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Short communication

Designing safer orally disintegrating tablets: Impact of antioxidants and polymer choice on nitrosamine formation

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Introduction

Orally disintegrating tablets (ODT) have gained increasing attention as patient friendly dosage forms, particularly for populations with swallowing difficulties, pediatric, geriatric or patients taking antidepressants. Despite the advantage of improving compliance and in some cases even exploiting rapid onset of action, the safety profile of ODT formulations as well as of other oral formulations, has come under scrutiny due to the potential formation of nitrosamine impurities (NI), a potent genotoxic impurities associated with significant health risks, among main cancer (Li et al., 2021).

In this context, formulation design, including composition, processing and packaging are crucial in mitigation of these risks. However, some active ingredients (APIs) are more prone to NI formation even when the composition and processing are designed to reduce their formation. In such cases, recent studies have proven that attenuation is achieved by the addition of excipients capable of nitrite scavenging (Bayne et al., 2023).

Besides being of crucial importance for the taste masking in ODT, polymers may influence the microenvironment, moisture content, and overall chemical stability of the formulation, while antioxidants as potent nitrite scavengers can inhibit oxidative pathways that promote formation of NI. Understanding how these formulation variables interact is essential for developing safer ODT products that meet both efficacy and regulatory requirements, yet are still being palatable.

The current work explores the impact of different antioxidants and polymer choice on specific N-nitroso API impurity (NNAi) formation in an oral antidepressant ODT formulation, aiming to provide insights into designing safer ODT formulations with high acceptability rate by the patients.

Materials and methods

Formulation, production process, testing conditions

Two different ODT formulations of an oral antidepressant drug were developed, one of which includes carbomer (Lubrizol, USA) as a taste masking polymer and the other Eudragit EPO (Evonik, Germany). Among other commonly used excipients, mannitol played the role of a main carrier (as spray dried grade purchased by Roquette, France, and as powder grade purchased by Merck, Germany) and crospovidone (Ashland, USA), sodium starch glycolate (DFE Pharma GmbH & Co. KG, Germany) and crosscarmellose sodium (DuPont, USA) assured suitable disintegrating properties.

The production process of the carbomer including ODT employed a standard wet granulation process followed by fluidized bed drying, mixing

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with extra-granular components and compression into ODT. The Eudragit EPO containing ODT comprised core granules formation by dry granulation using roller compaction, followed by subsequent granules coating with the taste masking polymer dispersion in fluidized bed, further mixing with extra-granular excipients and compression.

Two tablet strengths of the extremes (5 mg and 20 mg) from both formulations were tested on a forced degradation study after 15 days exposure at both 60°C and 80°C in an open petri dish, containing different quantities of butylatedhydroxyanisole (BHA), purchased from Paneac Quimica SLU, Spain, butulatedhydroxytoluene (BHT), purchased from Merck, Germany and DL-α-Tocopherol (DL-α-Toc), purchased from DSM, Switzerland.

Testing methods

A LC-MS screening for determination of the content of NNAi was conducted by Thermo Scientific Vanquish 2D UHPLC system equipped with Orbitrap Exploris 120 high resolution mass spectrometer using column Symmetry C8 3.5 µm (100 x 4.6 mm). NNAi was determined using atmospheric pressure chemical ionization with single ion monitoring in positive mode.

Results and discussion

The applied method demonstrated satisfactory performance, suitable for the selective and sensitive analysis of NNAi.

All antioxidants proved to reduce the NNAi formation compared to ODT without included antioxidant. Increased temperature and exposure time elevated NNAi levels, although higher antioxidant concentrations partially mitigated this effect. Compared to BHT, BHA demonstrated superior performance, achieving approximately 40% lower NNAi levels, despite BHT's more common use in oral solid dosage forms. This is advantageous because BHA has a higher acceptable daily intake (1 mg/kg body weight) than BHT (0.25 mg/kg body weight), as reported by the EFSA Panel (2011a, 2012b). Increasing BHA concentration significantly decreased NNAi formation, although approaching a near plateau effect was observed beyond 0.25% w/w.

Tablet strength of 5 mg showed approximately twofold higher NNAi levels compared to the highest strength of 20 mg, likely due to increased surface area and reactivity. Notably, although BHA exhibited strong scavenging capacity, it was significantly less effective in NNAi reduction than DL-α-Toc in Eudragit EPO-based ODT (140.5 ppm *vs.* 25.5 ppm), possibly due to different lipophilicity and distribution within the polymer matrix.

Among the tested formulations, carbomer based ODT containing 0.5% w/w BHA had the optimal stability/palatability balance. In contrast, DL-α-Toc increased API-related impurities in the carbomer based ODT, while no such effect was observed in Eudragit EPO ODT at 1% w/w. Despite the lipophilic nature of the antioxidants, carbomer-BHA and Eudragit EPO-DL-α-Toc ODT were both surprisingly bioequivalent with the reference product *in vivo*, and disintegrated for less than 3 minutes.

Conclusion

Antioxidants reduced NNAi formation in ODT, with BHA outperforming BHT but approaching a near plateau above 0.25% w/w. Their effectiveness was formulation dependent. Carbomer-BHA ODT combination provided optimal stability and palatability, while DL-α-Toc performed better in Eudragit EPO ODT. Overall, excipient selection proved as critical for controlling NNAi formation without compromising ODT performance.

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