Ascorbic acid as effective nitrite scavenger and nitrosamine mitigation agent in drug products

Anne-Cécile V. Bayne, Marta Pagliari, Manuela Baur, Andre Duesterloh, Fernanda Onofre, Zdravka Misic

Abstract

After N-nitrosamine contaminants were detected in pharmaceutical products in 2018, regulatory authorities set a framework for the risk assessment, testing and mitigation of N-nitrosamines in drug products. Specific nitrosamine limits have been put in place and vary depending on the risk of a given nitrosamine. The conditions for nitrosamine formation can be met at many steps during the production of drug products. Trace amounts of impurities in the excipients (e.g. nitrite) can have a negative impact on the formation of nitrosamines. In contrast, compounds with antioxidants or nitrite scavenging properties might be a viable way to mitigate the risk. Ascorbic acid exhibits nitrite scavenging abilities and was tested in this study for its nitrosamine mitigation properties in the context of solid drug dosage manufacturing. Results indicated that ascorbic acid is an effective scavenger of nitrite in solid drug dosages. It reduced API-related nitrosamine formation in two different model drugs with minimal impact on color after 1 month under stress conditions. Overall, these data support the evaluation of ascorbic acid as nitrosamine mitigation agent in solid dosage forms.

Introduction

N-nitrosamines are organic compounds that can be found in the environment, diet, and are also produced endogenously. Several N-nitrosamines are carcinogenic and can be present as contaminants in drug products (1).

After N-nitrosamine contaminants were detected in pharmaceutical products in 2018, regulatory authorities set a framework for the risk assessment, testing and mitigation of N-nitrosamines in drug products. One strategy to inhibit the formation of N-nitrosamines during the manufacture and storage of drug products involves the incorporation of nitrite scavengers in the formulation. Ascorbic acid is a known antioxidant that can scavenge nitrites, block nitrosation reactions, and ultimately prevent or significantly reduce the formation of nitrosamines. It has been tested in drug formulations, among other antioxidants, and showed its superior nitrite scavenging properties (2, 3). Moreover, the use of ascorbic acid to inhibit N-nitrosamine formation in pharmaceutical products has been specifically mentioned by the FDA (4).

In the first part of this study, we explored the effect of different concentrations of ascorbic acid and tablet manufacturing routes (direct compression vs wet granulation) on the nitrite content of placebo tablets. In the second part of the study, we studied the effect of ascorbic acid on the formation of specific API-related N-nitroso impurity in 3 different model drugs.

Materials and methods

Placebo mixtures of microcrystalline cellulose (MCC), starch, croscarmellose sodium, and ascorbic acid ultra fine powder (at 0.25%, 0.5% , and 1% w/w) were prepared and tableted *via* direct compression or wet granulation and stored at 40°C/75%RH for 7 days. The quantity of nitrite was measured at T0 and T7 days.

The first model drug formulation with an API containing a secondary amine was prepared with and without ascorbic acid at 1% w/w *via* direct compression. The tablets were produced with MCC spiked with KNO_2 solution and the final tablets contained approximately 166 ppm free nitrites. 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.

The second model drug (Drug 2) contains a tertiary amine, which is likely to develop the corresponding secondary amine impurity that can produce nitrosamines. Third model drug (Drug 3) contains two amines, and both can contribute to nitrosamine formation. Drug 2 and Drug 3 were formulated by direct compression with and without ascorbic acid at 0.5% w/w. Tablets were stored in PVC/PVDC blisters at 40°C/75% RH for 3 months and N-nitroso impurity content was measured over time.

Results

Ascorbic acid scavenges nitrite in solid dosages – To examine the effect of ascorbic acid in solid dosage forms, placebo tablets were first generated with varying levels of ascorbic acid under 2 manufacturing routes. Figure 1 shows the impact of ascorbic acid on the nitrite level in the tablets produced via direct compression or wet granulation for placebo mixtures. The scavenging effect was seen already at T0. The nitrite levels were significantly reduced with low amount of ascorbic acid (0.25%) and were further reduced with higher amounts of this scavenger. This confirms the strong nitrite scavenging ability of ascorbic acid.

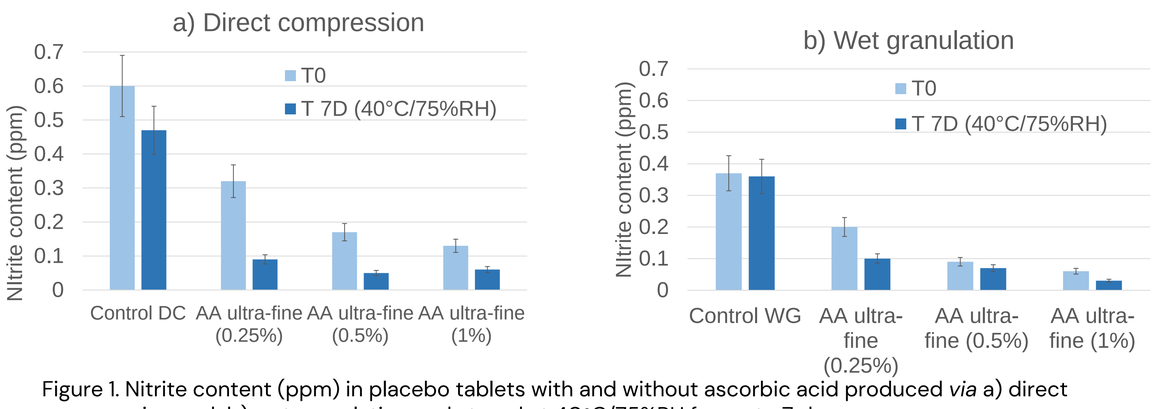

Figure 1. Nitrite content (ppm) in placebo tablets with and without ascorbic acid produced *via* a) direct compression and b) wet granulation and stored at 40°C/75%RH for up to 7 days.

Ascorbic acid reduces nitrosamine accumulation in solid drug dosages. – To evaluate whether the reduction in nitrite observed in the presence of ascorbic acid in solid dosages resulted in a decrease in nitrosamine content, a first solid dosage of a model drug was generated with and without 1% w/w ascorbic acid. Results, presented in figure 2, showed that ascorbic acid significantly reduced the formation of the N-nitroso impurity.

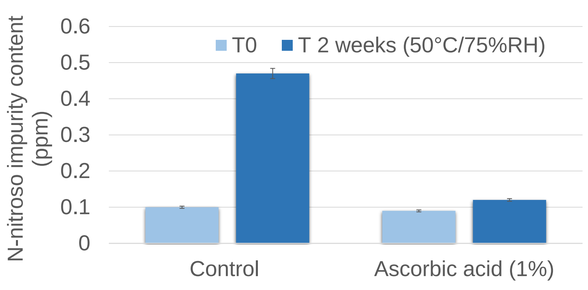

Figure 2. Effect of ascorbic acid on nitrosamine impurity reduction in a model drug formulation.

To further evaluate the effect of ascorbic acid on accumulation of API-related N-nitroso impurities with lower amount of ascorbic acid and over time, 2 more drug models were manufactured via fluid bed granulation followed by compaction with and without 0.5% w/w ascorbic acid. The second process was executed as follows:

Weighing of excipients
Dissolution of 0.5% of ascorbic acid ultra fine grade in water (1% solution)
→ Fluid-bed granulation → Admix of API (trituration) → Admix of other relevant excipients → Tableting

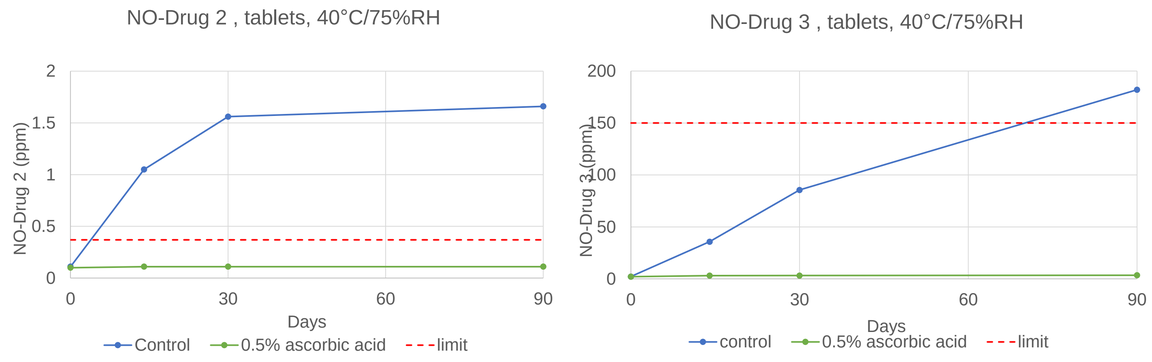

Figure 3. Effect of ascorbic acid on nitrosamine impurity accumulation over time in 2 different model drugs. The limit line indicates the FDA maximum nitrosamine content for the drugs as of December 2023.

Results, presented in Figure 3, showed that ascorbic acid was able to prevent accumulation of API-related nitrosamines in tablets containing Drug 2 and Drug 3, after storage at 40°C/75%RH.

Ascorbic acid can lead to discoloration of products when oxidized. To check the impact of ascorbic acid on color, the tablets generated for model drugs 2 and 3 were evaluated visually over time. Results, presented in Figure 4, indicated that the color was minimally impacted at 1 month under stress conditions tested.

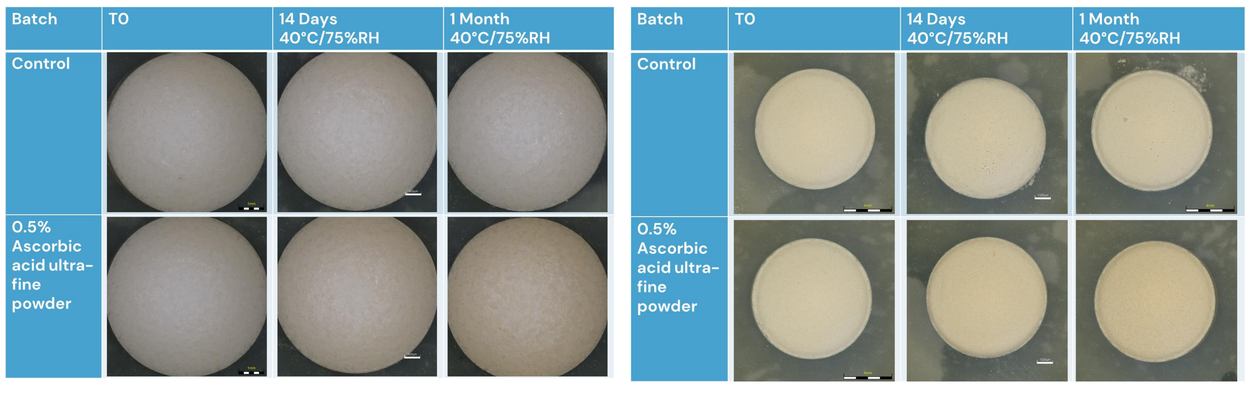

Figure 4. Effect of ascorbic acid on the visual aspect of the tablets over time. At time zero, after 14 days at 40°C/75% RH and after 1 month at 40°C/75% RH .

Conclusion

In this study ascorbic acid was highly effective in scavenging nitrites in placebo tablets, as well as preventing nitrosamine formation in three model drugs, at concentrations of as low as 0.5% w/w. While ascorbic acid might not be compatible with all drug formulas (for example, actives incompatibilities, pH sensitivity), the inclusion of a nitrite scavenger like ascorbic acid can be a simple and effective mitigation strategy to reduce the overall risk of N-nitrosamine formation and keep concentrations of such impurities within acceptable limits.

References

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