Abstract

Cancer diseases belong among most serious problems of modern medicine, after cardiovascular problems. In connection with finding the solution of this problem, in recent years there was a development of so-called targeted therapy, which uses nanoparticles in the treatment, which are supposed to make the treatment more effective. One of nanoparticles used in the targeted therapy, is apoferritin, which is naturally occurring transport and storage protein in the human body. Apoferritin has a cavity in its structure, into which a cytostatic agent can be incorporated. In addition, its structure is strongly dependent on the pH value, which makes the incorporation and the subsequent release of the drug in the desired location easily impressionable. These properties make apoferritin a suitable potential nanotransporter.

The drug studied in this thesis is the cytostatic drug called cabozantinib. It's tyrosinkinase inhibitor, used in the treatment of advanced metastatic medullary thyroid carcinoma, hepatocellular carcinoma and refractory renal carcinoma. In this thesis, the preparation of cabozantinib complex incorporated in apoferritin was optimized, and subsequently the release of the drug from apoferritin and the metabolism of this complex were monitored using liver microsomes and cytochromes.

The results show that the most suitable of the tested methods for preparing the complex of cabozantinib with apoferritin is the method of gradual addition of the drug. This method was used in the case of further experiments. The results obtained from observing the release of the drug from the complex show that cabozantinib is better released in a more acidic environment than in an environment with a physiological pH. This feature makes advantage when used in antitumor therapy.

During monitoring of the metabolism, there were found three main metabolites - desmethyl cabozantinib (M1), hydroxycabozantinib (M2) and cabozantinib-N-oxide (M3). In general, M3 was the most represented metabolite. Using liver microsomes, the free drug was better metabolized than the drug complexed with apoferritin. When monitoring metabolism using cytochromes, the efficiency of CYP450 3A4 alone was compared against the combination of CYP450 3A4 + cyt b5. When both cytochromes were used, the drug was metabolized much more effective than when CYP450 3A4 was used alone.

[In Czech]

Keywords: anticancer treatment, targeted therapy, nanoparticles, cabozantinib, apoferritin, microsomes cytochrome p450