

CHAPTER 9

Summary and general conclusions

In recent years, the susceptibility of newly discovered drug compounds towards oxidative degradation has been increasing, driven by their structure-activity relationship targeted during drug discovery. Despite the availability and knowledge on the currently applied mitigation strategies to prevent drug oxidation, insufficient protection has caused the need for antioxidant implementation in solid formulations. The main advantages of antioxidative compounds can be attributed to their ability to inhibit the oxidative process even after initiation. However, many hurdles should be overcome before these substances can be successfully included in pharmaceutical solid dosage forms. A thorough understanding of the processability and efficacy of antioxidants towards drug oxidation inhibition is crucial. This doctoral thesis investigated the challenges and feasibility of antioxidant implementation in pharmaceutical oral solid dosage forms. Ultimately, the suitability of the antioxidative compounds to inhibit drug oxidation was discussed.

In PART I, an overview of the basic principles and knowledge on the oxidative degradation of pharmaceuticals and antioxidants in the pharmaceutical industry is provided. **Chapter 1** introduced drug oxidation through mechanistic elucidation, pharmaceutically relevant examples and an extrapolation to solid dosage forms. **Chapter 2** covered various antioxidants currently used in the pharmaceutical industry with mentions of their classification, mechanism of action and safety.

PART II focusses on the processability of antioxidants in tablet formulations. In **Chapter 3**, several approaches to homogeneously implement antioxidants in tablets were investigated by studying the impact of particle size/morphology on the blending behavior using different blending techniques. Moreover, the addition of the antioxidant to the binder liquid for fluid-bed granulation was explored through a solubility enhancement screening, granule characterization and content uniformity analysis. Overall, homogeneous implementation of antioxidants was difficult to attain via conventional blending approaches, with a considerably small particle size and higher target concentration required to achieve uniform distribution. While the application of multi-step blending process improved the homogeneity of several antioxidants, overmixing of other compounds was observed. In contrast, the introduction of a fluid-bed granulation step provided favorable content uniformity in all cases. In general, this chapter highlighted the importance of an appropriate selection of antioxidant grade/supplier or the further manipulation of the substance (e.g. granulation) to obtain the desired properties to facilitate homogeneous distribution in tablets.

Chapter 4 described the development of a novel high-shear loading process of α -tocopherol onto mesoporous silica and its subsequent influence on tablet properties and content uniformity. A residual solvent screening identified DCM as a suitable organic solvent, and preliminary loading experiments were scaled up to a high-shear loading process, revealing an apparent dead zone underneath the impeller. A carrier screening and comprehensive characterization of the loaded materials identified Aeroperl[®] 300 Pharma as the most suitable carrier. Through a design-of-experiments approach, the

impact of various process parameters was examined, yielding the optimal process parameters for loading α -tocopherol onto mesoporous silica with maximal loading efficiency and minimal dead zone. Ultimately, the loaded material provided homogeneous implementation of α -tocopherol in tablets despite negative influence on tablet properties, albeit in silica content irrelevant to drug development.

In **Chapter 5**, the physical instability of BHT in solid dosage forms during storage and coating was addressed by investigating the effect of particle size and loading onto silica on the sublimation behavior in tablets. Sublimation of pure BHT was found to be independent of its particle size, with all tablets displaying superficial pore formation after storage at room temperature and above, while tablets containing larger BHT particles retained higher residual BHT content after storage. X-ray μ CT scans revealed larger peripheral pores at higher BHT particle sizes, implying a lower sublimation rate in the tablet core. Stability studies indicated increased BHT sublimation with higher temperatures and prolonged exposure time for all size fractions. The influence of BHT particle size was more pronounced at elevated temperatures, but the effect receded with extended exposure. Similar trends were observed in film-coated tablets as the short exposure time to a higher temperature caused a gradient in pore size in tablets containing smaller particle sizes, with peripheral pores being larger in uncoated tablets. Superficial pores disappeared when a film coating was deposited onto the tablets, and film-coated tablets exhibited reduced BHT sublimation compared to uncoated tablets. Although the coating did not prevent sublimation, it effectively slowed the process.

PART III discusses the applicability of different antioxidants on the inhibition or prevention of the various oxidative pathways through model compound screening and efficacy studies in tablets. **Chapter 6** aimed to identify model compounds for the various oxidative degradation pathways in solid dosage forms. Liquid stress testing verified the DFT calculations for selected compounds, highlighting the suitability of various compounds as model compound in liquid formulations. Upon exposure to H_2O_2 vapors, the solid drug powders of amlodipine besilate, cetirizine HCl and omeprazole

degraded considerably, albeit reduced when included in tablets. Although paracetamol decomposed drastically in tablet formulations with transition metals and acidifiers, alternative degradation pathways confounded stress testing in tablets. While no definitive decomposition pathway could be established for tablets containing cetirizine HCl, the presence of the oxidative degradants of amlodipine besilate and omeprazole was confirmed, demonstrating their suitability as model compounds in solid dosage forms.

Chapter 7 combined the knowledge obtained from preceding chapters to evaluate the efficacy of antioxidants on their protective capability towards nucleophilic/electrophilic oxidation of omeprazole in tablets. Although accelerated studies confirmed the applicability of antioxidants for stress testing, the long-term stability of ascorbyl palmitate, BHA and propyl gallate was considered insufficient. Primary phenolic antioxidants exhibited pro-oxidative tendencies in tablets related to an alkaline microenvironmental pH, while carrier-loaded antioxidants (i.e. hydroxytyrosol and α -tocopherol) effectively reduced oxidation. Despite secondary antioxidants posing an increased risk of acidic hydrolysis, their potential protective effect in tablets was evident. In general, the inhibition of nucleophilic/electrophilic oxidation of omeprazole was achieved through antioxidant implementation, albeit with some remaining issues with regards to long-term stability and pro-oxidative effects of some antioxidants and the induction of alternative degradation pathways. Further optimization of antioxidant concentrations is necessary to maximize oxidative stability.

Finally, **Chapter 8** discusses this doctoral thesis's broader international context and relevance, combined with the future perspective of this work.