Mitigation studies for nitrosamines in pharmaceutical formulations

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Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

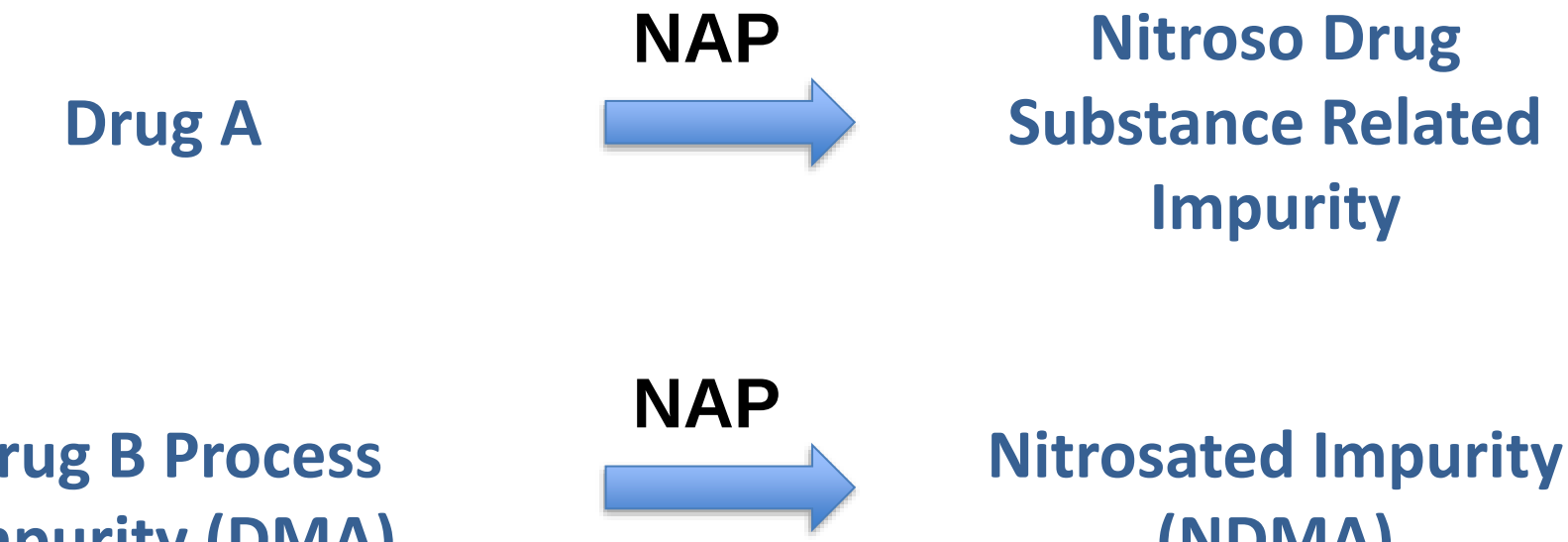
assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

NAP

- In 1978, a WHO Expert Group suggested the nitrosation assay procedure (NAP test) as a general *in vitro* test system under standard conditions (10 mmol/L drug, 40 mmol/L nitrite, 37°C, pH 3-4, with reaction times 1-4h) to study the nitrosation ability of drug substances

Drug A and Drug B



NAP conditions are favorable for nitrosamine formation. Drugs containing reactive amines may never experience these conditions.

Lhasa Database Report

Research Article

A Nitrite Excipient Database: A Useful Tool to Support *N*-Nitrosamine Risk Assessments for Drug Products

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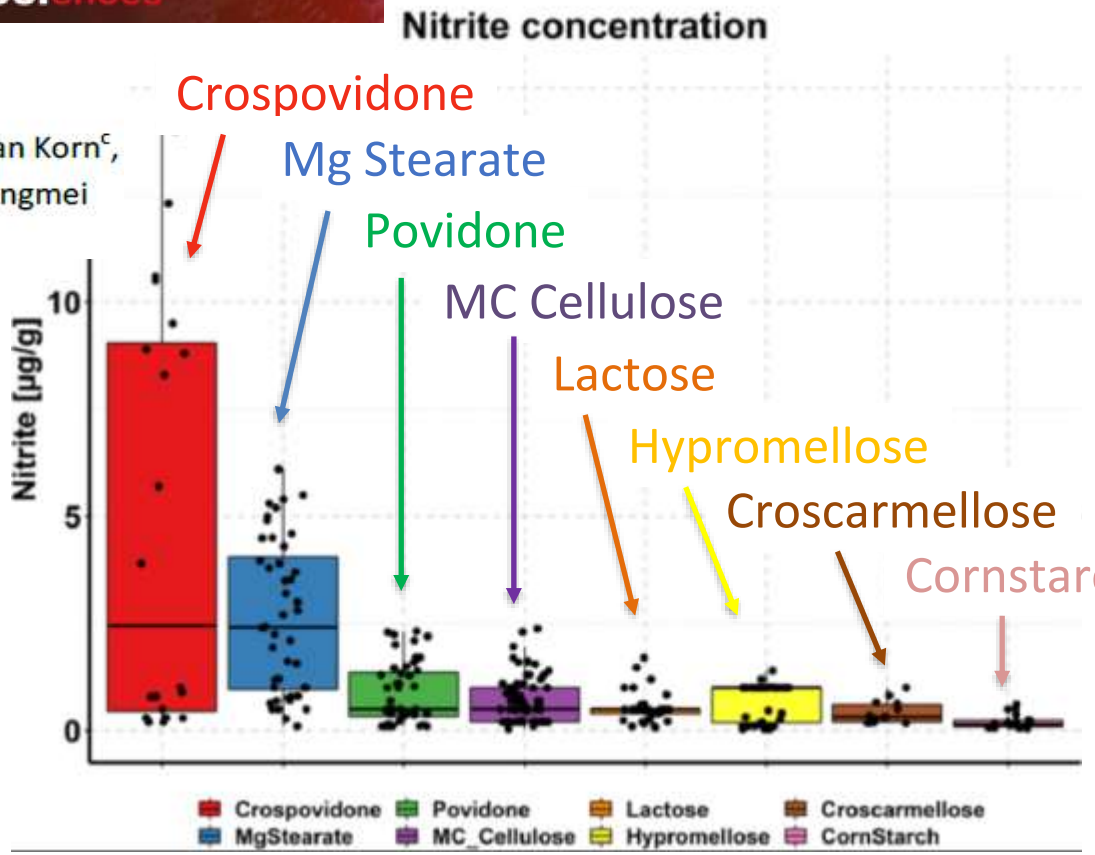


Nitrite concentration in selected excipients

- In a typical formulation: an average value of **1 µg/g (1 ppm)** nitrite

Nitrosamine Mitigation by Formulation (Drug A and Drug B)

Problem:

- Nitrosamines identified in marketed drug products dependent on the formulation.

Approaches:

- Evaluation of the effect of antioxidant & pH on mitigation of nitrosamine levels in drug products.
- https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities

Deliverables:

- Widely share results and findings via available pathways.
- Provide examples of potential strategies to mitigate nitrosamine formation in products

OTR Manufacturing process

Sieving:
Drug (active ingredient) and single excipients (sieve #30)

Mixing:
Drug and antioxidants by geometric dilution (to ensure homogeneity)

Granulation:
Binder Povidone K-30 in H_2O. (intragranular blend)/Nitrite and DMA was spiked here/

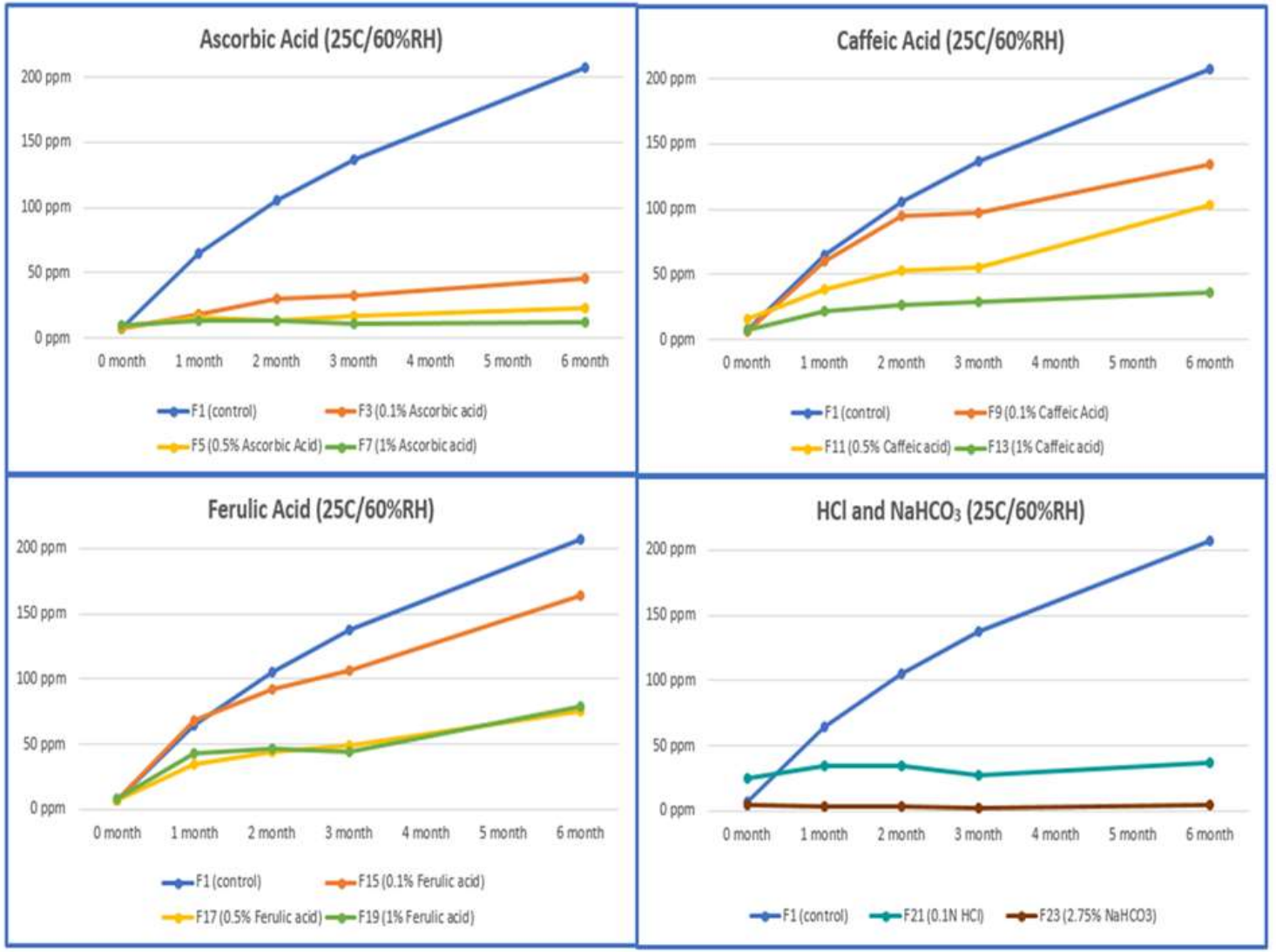
Semi-Drying & Drying:
Using a fluidized bed dryer.
airflow: $20m^3/h$
temp.

Granules:
Moisture content (< 2%)

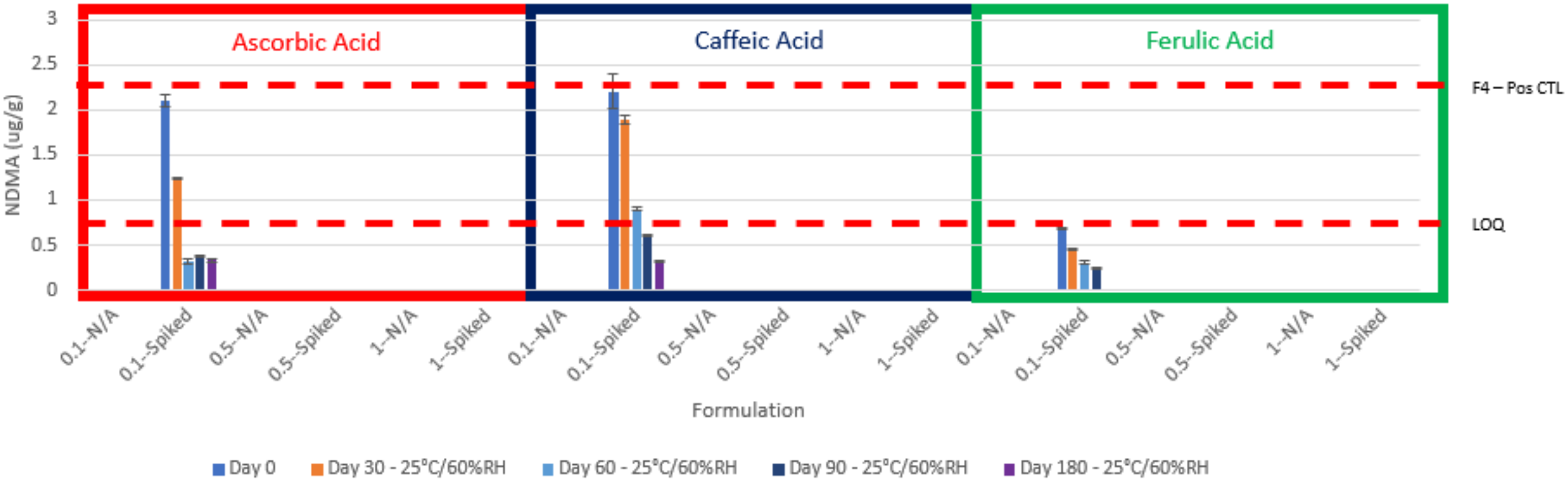
Tableting:
Granules mixed with EG mixture,
And ready for compression.

N-Nitroso-Drug A (NDSRI) in Stability Samples – With Antioxidant OR pH Modifier; 25°C/60% RH

NDSRI Amounts formed



Stability: NDMA in Drug B 6 months 25^{0}C/60%RH



Preliminary Observations (1)

- **Antioxidants:**
  - For the first drug substance the highest inhibition of NDSRI formation among the antioxidants was observed as ascorbic acid > caffeic acid > ferulic acid.
  - For the second drug substance tested the rank order potency was reversed: ferulic > caffeic = ascorbic.
  - Antioxidants need to be fit-for-purpose and their effectiveness depends on the drug substance, manufacturing and formulation
  - **An increase in antioxidant concentration improved the NDSRI mitigation.**

Preliminary Observations (2)

- **pH manipulation**
  - Acidic conditions facilitated nitrosating reactions.
  - Maintaining neutral pH of the drug product served as a protective strategy against nitrosamine formation. An alkali modifier (sodium bicarbonate) had the most effective inhibition of NDSRI formation for the two drug substances tested.

Preliminary Observations (3)

- **Heat and Moisture Control**
  - The data suggested that formation of nitrosamines was greater under conditions of elevated heat and moisture.
  - Nitrosamines or the main progenitors were introduced or formed during the drying step of wet granulation.
  - This might be due to the presence of a secondary amine and NOx (Oxides of nitrogen) in the wet mass which was then converted into a nitrosamine impurity during drying.

General Observations

- Antioxidants and pH mitigate formation of nitrosamines in Drug A and Drug B formulations.
- The effectiveness of the mitigation strategy was product dependent.

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