ABSTRACT

Wilson's disease is a hereditary disorder of copper metabolism, which causes copper accumulation in organism, especially in the liver, kidneys and brain. Current treatment is based on using low-molecular weight copper chelators and high doses of zinc salts. Unfortunately, they can induce some severe side effects due to systemic action.

The aim of this thesis is to improve the treatment of Wilson's disease by using of polymeric drug delivery systems. The size of polymer particles in tens of microns should provide non-resorbability of the drug after oral administration. Synthetic microparticles of poly(glycidyl methacrylate-co-ethylene dimethacrylate), natural microcrystalline cellulose and cross-linked chitosan were used as polymer matrices. N,N-di(2-pyridylmethyl)amine, triethylenetetraamine and 8-hydroxyquinoline were selected as specific copper chelators, which can complex copper cations with high efficiency. The principle of the proposed treatment is that the polymeric carrier-bound chelator complex copper directly from the food in digestive tract of the organism. Because of non-resorbability, the entire complex should be eliminated from the body together with stools. This virtually eliminates systemic side effects.

The ability of adsorption of copper and the stability of polymer complex under conditions simulating stomach and intestine environment were tested first. Further, non-resorbability and biodistribution of polymers with bound chelators were investigated in vivo in laboratory animals after oral administration of radiolabelled polymers with isotopes ^{125}I and ^{64}Cu. The long-term experiment with synthetic polymer microparticles was also performed. The aim was to verify therapeutic effects and sufficient reduction of copper content in the body after oral administration.

We have shown that all types of polymeric carriers are almost entirely non-resorbable from the gastrointestinal tract after oral administration in laboratory animals. The studies under simulated conditions also confirmed highly efficient complexation of copper and sufficient stability of polymer complexes. The most important result was the finding that synthetic polymer microparticles were able to reduce copper content in laboratory animals significantly, which is a necessary requirement of therapy.

Key words: polymer microparticles, copper chelators, Wilson's disease, non-resorbability of polymer complexes, oral administration, therapeutic effect, laboratory animals, radioactive isotopes ^{125}I and ^{64}Cu.