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Amphiphilic star copolymers containing cyclodextrin core and their application as nanocarrier

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ABSTRACT

Amphiphilic copolymers containing β-cyclodextrin (β-CD) core were synthesized successfully. Synthesis was initiated from tosylated cyclodextrin ($(Tosyl)_7$-β-CD) which is containing two types of functional groups. Hydroxyl functional groups of $(Tosyl)_7$-β-CD were used as initiator for ring opening polymerization of lactide. This step led to star polymers containing tosylated cyclodextrin core and polylactide arms (PLA–$(Tosyl)_7$-β-CD). In the next step, tosyl groups of PLA–$(Tosyl)_7$-β-CD were used as initiator for ring opening polymerization of 2-ethyl-2-oxazoline and amphiphilic copolymers containing cyclodextrin core, PLA and poly(2-ethyl-2-oxazoline) arms (PLA–β-CD–POX) were obtained. Loading of Congo red as guest molecule by amphiphilic copolymers was investigated. The release of guest molecule from chloroform solution of copolymers to water phase was also investigated.

1. Introduction

Cyclodextrins (CDs) are a group of cyclic oligosaccharides composed of α(1,4)-linked glucopyranose units and containing nano-cavities [1]. Hydrophobic inside, hydrophilic outside and presence of two types of hydroxyl functional groups on the top and bottom of their nano-cavity make them excellent candidates for variety of applications from drug delivery to molecular machines [2]. Due to their biocompatibility, CDs has been found useful in the medicine and pharmaceutics and may one of their important applications be in the biological systems [3,4]. Conjugation the macromolecules include polymers onto CDs can lead to the new macromolecules possessing interesting properties [5–8]. For example conjugation the poly(ethyleneimine) and poly(ethylene glycol) onto cyclodextrins lead to new macromolecules useful for gene delivery [6]. Preparation of variety of useful amphiphilic materials from selective membranes to sensors and filters also is possible through conjugation of hydrophobic or hydrophilic polymers onto cyclodextrins [7,8].

On the other hand poly(lactide)s (PLAs) are known as biocompatible polymers which could be used in a wide range biological applications ranging from drug delivery to tissue engineering. PLA is used as bioresorbable surgical sutures and these polymers are also widely being investigated for other applications, e.g. in orthopedics (e.g., screws, pins, scaffolds), wound closure (e.g., staples, dressings, meshes) and drug delivery (e.g., microspheres, hollow fibers) so that incorporation of these biocompatible polymers in other biocompatible macromolecules such as cyclodextrin represents a new way to create well-defined structures and their applications in biomedical and biological systems [9,10]. Poly(2-oxazoline)s and their random [11], block [12], graft [13] and alternating [14] copolymers are synthesized in several past decades. Non-toxicity and biocompatibility of these polymers and copolymers has also been evaluated for a long time ago [15]. Water solubility and biocompatibility of POX derivatives; make them promising materials for application in the

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pharmaceutics and medicine fields [16]. Variety of biocompatible and amphiphilic derivatives of poly(oxazoline)s are synthesized in the past few years [17].

As a conclusion; due to hydrophilicity of outside of CDs and POX and hydrophobicity of inside of CDs and PLA and also biocompatibility of PLA, β-CD and POX, conjugation of these macromolecules can lead to new class of amphiphilic biocompatible macromolecules with interesting properties.

We have reported different amphiphilic and linear-dendritic macromolecules containing PLA and other linear or hyperbranched macromolecules during several years ago [18,19]. In this work tosylated β-CD was used as initiator for ring opening polymerization of lactide and 2-ethyl-2-oxazoline step by step and amphiphilic copolymers containing a cyclodextrin core, poly(lactide) and poly(oxazoline) arms were obtained. Loading of the guest molecules by amphiphilic copolymers was also investigated.

2. Experimental

2.1. Materials and methods

β-CD was purchased from Merck and it was tosylated according to reported procedures in the literatures [20]. Lactide was purchased from Aldrich and was recrystallized in dry toluene before using. Stannous-2-ethylhexanoate ($Sn(Oct)_2$) was purchased from Sigma. 2-Ethyl-2-oxazoline was purchased from Merck.

2.2. Characterization

^1H NMR spectra were recorded in $CDCl_3$ solution, on a Bruker DRX 400 (400 MHz) apparatus with the solvent proton signal for reference. ^{13}C NMR spectra were recorded on the same instrument using the solvent carbon signal as a reference. The molecular weight distributions were determined by size exclusion chromatography (SEC) using Agilent 1100 using PSS GRAL 100 Å column connected to a differential refractometer, RI and UV detector with chloroform as the mobile phase at 25 °C. Poly(styrene) standard samples were used for calibration. IR measurements were performed using a Nicolet 320 FT-IR. Differential scanning calorimeter diagrams were recorded using a Shimadzu DSC 60 apparatus. The zeta potential, static and dynamic light scattering experiments were made by a commercially available equipment Zetasizer Nano from Malvern using a 4 mW He–Ne laser (633 nm wavelength) with a fixed detector angle of 173°. TEM images were recorded using Philips CH 200, LaB_6–Cathode 160 kV.

2.3. Preparation of tosylated β-CD

Tosylated β-cyclodextrin was prepared according to reported procedures in the literatures [18]. Briefly, a freshly dried β-CD (2.27 g, 2 mmol) was dissolved in dry pyridine (40 ml) at room temperature. Then *p*-toluene sulfonyl chloride (2.9 g, 15.26 mmol) was added to the solution of β-CD and it was stirred for 24 and 18 h at 5 °C and room temperature, respectively. Mixture was poured into cold water (1 l). A white precipitated compound was collected by filtration and washed with water (100 ml) and diethyl ether (100 ml). The solid product was stirred in methanol for 30 min at 62–65 °C. Then the purified product was collected by filtration and it was dried using vacuum oven.

2.4. Preparation of PLA–$(Tosyl)_7$-β-CD star polymers

1 ml of toluene solution of $Sn(Oct)_2$ (1×10^{-3} M) was poured into a polymerization ampule equipped with magnetic stirrer, vacuum and argon inlets. Toluene was evaporated at 60 °C using vacuum. Then $(Tosyl)_7$-β-CD (0.05 g, 2×10^{-4} mmol) and lactide (0.4 g, 0.003 mmol) were added to polymerization ampule. Polymerization ampule contents were degassed and purged with argon three times, then they were left under vacuum at 80 °C for 1 h. Polymerization ampule was sealed under vacuum and mixture was stirred at 115 °C for 8 h. Polymerization ampule was cooled and contents were dissolved in chloroform. $(Tosyl)_7$-β-CD–PLA was precipitated in diethyl ether as a white solid compound and it was dried using vacuum oven at 60 °C for 1 h. The yield of reaction was 90%.

2.5. Preparation of POX–β-CD–PLA bock copolymers

$(Tosyl)_7$-β-CD–PLA star polymer (0.2 g) was added to a reaction flask containing 20 ml of dried acetonitril and equipped with an argon inlet and magnetic stirrer. 2-ethyl-2-oxazoline (3 ml, 0.03 mmol) was added to reaction flask and it was stirred at 80 °C for 72 h. Then *o*-methoxy aniline or diethanolamine was added to reaction at 50 °C and it was stirred for 4 h. Mixture was cooled and filtered and solvent was evaporated. Product was precipitated in diethylether and a viscose yellow compound was obtained. Product was dried using vacuum oven at 50 °C for 1 h. The yield of reaction was 70%.

2.6. Preparation of β-CD–POX star polymers

0.2 g (8×10^{-4} mmol) of $(Tosyl)_7$-β-CD was added to a reaction flask equipped with an argon inlet and magnetic stirrer and containing 20 ml of dried acetonitrile. 3 ml (0.03 mmol) of 2-ethyl-2-oxazoline was added to this reaction flask and it was stirred at 80 °C for 72 h. Then reaction was quenched using *o*-methoxy aniline. Mixture was cooled and filtered and solvent was evaporated. Product was precipitated in diethylether and a viscose yellow compound was obtained. Product was dried at 50 °C for 1 h using vacuum oven. The yield of reaction was 60%.

2.7. Preparation of POX–β-CD–PLA block polymers

Toluene solution (1 ml) of $Sn(Oct)_2$ (1×10^{-3} M) was poured into a polymerization ampule equipped with vacuum and argon inlets and magnetic stirrer. Toluene was evaporated at 60 °C using vacuum. Then POX–β-CD (0.15 g) and lactide (0.43 g, 0.003 mmol) were added to polymerization ampule. Polymerization ampule contents were degassed and poured in argon three times, then they were left under vacuum at 80 °C for 1 h. Polymerization ampule was sealed under vacuum and mixture was stirred