

Abstract:

This diploma thesis brings new data about design, synthesis, physico-chemical characterisation and biological efficacy of the novel star-like HPMA-based conjugates intended for treatment of solid tumors.

Recently, many different water-soluble drug delivery systems based on *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymers have been described. Here, we report synthesis and physico-chemical characterisation of high molecular weight star-like HPMA-based polymer carriers with low polydispersity prepared by controlled grafting of HPMA copolymers onto PAMAM dendrimer core. With the aim to keep the polydispersity of drug delivery system as low as possible, reversible Addition-Fragmentation Chain Transfer (RAFT) polymerisation was used for HPMA-based polymer precursor preparation. The end groups of the polymer precursors was afterwards used for grafting using carbodimide condensation reaction or copper free click chemistry on polyamidoamine (PAMAM) dendrimers resulting in a formation of star-like high-molecular-weight (HMW) drug carriers.

Described synthetic procedure provided preparation of star-like HMW drug carriers with M_w between $1.10^5 - 3.10^5$ g/mol and narrow distribution of M_w . The model drug, doxorubicin (Dox), was attached to the hydrazide group containing polymer carriers by pH-sensitive hydrazone bond stable in conditions simulating blood circulation (buffer, pH 7.4) and releasing active drug in conditions modelling endosomes and lysosomes of tumor cells (pH 5 - 6). Disulfidic spacer between HPMA copolymer and PAMAM dendrimer core facilitate degradation of HMW structure in cytosomal compartment of tumor cells to polymer fragments eliminable by glomerular filtration from the body.

HMW drug carriers, linear polymer drug carriers (3.10^4 g/mol) and free Dox were tested *in vitro* and *in vivo* for cytostatic effect and anti-tumor efficacy. The novel HMW star-like drug carrier demonstrated the highest effectivity in treatment of EL4 T-cell lymphoma in mice. „In Czech“