

Vitamins C and E are safe and effective nitrite scavengers and nitrosation blockers.

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Ascorbic acid as an effective nitrite scavenger and nitrosamine mitigation agent

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Introduction

Regulatory authorities are putting the Pharma industry under pressure to assess and minimize risk of nitrosamine formation in launched and in-development drug products. Mitigation strategies, including the possibility of reformulation, are imperative. Ascorbic acid and alpha-tocopherol are known antioxidants that can scavenge nitrites, block nitrosation reactions, and ultimately prevent or significantly reduce the formation of nitrosamines. Well established science and safety of these molecules make them one of the suggested routes of nitrosamine mitigation by the FDA.

Methods

- Placebo mixes of MCC, starch, croscarmellose sodium, and ascorbic acid (at 0.25%, 0.5%, and 1%) were prepared and tableted via direct compression or wet granulation, and stored at 40°C/75% RH for 7 days. The amount of nitrite was measured at T0 and T7 days.
- A model formulation with an API was prepared with and without ascorbic acid at 1% via direct compression. The formulations were spiked with KNO₂ to accelerate nitrosamine formation. Tablets were stored in open containers at 50°C/75% RH for 2 weeks and N-nitroso impurity content was measured over time.

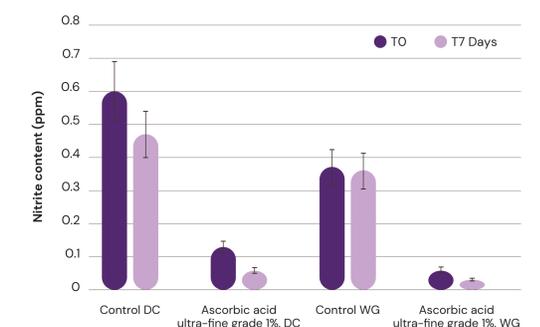
Results

- At 1%, ascorbic acid reduced the nitrite levels by as much as 87% after 7 days compared to the control in the placebo model. The scavenging effect was seen as soon as a few hours after incorporation into the powder blend.
- Ascorbic acid significantly reduced nitrosamine formation in the model formulation, with a decrease of about 75% in the nitrosamine concentration when compared to the control.

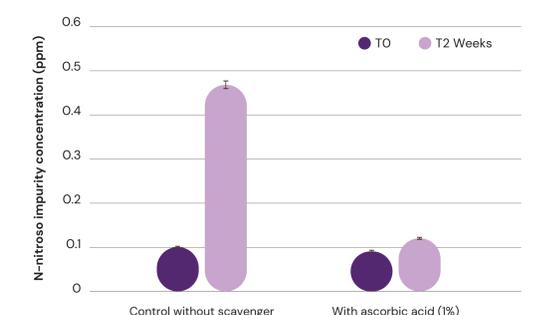
Conclusions and recommendations

- Ascorbic acid has proven efficacy in scavenging nitrites and preventing nitrosamine formation in a model formulation, in concentrations as low as 0.25% (data not shown but available upon request).
- Ascorbic acid is a safe and easy-to-use solution in direct compression or wet granulation processes. Talk to us about process and formulation tips to make your product successful.

Placebo tablets with and without ascorbic acid as nitrite scavenger
Stress test at 40°C/75% RH for 7 days



Effect of Ascorbic acid on nitrosamine concentration in a model formulation
Stress test at 50°C/75% RH, with nitrite spike (KNO₂)



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