SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF THE BIODEGRADABLE POLYESTER/BISPHOSPHONATE CONJUGATES FOR COATING OF THE APATITE MATERIALS

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Introduction

Biomaterials are widely used in medicine and pharmacy nowadays [1]. The development of composites is one of many possibilities widespread use of biomaterials. Especially promising are biodegradable polymer/ hydroxyapatite composites that can be used for filling bone or tooth defects as well as drug carriers in a targeted therapy [2]. Disodium pamidronate (PAM) belongs to the second generation of bisphosphonates. PAM disturbs the function of osteoclasts, thereby inhibiting bone resorption of osteoclast. It is used to treat Paget's disease and osteoporosis [3-5]. Furthermore, the presence of an amino group in the PAM molecule allow to obtain the biodegradable polymeric carrier/PAM conjugate as a component of the implantation therapeutic system. Therefore, the aim of this study was the synthesis and physicochemical and biological characterization of the copolymeric carriers obtained through the ROP of a cyclic ester in the presence of 2-hydroxyethyl methacrylate (HEMA) and hyperbranched bis-MPA initiators; covalent conjugation of the PAM to the synthesized matrices as well as the coating of the porous hydroxyapatite doped with selenium ions by the synthesized conjugates.

Materials and Methods

The ROP of cyclic esters was carried out under an argon atmosphere. The cytotoxicity test was carried out according to the procedure described in our previous paper [6]. The copolymeric conjugates of PAM were synthesized by multi-step chemical synthesis. The copolymerization products and conjugates were characterized by means of ^{1}H- and ^{13}C-NMR (300 MHz, recorded in DMSO-d_6 spectroscopy). Number-average molecular weight (M_n) and polydispersity were determined by gel permeation chromatography (GPC).

Results and Discussion

The biodegradable copolymeric matrices were prepared though the ROP of ε-caprolactone (CL) and L,L-lactide (LLA) in the presence of linear and branched initiators. The cytotoxicity of the synthesized copolymers was evaluated with a bacterial luminescence test and protozoan assay, which showed that the obtained polymers were not cytotoxic. The M_n values of CL/LA copolymers determined by the GPC were in the range of 11800-21000 g/mol. The macromolecular conjugates of bisphosphonate were obtained from the synthesized copolymers and PAM. The drug was coupled to the copolymeric carrier by an amide bond (FIG. 1).

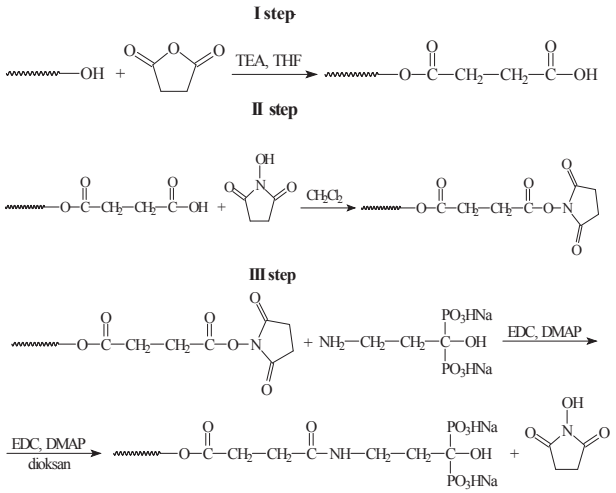

FIG. 1. The scheme of the synthesis of the biodegradable copolymer/PAM conjugates.

In the first step of this synthesis, the addition of succinic anhydride to the copolymer chain in the presence of TEA catalyst was carried out. The next step has led to the functionalization of the terminal carboxyl group of the copolymer chain with *N*-hydroxysuccinimide. The third and final step consisted covalent conjugation of the PAM to a functionalized copolymer carrier. The reaction was carried out in the presence of 1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide and 4-dimetyoaminopirydyna catalyst. The synthesized macromolecular conjugates were characterized by ^{1}H- and ^{13}C-NMR spectroscopy.

Conclusions

As a result of this research, the biodegradable copolymeric matrices were synthesized though the ROP of cyclic esters and spectrally characterized. The biodegradable copolymeric conjugates of PAM were obtained in the further step of this work. A new amide bond was formed between the hydroxyl end-groups of the synthesized copolymer matrices and an amine group of bishosphonate. The structure of the polymeric conjugates was characterized by various spectroscopy techniques.
The porous hydroxyapatite doped with selenium ions was coated with the synthesized conjugate in the last step of this work. The *in vitro* release profile of PAM is currently carried out in our laboratory.

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