Stabilization of antioxidative drugs against premature oxidation

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Summary

The secondarily generated reactive oxygen radical species (ROS) play a crucial role in the radiotherapy due to their cell toxicity. Topically applied antioxidants to skin or open tissues are targeted to protect healthy tissue against irradiation associated damages. While the radioprotective effects of the antioxidants to the keratinocyte cell line HaCaT and the breast tumor cell line MCF-7 can be demonstrated by radiation experiments, their stability against oxygen in the formulation phase is insufficient. Stabilization against oxidation by cyclodextrin (CD) inclusion complexes and liposomes seems be a promising option.

Introduction

The application of antioxidants against ROS and oxidative stress is widely accepted. The premature oxidation of antioxidants causes serious problems in the life-time of drug formulations. CD inclusion complexes are recommended to stabilize against oxidation . Disadvantage of these inclusion complexes is the minor solubility in water, and in usual solvents as well. Loading liposomes with these drugs seems to be a promising alternative. With focus on the most sensitive hydroxytyrosol, several cyclodextrin complexes were investigated and characterized, as well as the protecting effect of liposomes.

Methods

CD complexes and antioxidants loaded liposomes were added to cell cultures, which were irradiated with 2Gy X-ray using the electron beam accelerator (VARIAN trueBeam T02) with a dose rate of 4.8Gy/min. Complexes of hydroxytyrosol, tocopherol, tocotrienol and selenoxanthene were prepared. Hydroxytyrosol (HT) undergoes rapidly a redox equilibrium forming in aqueous solutions a quinone like structure demonstrated by UV/vis-spectrometry. Stabilization against that redox reaction was possible by complexation of HT with CD. In contrast to FT-IR, the ^{1}NMR-spectroscopy indicates host-guest interactions in the inclusion complex. Light microscopy and SEM complete the investigations. Liposomes prepared according the film method were also loaded with HT in order to check the oxidation protecting effect of the lipid double layer.

Results

The complexation of antioxidants with cyclodextrins stabilizes against premature oxidation follows obviously the series β-CD-HP > β-CD-M > β-CD which corresponds with the solubility. The lipophilic and amphiphilic antioxidants are located in the lipophilic double layer of the liposomes which achieves also stabilization against premature oxidation.

Acknowledgement

The research has been partly supported by the Tomsk State University Competitiveness Improvement Program.