Applied Radiation and Isotopes 88 (2014) 89–93

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Drug delivery system design and development for boron neutron capture therapy on cancer treatment

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HIGHLIGHTS

- Herein, we have synthesized boron-modified diblock copolymer.
- Bpin-PLA-PEOz, which will be served as new boron containing vehicle for transporting the boron drug.
- This boron containing Bpin-PLA-PEOz micelle was low toxicity can be applied to drug delivery.

ARTICLE INFO

Article history:
Received 24 December 2012
Received in revised form
20 December 2013
Accepted 21 December 2013
Available online 27 December 2013

Keywords:
BNCT
PLA
PEOz
Drug delivery
Micelle

ABSTRACT

We have already synthesized a boron-containing polymeric micellar drug delivery system for boron neutron capture therapy (BNCT). The synthesized diblock copolymer, boron-terminated copolymers (Bpin-PLA-PEOz), consisted of biodegradable poly(D,L-lactide) (PLA) block and water-soluble polyelectrolyte poly(2-ethyl-2-oxazoline) (PEOz) block, and a cap of pinacol boronate ester (Bpin). In this study, we have demonstrated that synthesized Bpin-PLA-PEOz micelle has great potential to be boron drug delivery system with preliminary evaluation of biocompatibility and boron content.

1. Introduction

Cancer is currently the most dangerous threat on human being, and causes one of the biggest casualties among people of all races across the world. Countless resources and efforts have been devoted into this World War against cancer, in order to annihilate this tough enemy. In 1936, Locher proposed the concept of boron neutron capture therapy (BNCT) (Locher, 1936) just after Chadwick found the neutron in 1932 (Chadwick, 1932): a binary therapeutic strategy that deploys the selective delivery of non-radioactive boron-10 to cancer cells and irradiation with low energy (0.0025 eV) thermal neutrons. Combining this two elements in the same time will cause a nuclear capture and fission reactions, $^{10}B(n,\alpha)^{7}Li$, which produce α particles (^{4}He) and recoiling lithium-7 (^{7}Li) with high linear energy transfer (LET) properties, and precisely cause cytotoxic effect to boron containing cells with single cell range (5–9 μm). Therefore, the key to make BNCT more reliable cancer therapy is the effective delivery and accumulation of boron compounds to the cancer cells. The functionally important requirements of boron deliver agent for BNCT are as follows: (1) low toxicity; (2) high tumor tissue uptake with a tumor:normal tissue and tumor/blood boron concentration ratios of ~3; (3) sufficient boron deposit in tumor tissue with ~20 μg ^{10}B/g tumor; and (4) rapid clearance from blood circulation and normal tissues but persistence in tumor (Barth et al., 2012). From 1950s to present, lots of boron drugs for clinical trials have been developed, form boronic acid derivatives, to sodium mercaptoundecahydro-*closo*-dodecaborate (BSH) and boronophenylalanine (BPA); still, no clinical boron reagents could, specifically and efficiently, deliver boron to tumor sites. New forms of potential boron deliver systems are urgently needed to be invented for therapeutic investigation.

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http://dx.doi.org/10.1016/j.apradiso.2013.12.025

Recently, nanotechnology based drug delivery systems, such as liposomes (Ueno et al., 2010), and polymeric micelles (Sumitani et al., 2011) have emerged as attractive boron carriers for BNCT. Thanks to the passive tumor-targeting property of nanoparticles, the nano-scale particles can be accumulated in tumors through the enhanced permeability and retention (EPR) effect, which is caused by leaky neovascular walls and uneffective lymphatic drainage (Iyer et al., 2006). To our interest, micelles are one of the beneficial drug carriers for the delivery of hydrophobic drugs or highly cytotoxic chemotherapeutics; the modified functional polymer micelles have some impressive features such as targeting delivery, elevating drug efficiency, minimizing therapeutics cytotoxicity, and lower cost comparing to other drug carriers. Furthermore, the nanoscopic polymeric micelles can escape the surveillance of mononuclear phagocyte system (MPS) and reticular epithelial system (RES), leading to prolonged blood circulation time (Oku et al., 1992; Kwon and Okano, 1996). In this research, the poly(2-ethyl-2-oxazoline)-poly(D,L-lactide) (PEOz-PLA) diblock copolymer was served as core structure of micelle, which was shown as potential drug carrier with pH sensitivity, low cytotoxicity, low cytotoxicity, and a pKa value near neutral pH that can facilitate drug release in an acid environment (Hsiue et al., 2006; Wang et al., 2005; (Shieh et al., 2010). This diblock copolymer consists of two primary components, one is biodegradable polylactide (PLA), and the other is water-soluble polyelectrolyte polyoxazoline (PEOz); both are FDA approved biomaterials for application in clinical trial. In this study, we synthesized boron-terminated PLA-PEOz diblock copolymer (Bpin-PLA-PEOz) by ring-opening polymerization with a pinacol boronate ester-containing (Bpin) as initiator of reaction. Procedure of Bpin-PLA-PEOz was modified form synthesis of diblock copolymer, PLA-PEOz (Syu et al., 2012). After micellelation, the boron moiety of copolymers was embedded into the core of the micelle, and the hydrophilic PEOz section of copolymers was exposed to the water solution. The micellar structure could also encapsulate hydrophobic boron compound to increase boron content; in this study, we selected and synthesized poor water soluble phenylboric acid derivative (PBAD), which was already evaluated with lipiodol entrapping (Liao et al., 2010).

2. Materials and methods

2.1. Materials

Acetone and toluene were purchased from Merck GmbH; Dichloromethane, ethyl acetate, hexane, and tetrahydrofuran were purchased from Mallinckrodt Chemical Co. Acetonitrile, anhydrous ether, and methanol were bought from J.T. Baker Reagent Chemicals. Acetontrile, and dichloromethane were dried and distilled from CaH_2. Tetrahydrofuran was dried by distillation from sodium and benzophenone under an atmosphere of nitrogen. Benzyl alcohol, pinacol, D,L-lactide, triethylamine, mesyl chloride, potassium carbonate (K_2CO_3), and 2-ethyl-2-oxazoline were purchased from Alfar Aesar Company. 4-Hydroxylphenylboronic acid was bought from luminescence technology corporation, Taiwan. Tin (II) octanoate [$Sn(Oct)_2$] was acquired from Sigma-Aldrich. Potassium hydroxide and magnesium sulfate ($MgSO_4$) was gained from Showa, Japan. The ultrapure water employed in all experiments was obtained from a Millipore-Milli-Q system. Membrane for dialysis (MW 3000) was acquired from Spectrum Inc.

2.2. Synthesis and characterization of Bpin-PLA-PEOz diblock copolymer

For Bpin-PLA-PEOz diblock copolymer synthesis (Fig. 1), first, pinacol (2.33 g, 19.70 mmol, 1.2 equiv) and 4-hydroxylphenylboronic acid (2.50 g, 16.45 mmol, 1.0 equiv) were dissolved in THF (50 mL) and stirred until homogeneous. $MgSO_4$ (1.00 g) was added and the reaction was heated at 50 °C overnight. The reaction was allowed to cool to room temperature and the $MgSO_4$ was removed with a syringe filter. The filtrate was vaporized to dryness and the crude material was purified using a solvent gradient of 7–25% ethyl acetate in hexane with Teledyne Isco Combi*Flash*® Rf flash chromatography system. The desired product, pinacol boronate ester (3.9 g, 98%), was isolated as a transparent viscous liquid.

D-L Lactide (30.0 g, 208 mmol) was added to a two-necked round-bottle flask with a condenser, and was treated with three times nitrogen replacement. After toluene (94 mL) as solvent was injected with syringe, the ambient temperature was elevated to 140 ± 3 °C, and then pinacol boronate ester (2.47 g, 11.97 mmol)

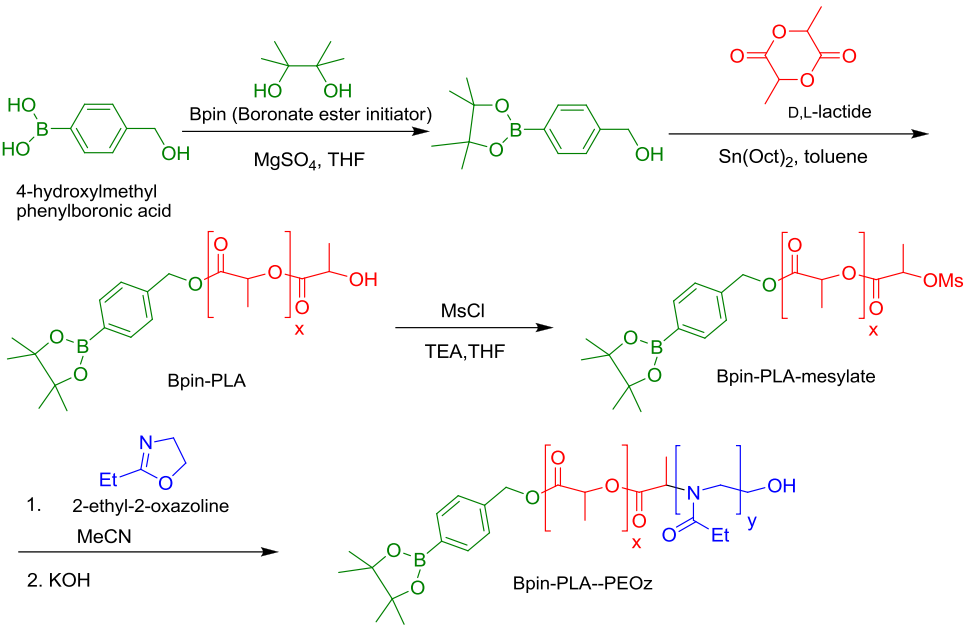

Fig. 1. Synthsis of Bpin-PLA-PEOz.