Summary

The aim of this dissertation thesis was preparation of drug delivery systems for polyene antimycotics, especially amphtoricin B(AmB). Series of pH-sensitive conjugates of AmB with substituated poly(ethylene glycols) (PEG) have been synthesized and characterized for this purpose. The intermediate PEGs possess a 1,4-disubstituted benzene ring with aldehyde group at the end of the chain. The benzene ring is connected with PEG at its 4-position (with respect to the aldehyde group) by various functional groups (ether, amide, ester). Reaction of terminal aldehyde group of the substituted PEGs with AmB gave conjugates containinga pH-sensitive imine linkage, which can be presumed to exhibit antimycotic effect at sites with lowered pH value. The stability of prepared conjugates under the different physiological conditions was studied. Phosphate buffers (pH = 7,4 or 5,5) were used as model media. Stability of conjugates in human blood plasma and human blood serum was examinated. The imine linkage is split to give free AmB with half-lives of 2–45 min. The rate of acid catalysed hydrolysis depends upon substitution of the benzene ring; however, it does not depend on molecular weights ofthe PEGs used. The conjugates with ester linkage undergo enzymatic splitting in human blood plasma and/or blood serum at pH 7.4 (37 ^{o}C) with half-lives of 2–5 h depending on molecular weights of the PEGs used (M = 5000, 10,000, 20,000). At first, the splitting of ester linkage produces the relatively stable pro-drug, that is, 4-carboxybenzylideniminoamphotericin B, which is decomposed to AMB and 4-formylbenzoic acid in a goal-directed manner only at pH 7 (t1/2 = 2 min, pH 5.5, 37 ^{o}C). The LD_{50} values of prepared conjugates were determined in vivo (mouse).

Another goal of this thesis was preparation of poly(ethylene glycol)-*b*-poly(amino acid) block copolymers. Twelve molecules of AmB were attached to block copolymer poly(ethylene glycol)-*b*-poly(L-lysine) via pH-sensitive imine linkages. In vitro drug release studies demonstrated the conjugate (Mw = 26,700) to be relatively stable in human plasma and in phosphate buffer (pH 7.4, 37 ^{o}C). Controlled release of AMB was observed in acidic phosphate buffer (pH 5.5, 37 ^{o}C) with the half-life of 2 min. The LD_{50} values of prepared conjugate was determined.

Last part of the thesis was dedicated to study of physical-chemical properties of poly(ethylene glycol)-*b*-poly(amino acid) block copolymers. A set of chiral block copolymers based on PEG with chiral glutamic acid oligopeptide segments (PEG_{113}-*b*-(+)-(S)-Glu_{20}) were synthesized and employed as additives in the crystallization of rac118 threonine. CD spectroscopy demonstrates that structures of chiral polymers could be switched between a helical and a disordered random coil by pH. The effect of these polymers at different conformations on the crystallization kinetics, crystal morphology and chiral resolution of rac-threonine is reported. Our study demonstrates that only chiral polymers with α −helical conformations of the chiral segment are effective as additives for chiral resolution throughout crystallization. Overall, our results provide useful guidelines for the selection and design of chiral polymer additives that will act efficiently for chiral resolution by crystallization.