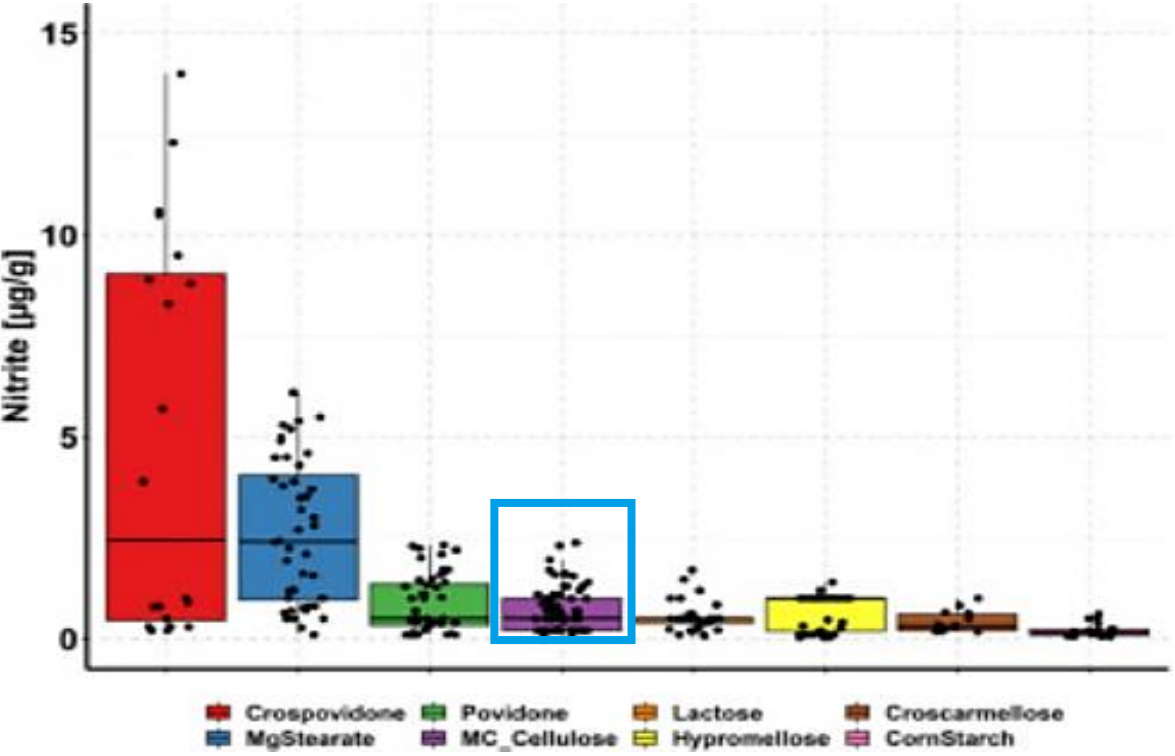
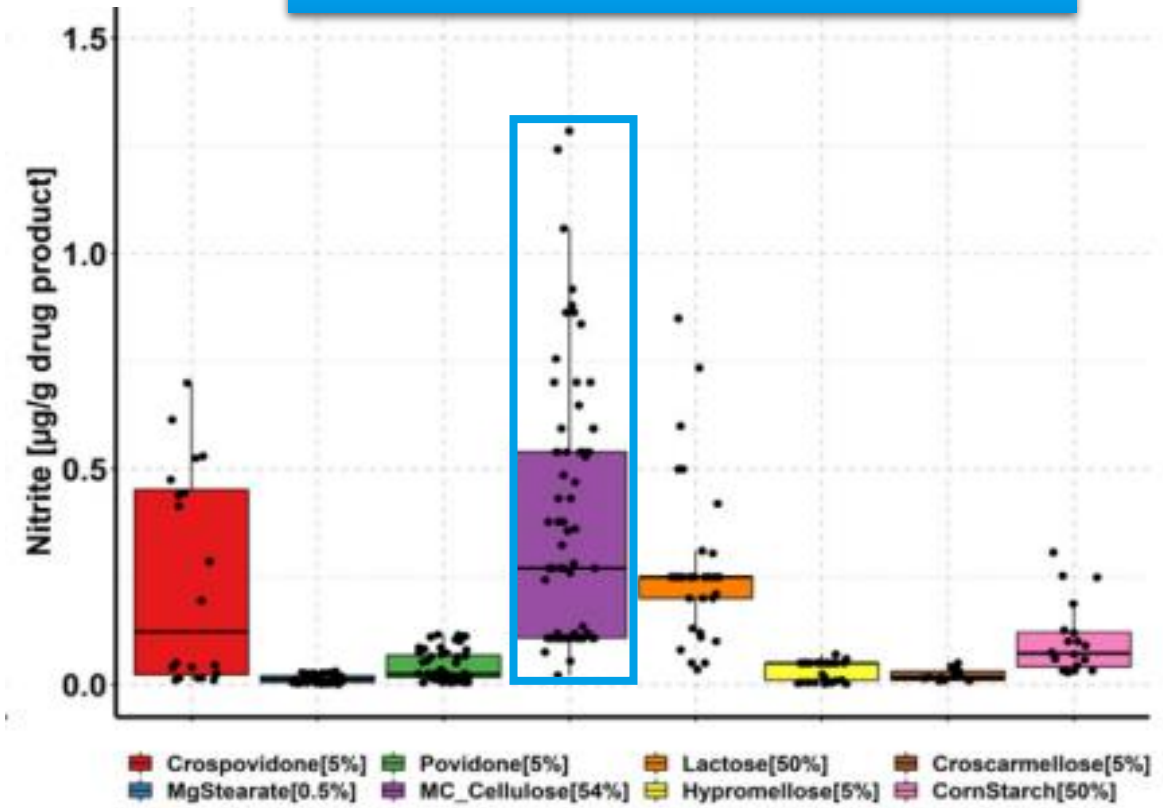
Nitrite Concentration in Excipients



Nitrite Contribution in Drug Products



- The fillers/diluents (such as MCC) which are typically used in larger proportions should be considered as a potential risk factor

R. Boetzel et al. / A Nitrite Excipient Database: A useful Tool to Support N-Nitrosamine Risk Assessments for Drug Products /Journal of Pharmaceutical Sciences 00 (2022) 1−10

Summary of Risk Identification Step

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Stage/Source	Risk of Nitrosamine formation	Notes
Secondary Amine in Drug Structure	**High**	**Target site for Nitrosation reaction**
Drug impurities and nitro salt in manufacturing	Low	API manufacturing process does not involve Nitrite/Nitrate contamination, and the Drug Substance is not a salt form
Drug in base form (no salt)	Low	HCl or other salt may create acidic environment- conducive for nitrosamine
Drug product manufacturing process: Direct Compression	Low	Low risk of nitrosamine formation from Direct Compression process
Nitrite in Excipient	**High**	**Source of Nitrite for nitrosamine**

Managing Nitrosamine Risk

Drug Product Formulation

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Ingredients	Function	Concentration used (%w/w)
API	Active	<2
MCC PH-102	Diluent	20-40
Anhydrous Lactose	Diluent	20-40
Pregelatinized Starch	Binder	10-20
Magnesium Stearate	Lubricant	0.5

High nitrite/Replacement warranted

Drug Product Manufacturing Process

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The drug product was formulated using directly compressible grade excipients.

The drug and other ingredients were co-sifted through a #30 US mesh and blended in a bin blender.

Blends were lubricated with magnesium stearate after passing it through #40 US mesh.

The lubricated blends were compressed into tablets

Nitrosamime Mitigation Strategies

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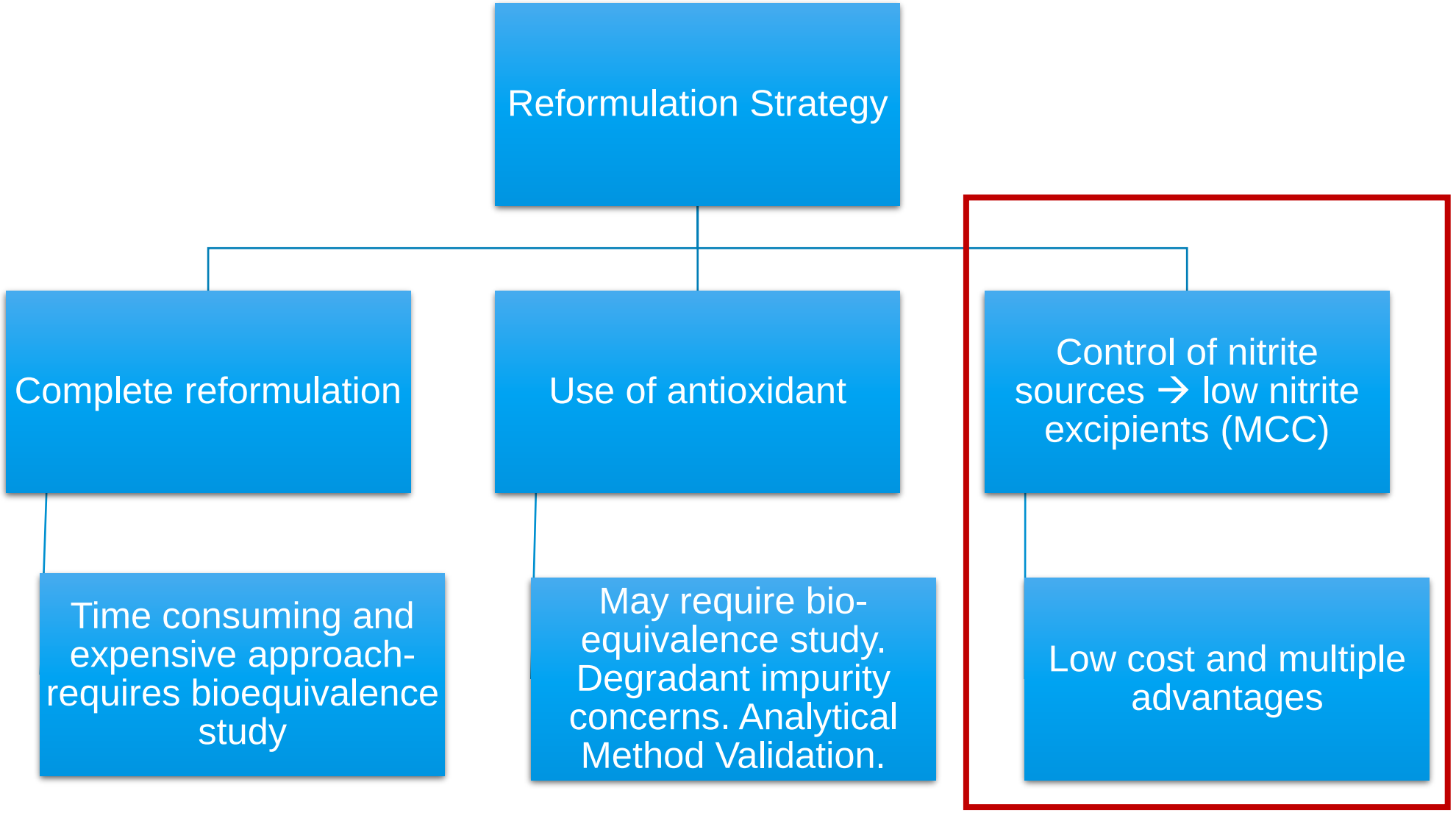

Nitrosamine Mitigation Strategy (Contd…)

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Switching to low nitrite excipient has following advantages:

- No need to develop alternative formulation
- Switching of excipient considered as minor change
  - Only one batch for each strength is sufficient to demonstrate scalability
- Analytical methods and validation remains same for the formulation
  - Significant cost and resource burden can be reduced
- Remanufacture of three (3) exhibit batch X number of strength→ **Not required**
- Repeat of pivotal bioequivalence study → **Not required**
- ANDA amendment resubmission required

- Control of nitrite sources in MCC was cost effective and best strategy to mitigate nitrosamine formation

Role of Excipient Supplier – Need for Low Nitrite MCC

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AsahiKASEI Issued by ASAHI KASEI CORPORATION

Healthcare Materials Division
1-1-2 Yurakucho, Chiyoda-ku, Tokyo 100-0006, Japan
TEL +81-(0)3-6699-3351 FAX +81-(0)3-6699-3467
Manufacturing site: Ceolus Plant
304 Miyashiro-machi, Nobeoka-shi, Miyazaki 882-0011, Japan

Cert. No. 0123456789012345
Date: XX-YY, ZZZZ

CERTIFICATE OF ANALYSIS

Compendial name : Microcrystalline Cellulose NF, Ph. Eur., JP

Trade name : Ceolus™PH-101
Lot No. : XXXX

Manufacturing Date : XX-YY, ZZZZ
Re-evaluation Date : XX-YY, ZZZZ

Organic solvent : Not used in our process

Compendial Standards	Specifications	Lot Analysis
Description (color, shape)	Passes	Passes
Identification B (JP (1))	Passes	Passes
Identification A (JP (2))	Passes	Passes
Identification C (JP (3))	100 – 300	OOO
pH	5.0 – 7.5	OOO
Water-soluble substances (mg)	NMT 12.5	OOO
Ether-soluble substances (mg)	NMT 5.0	OOO
Conductivity (μS/cm)	NMT 75	OOO
Loss on drying (%)	2.0 – 6.0	OOO
Residue on ignition (%)	NMT 0.1	OOO
Bulk density (g/cm^3)	0.26 – 0.31	Passes
Solubility in copper tetrammine (Ph. Eur.)	Passes	NMT 1000
Total aerobic microbial count (cfu/g)	NMT 1000	NMT 100
Total combined molds and yeasts count (cfu/g)	NMT 100	Absent
Escherichia coli	Absent	Absent
Pseudomonas Aeruginosa	Absent	Absent
Staphylococcus Aureus	Absent	Absent
Salmonella species	Absent	
ASAHI Standards		
Particle size, wt. % >250 μm (60 mesh)	LT 0.5	OOO
Particle size, wt. % >75 μm (200 mesh)	10 – 30	OOO
Nitrite (ppm)	NMT 0.1	OOO

- Asahi Kasei offers Ceolus MCC with nitrite concentration of **0.1 ppm or less**
- Every lot offer of Ceolus nitrite value → effective control strategy

Trend Analysis (Latest 50 Lots): Nitrite Value of Ceolus™ PH-102

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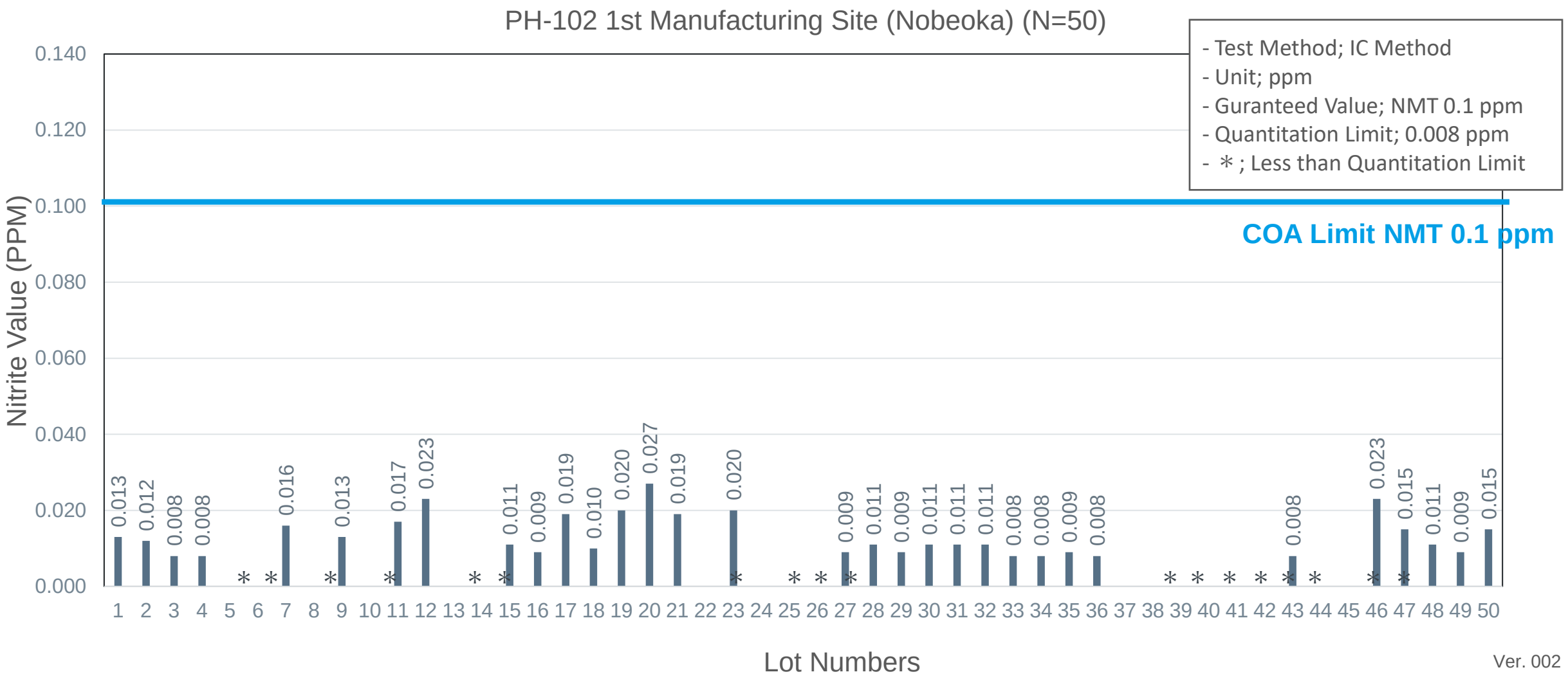


Ver. 002

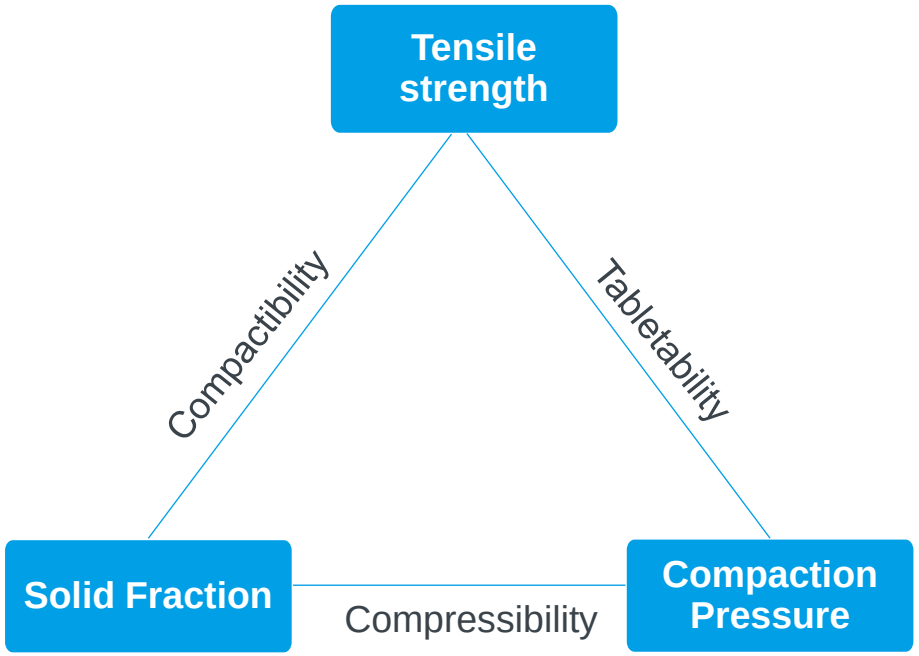
Understanding Compression Characteristic of Ceolus to Minimize Risk of Grade Replacement

USP <1062> Tablet Compression Characterization

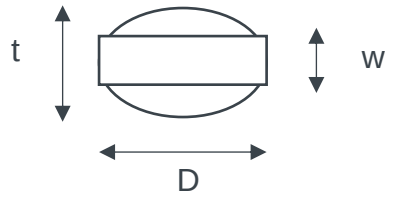
USP<1062> profiling:

Tableting Parameter	Value
Compaction pressure (Mpa)	25, 50, 75, 100
Tablet tooling	Standard Concave 11mm (B-tooling)
Elastic recovery time	24hrs
Sampling and data analysis	Triplicate

USP<1062> Parameters



$$Tablet\ Mechanical\ Strength\ = \frac{2}{3}\left(\frac{10P}{\pi D^2\left(2.84\frac{t}{D} - 0.126\frac{t}{w} + 3.15\frac{w}{D} + 0.01\right)}\right)$$

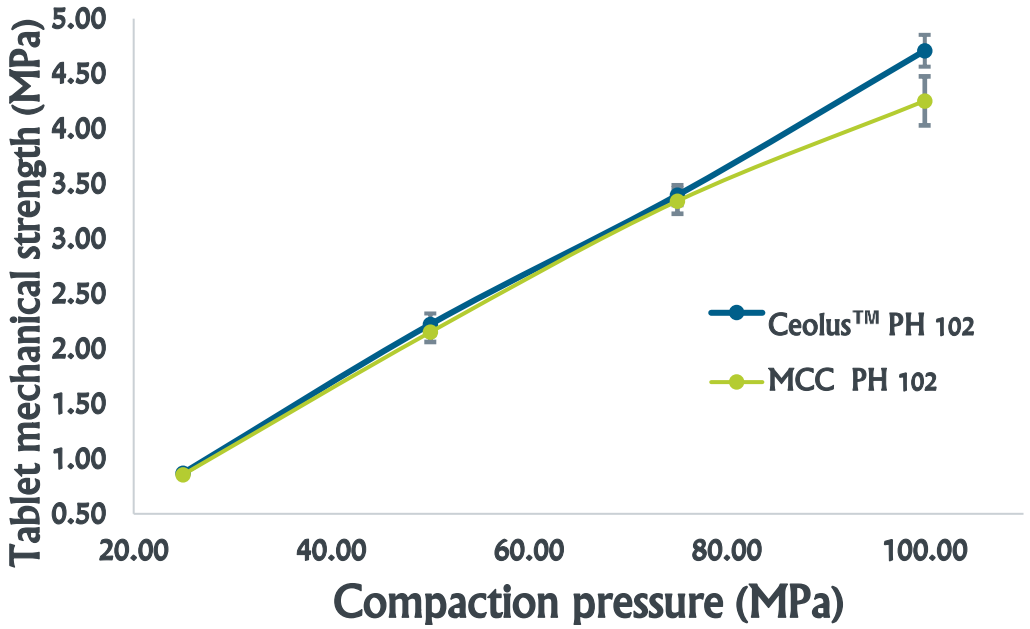


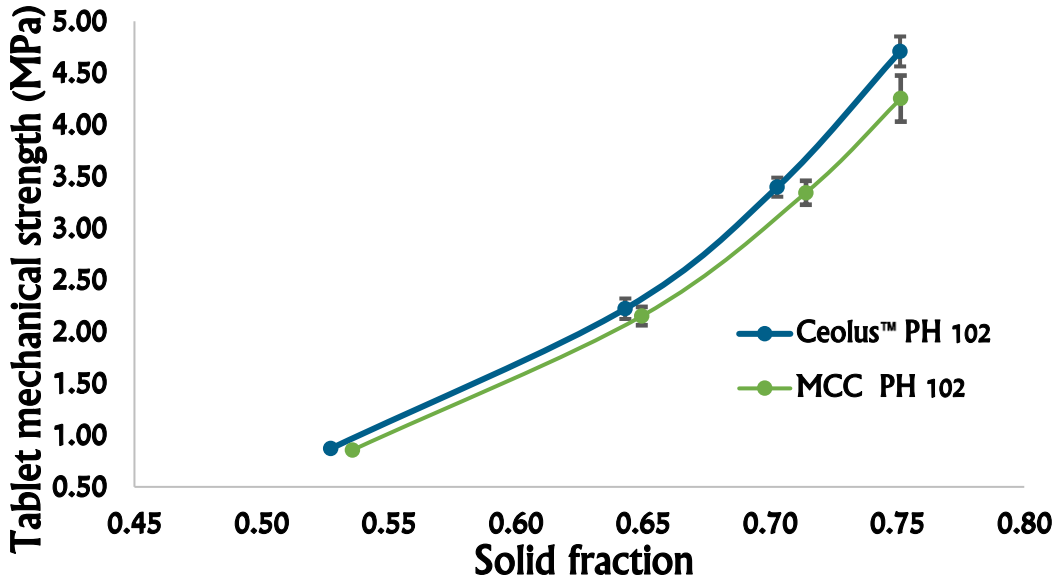
Where,
P = tablet breaking force,
D = length of short axis,
t = overall thickness, and
W = wall height of the tablet.

$$Compaction\ Pressure = \frac{Compaction\ Force}{Applied\ Area}$$

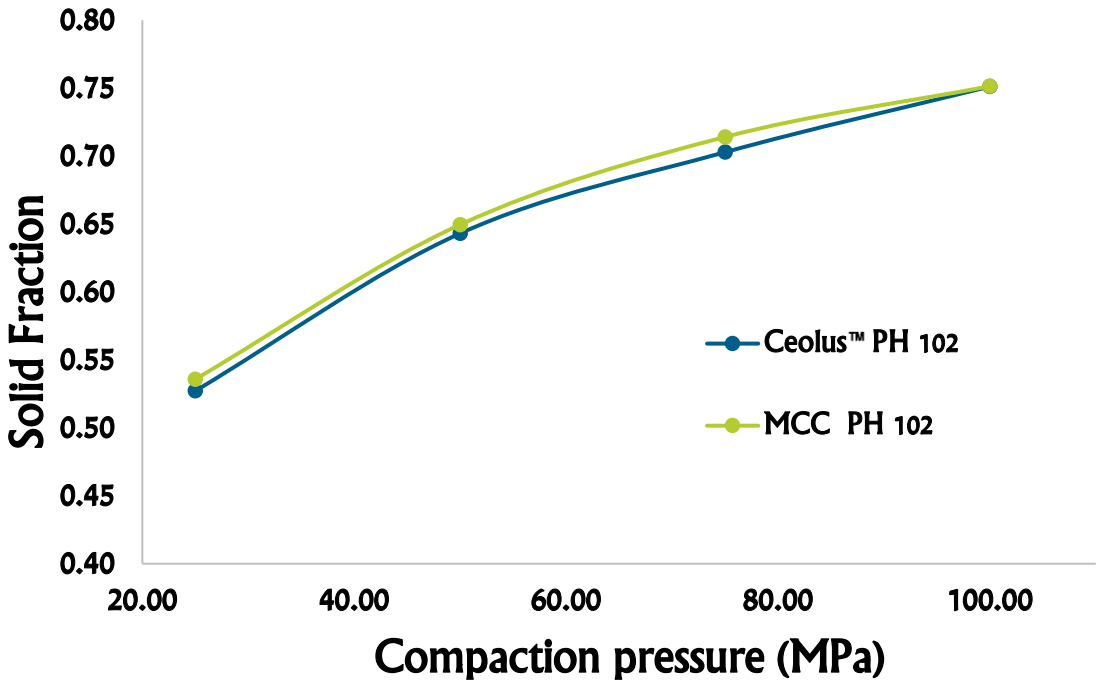
$$Solid\ Fraction = \frac{Tablet\ Density}{Material\ True\ Density}$$

Tabletability & Compactibility





Compressibility



- Equivalent tableting performance observed between Ceolus MCC and alternative MCC grades PH-102
- This evaluation further de-risk current MCC grade replacement with low nitrite Ceolus MCC

Nitrite and Nitrosamine Analytical Method

Nitrite Test Method

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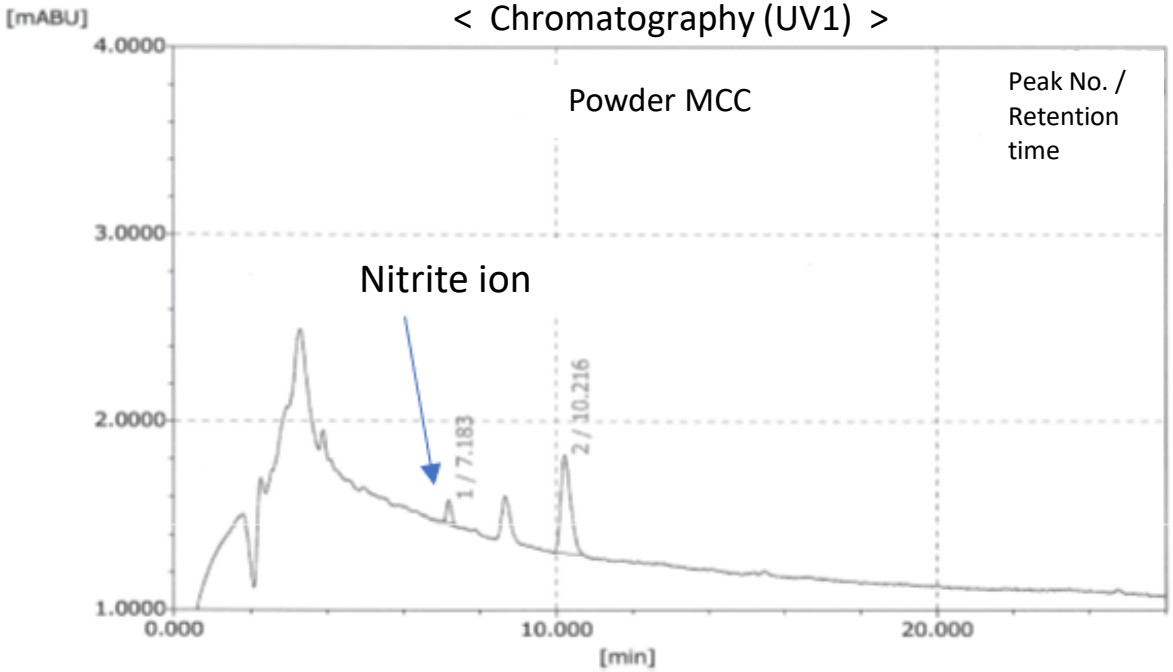
Ion chromatography method (IC)

Method Parameters	Value
Test methodology	Suppressed ion chromatography
Column	Anion Exchange Chromatography Column (4.6mm I.D × 15cm)
Mobile phase	Sodium Carbonate / Sodium Hydrogen Carbonate eluent solution
Flow rate	1.0 mL/min
Oven temperature	40° C
Sample injection volume	100μL
Detector	UV-VIS detector (Wavelength 210 nm)
Detection limit	**0.008μg/g (ppm)**

< Chromatography (UV1) >



Estimation of N-nitroso Impurity in Drug Product

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Liquid Chromatography with Mass Spectroscopy (LC-MS)

Method Parameters	Specification
Test methodology	HPLC with LC UV/PDA Detector equipped with MS
Column	Zodiac C18, 250mm X 4.6mm; 5µm
Mobile phase	Mobile Phase-1: Formic Acid Solution, Mobile Phase-2: Methanol: Water 950:50 (v/v)
Flow rate	0.7 mL/min
Column temperature	45° C
Auto Sampler temperature	5° C

Method Parameters	Specification
Sample injection volume	5 µL
Detector	UV/PDA Detector
Elution	Isocratic
Scan Type (MS)	MRM
Polarity	Positive
MRM Mode	Q1 Mass
Quantification limit	**12.024 µg/g (ppm)**
Detection limit	**3.968 µg/g (ppm)**

Estimation of N-nitroso impurity in Drug Product

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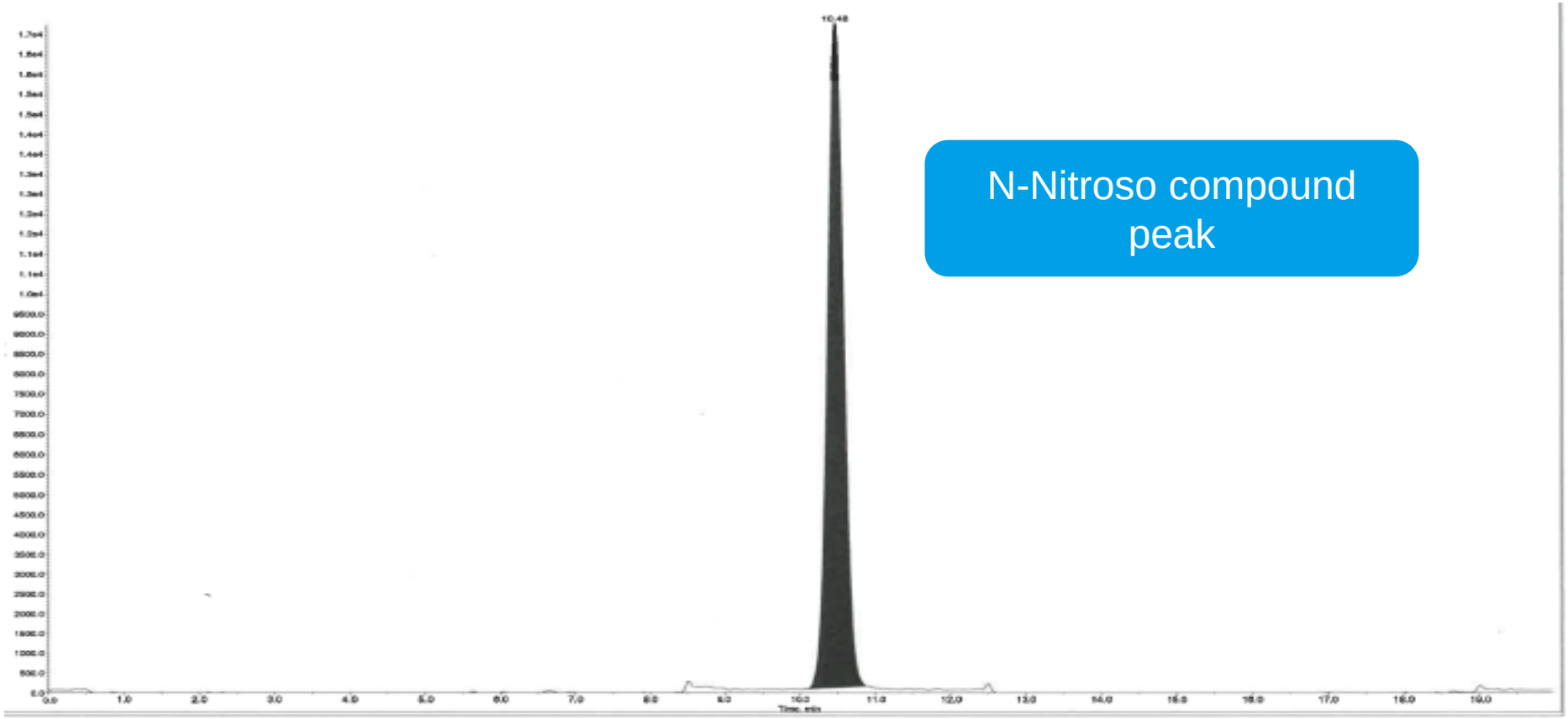
Reference chromatogram of Control Sample (Strength-3)



Reformulation Results

Comparison of Blend characteristics

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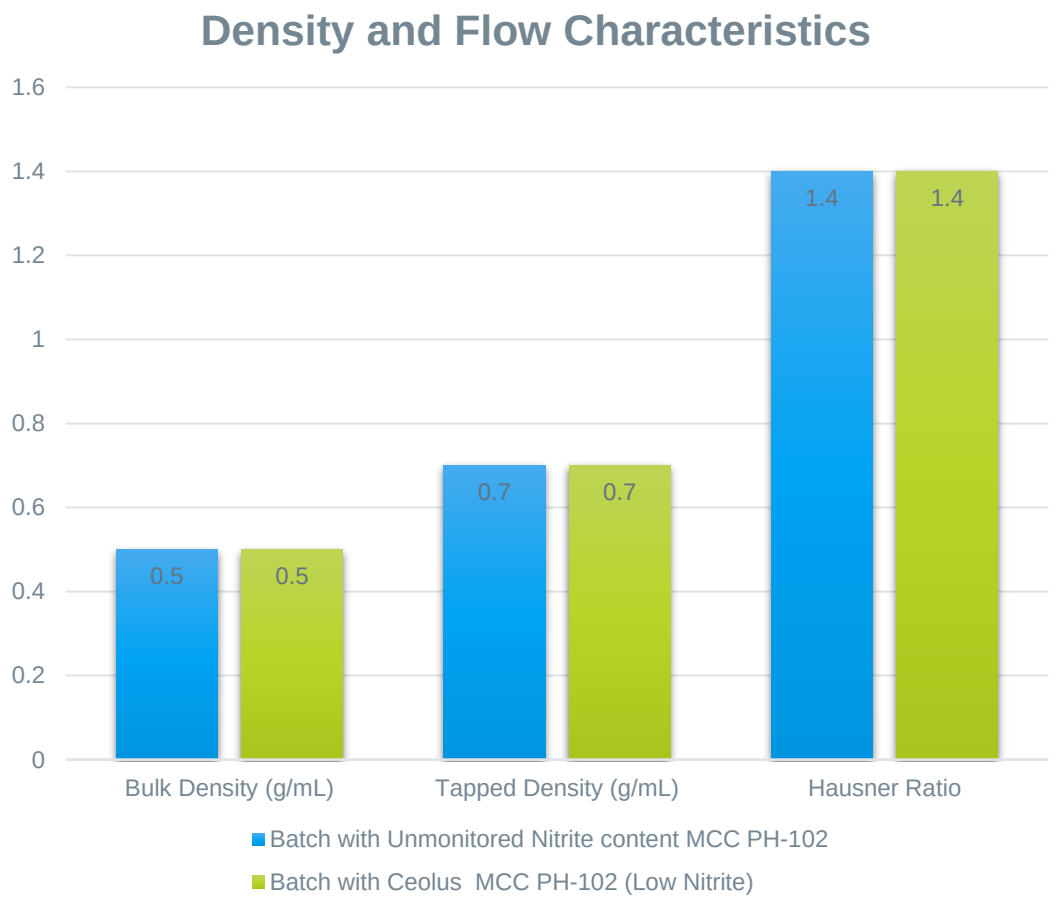
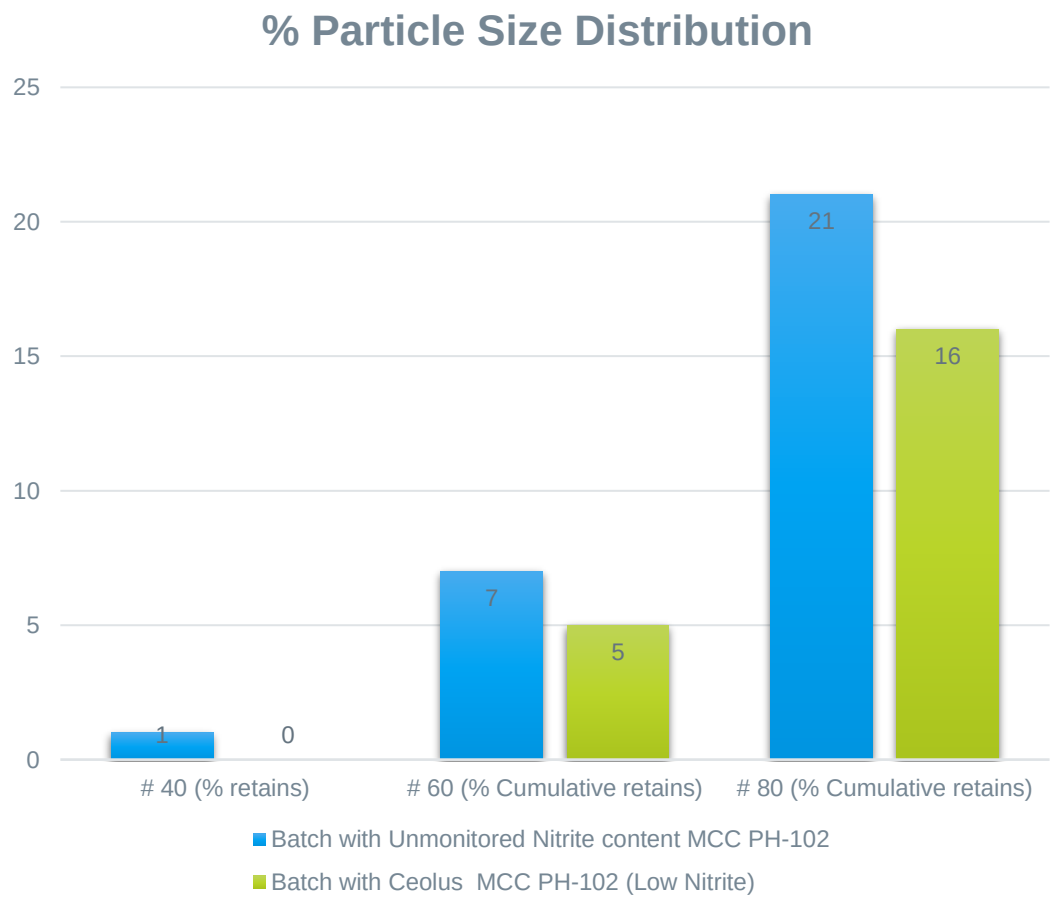
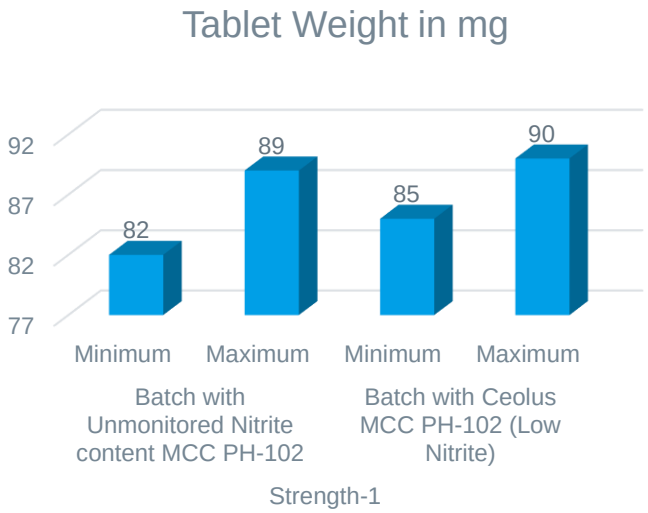
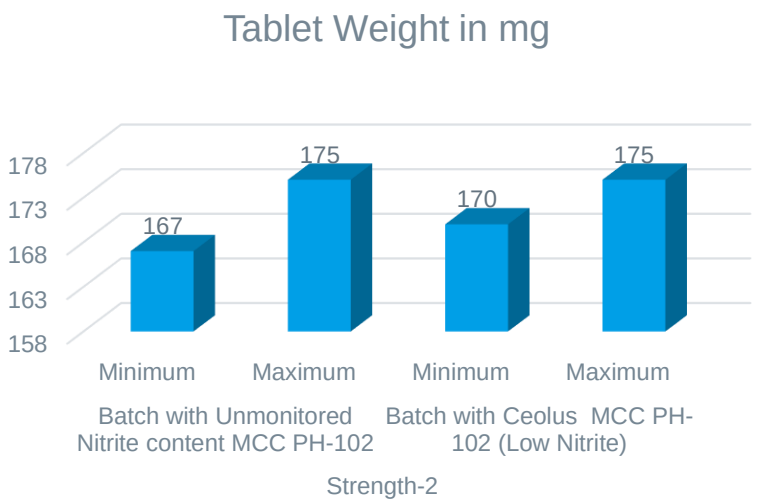
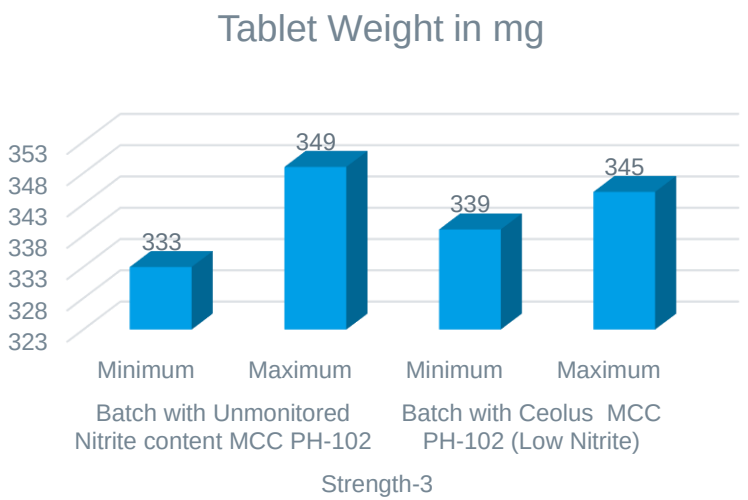




Comparison of Tablet Physical Parameters







Tablet Properties: Hardness & Friability Comparison

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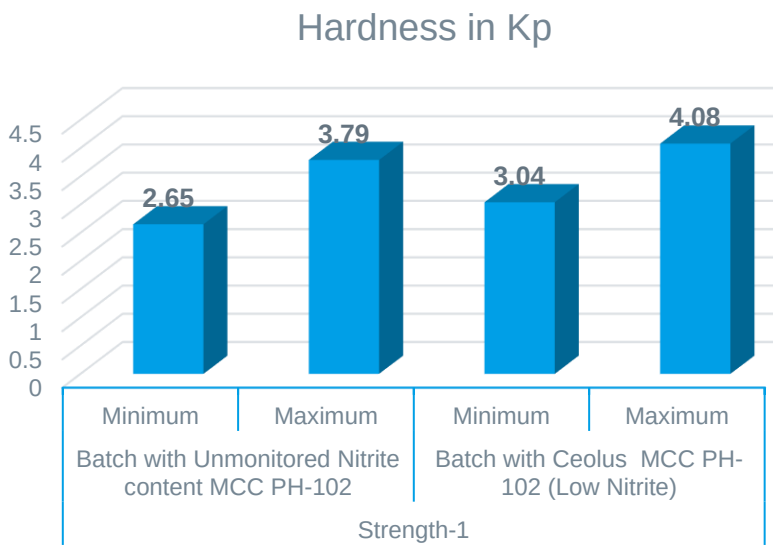
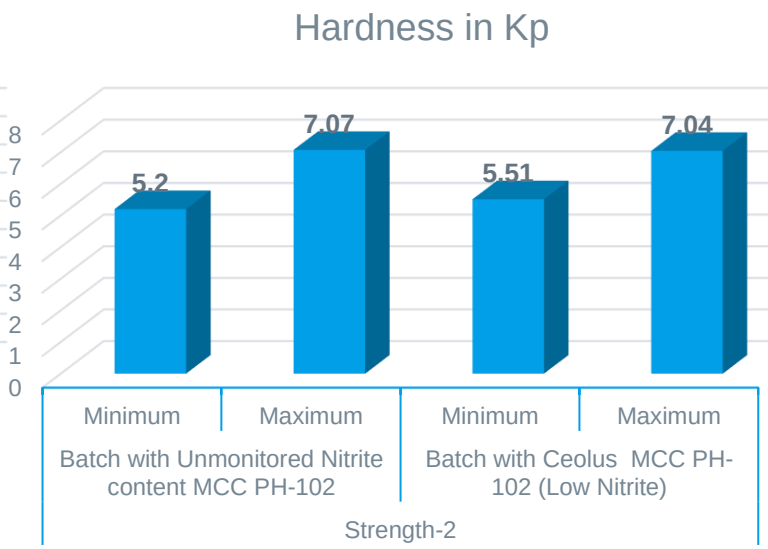
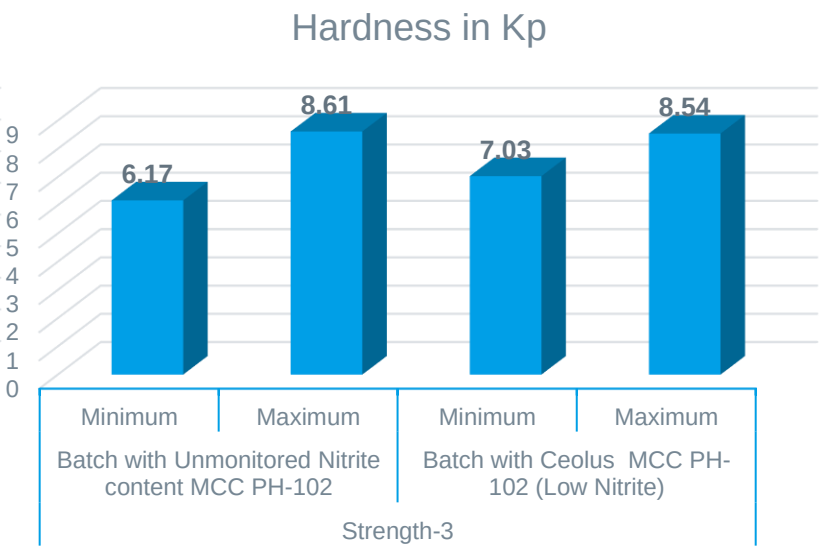
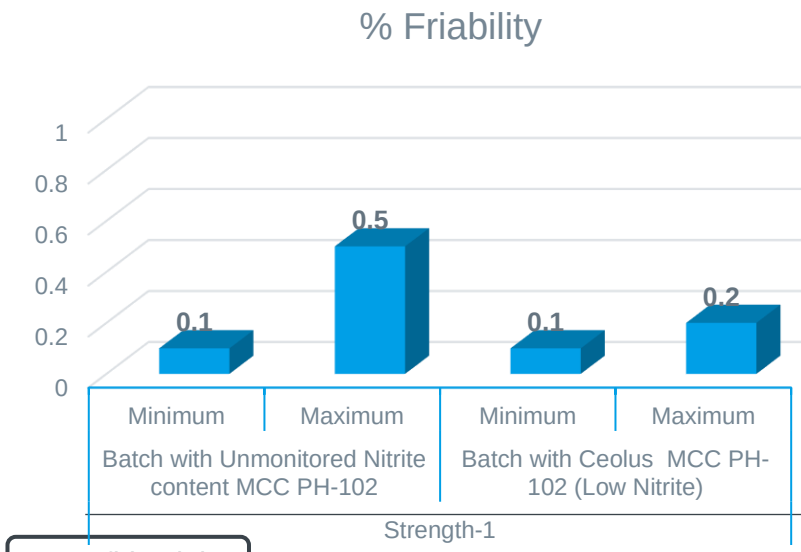
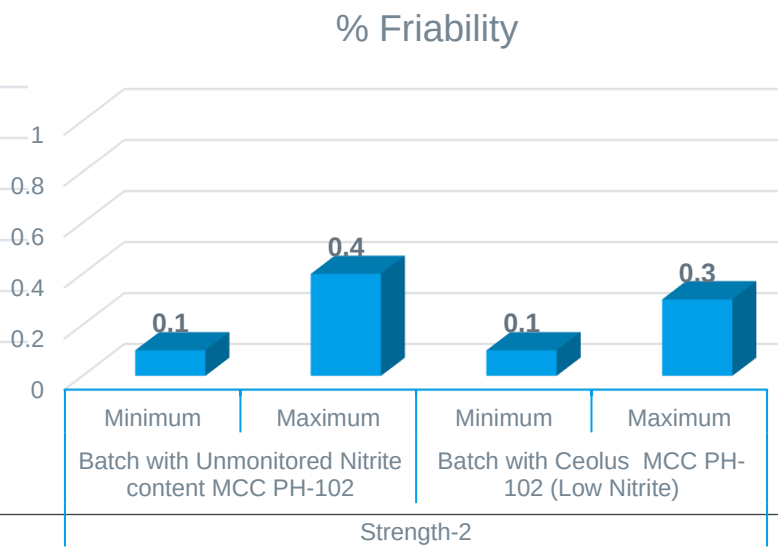
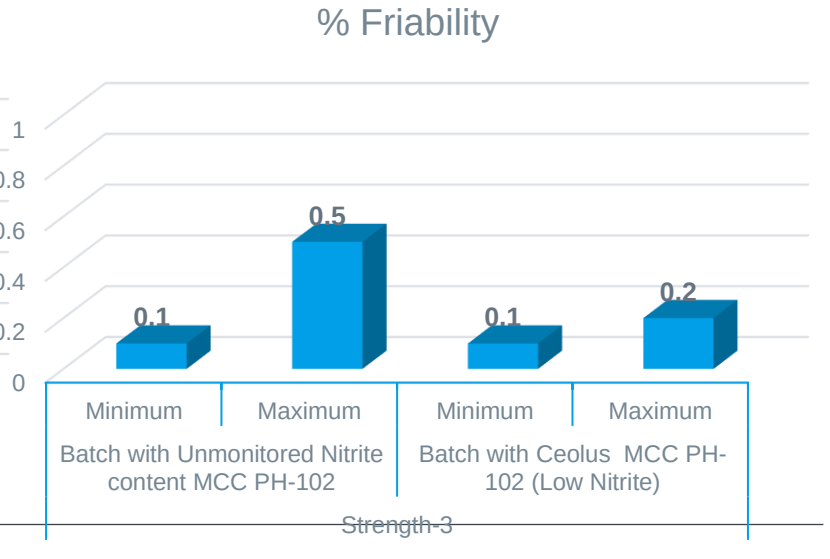




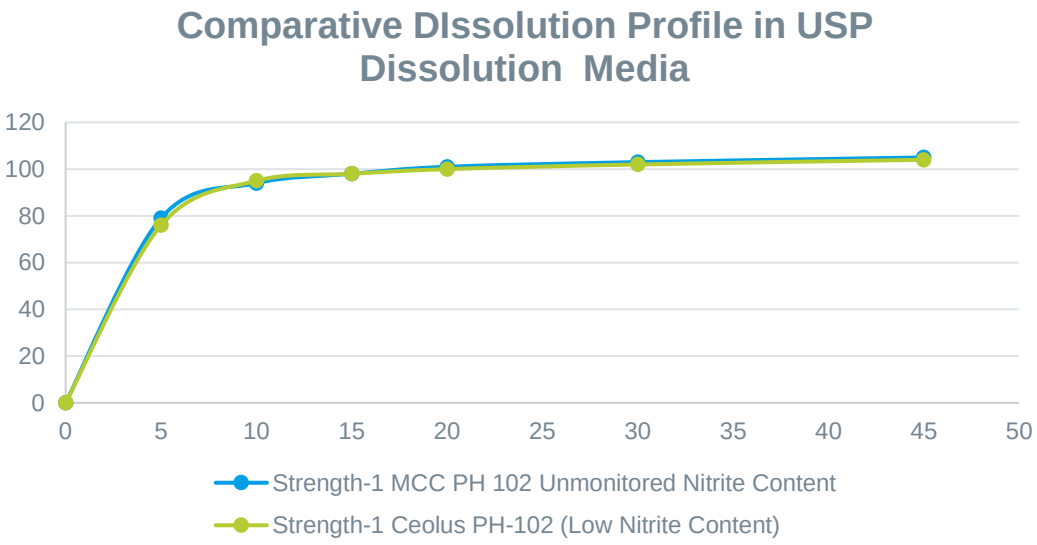


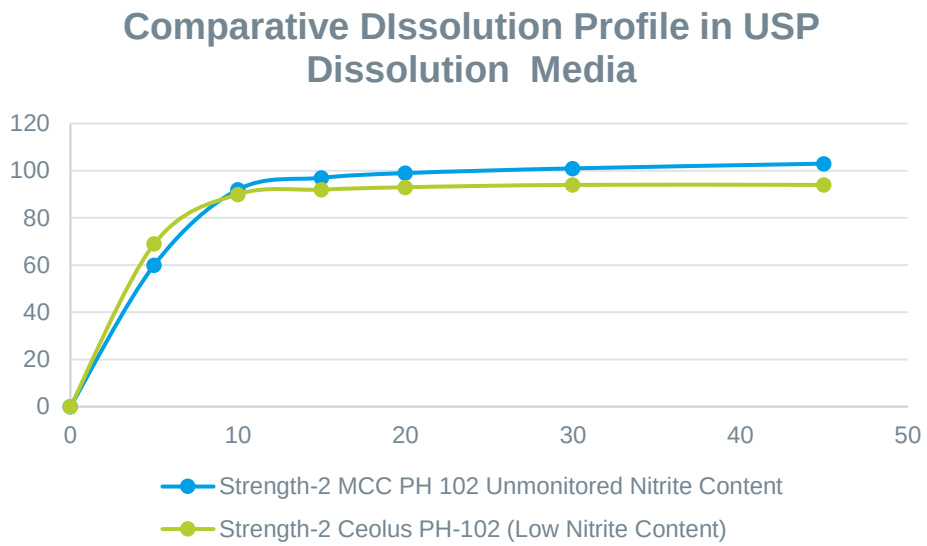


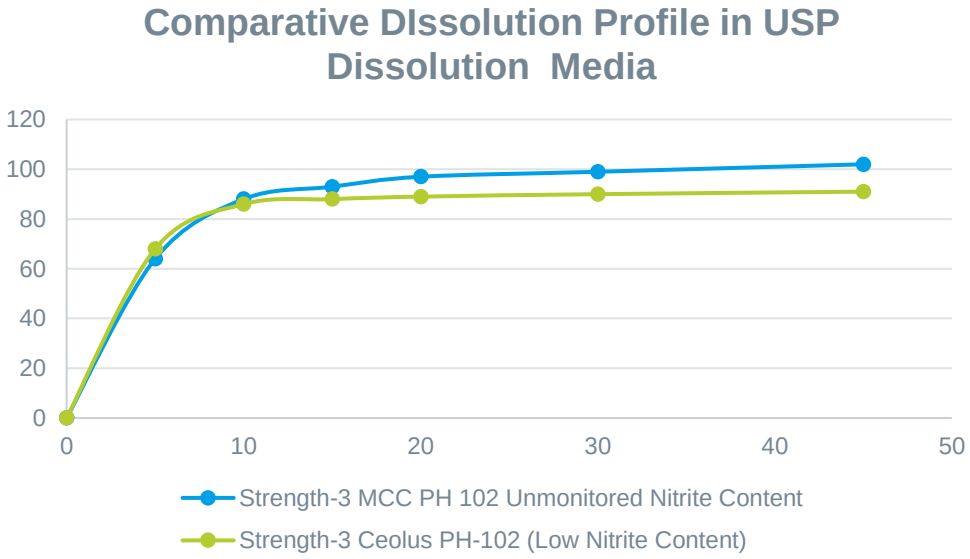




Drug Release Profiles

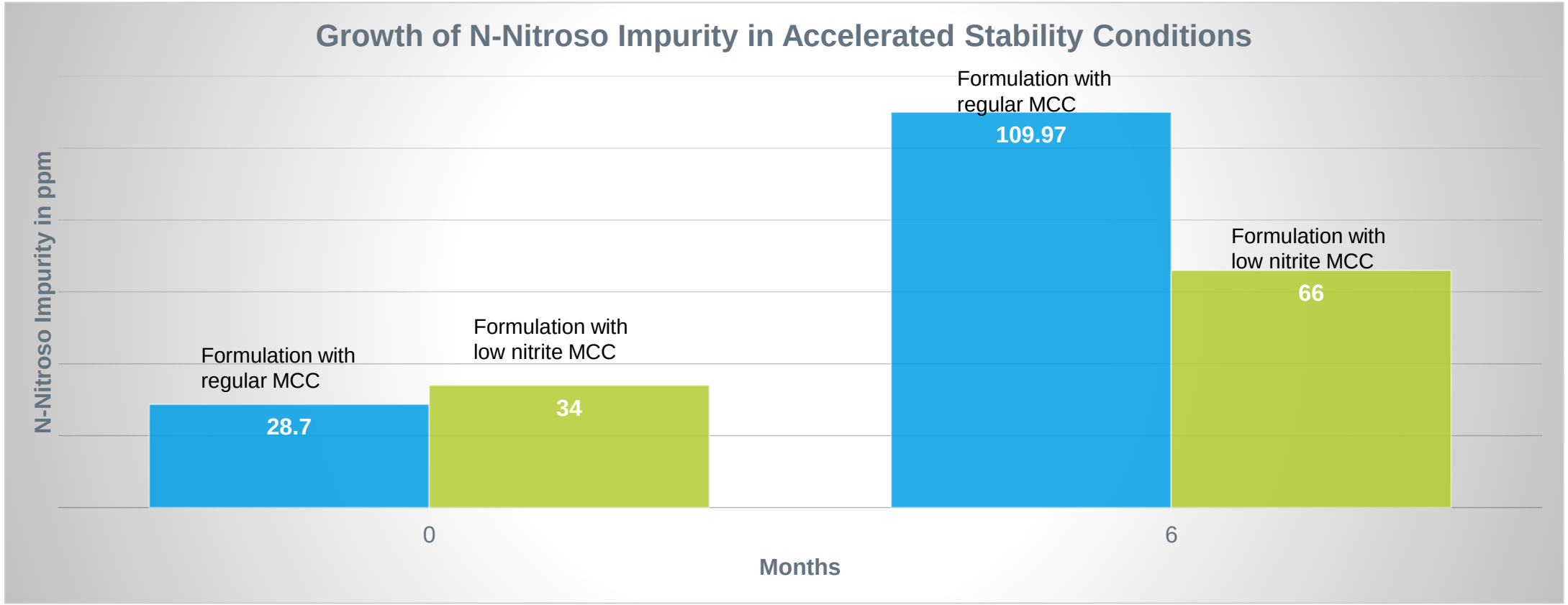






Monitoring the Nitrite Results under Stability

Nitrosamine Impurity During Accelerated Stability



- About 40% reduction in N-nitroso impurity was observed by switching to a low-nitrite Ceolus MCC.
- This directly demonstrates the correlation between excipient nitrite content and levels of nitrosamine, highlighting the critical role of raw material control in pharmaceutical risk management.

Summary of the Case Study

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Critical Quality Attributes	• **Replacement of MCC with Ceolus offers equivalent compression, flow and the drug release characteristics**
Reduction of Nitrosamine	• **40% reduction of NDSRI observed with Ceolus**
Use of low nitrite MCC/excipients	• **Cost effective, fast and efficient strategy to address nitrosamine concerns**
Ceolus MCC grades nitrite value $\leq$ 0.1PPM	• **Additional safety for high-risk formulation**

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Thank You!