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# Zwitterionic hyperbranched polyester functionalized cardiovascular stent and its biocompatibility

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ABSTRACT

Zwitterionic hyperbranched polyester (HBPE) synthesized on bare metal stents (BMS) surface by surface-initiated atom transfer radical polymerization (SI-ATRP) method. The modified BMS obtained was tested for its blood compatibility. The blood compatibility studies were including, platelet adhesion tests, hemolysis assay, morphological changes in RBCs, coagulation tests, PRT assay, complement activation, platelet activation, and the cytotoxicity was also investigated. The modified BMS surface does not cause platelets adherent, red blood cell disruption, hemolysis and does not induce complement and platelets activation. All results indicated that the modified BMS was blood compatible and no cytotoxicity. It has the potential use for biomedical applications.



## 1. Introduction

In the past few years, metallic coronary stents dominated in percutaneous coronary interventions. In another word, implantation of stents was the most effective means to treat symptomatic coronary artery diseases [1–3]. However, the clinical performance of both bare metal stents (BMS) and drug eluting stents (DES) was less than ideal and causes significant adverse patient outcomes [4,5]. So different approaches had been used in developing new coronary stents to protect against thrombosis and minimize restenosis [6–11]. The sulfated [12], heparinized [13–15], PEGylated [16–18] and phosphatidylcholine [19,20] modified surfaces of metallic stents and their biocompatibility were investigated in detail by some research groups of the world. Passive coating with an artificial layer with biocompatible chemical composition would provide a biologically inert barrier among the stent surfaces, vessel wall and circulating blood, which is likely to minimize potential for thrombotic and inflammatory reactions and thus prevent late stent thrombosis [12].

Based on molecular engineering, our group postulated the "normal conformation" hypothesis in 1984 [21], and further suggested that materials with zwitterionic structures could maintain the normal conformation of biomacromolecules that contacted with materials directly and improve biocompatibility [22]. Now, more and more research groups realized that zwitterionic polymers may design to mimic phosphatidylcholine (lecithin) which was abundant in cell membranes. The phosphatidylcholine could meet the requirements for biomedical applications of long-term stability and effectiveness in resisting thrombosis [23–31]. They have received growing attention in the new generation of nonfouling materials.

In the past decade, hyperbranched polymers (HBPs) have attracted a great deal of attention [32,33]. A large number of work have been done in facile modification of the HBPs by bonding functional terminal groups, such as carboxy, hydroxy, vinyl and amino groups for providing unique properties [34–37]. They have been used extensively in the field of biomaterials. The most popular filed is used as drug delivery materials. Yan's group have synsthesized a lot of new type hyperbranched copolymers [38,39].

Inspired by this idea, we designed and synthesized zwitterionic hyperbranched polyester (HBPE) architecture. The synthesis pathway is shown in Scheme 1A. Although the applicability of zwitterions in biomedical fields has been extensively investigated, very few studies have been reported based on fabrication of zwitterionic structures on the surface of bare metal stents. In this case, 3-dimethyl (methacryloyloxyethyl)ammonium propane sulfonate (DMAPS) was grafted from bare metal stents using surface-initiated atom transfer radical polymerization (SI-ATRP) for blood compatibility improvement.

## 2. Experimental section

### 2.1. Materials

316L stainless steel cardiovascular stent was used as bare metal stent (BMS) purchased from Yinyi Co. (Dalian, China), glutaraldehyde, Trizma® phosphate monobasic (TPM), dimethylolpropionic acid (DMPA), 3,4-dihydroxyphenylalanine (DA), p-toluene sulfonic acid, CuBr (99%), 2,2′-bipyridine (bpy), 2-bromoisobutyryl bromide

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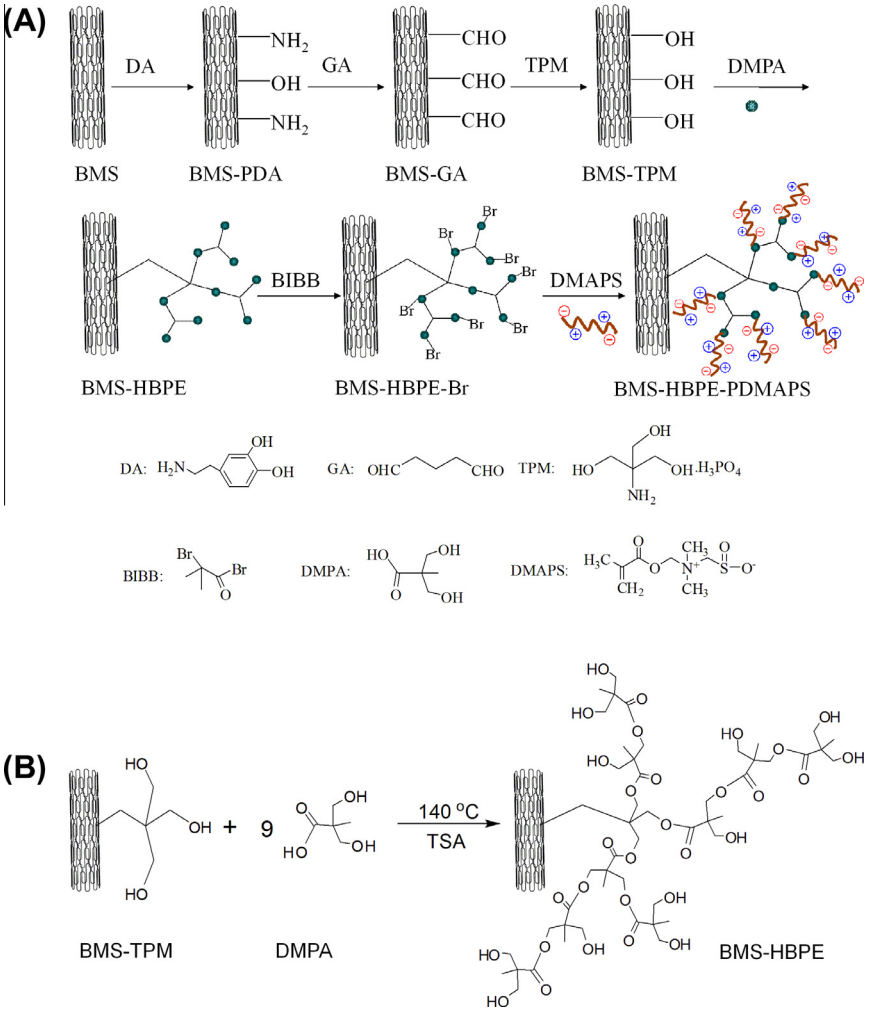


**Scheme 1.** Schematic diagram illustrating the synthetic route of BMS-HBPE-PDMAPS (A) and the detailed procedure of hyperbranched polymers growing from the surface of BMS-TPM (B).

(BIBB), triethylamine (TEA, 98%), 3-dimethyl(methacryloyloxyethyl)ammonium propane sulfonate (DMAPS), trihydroxymethyl aminomethane (Tris, 97%) from Sigma–Aldrich Chemical Co. (St. Louis, MO) and was used without further purification. All other chemical reagents and solvents were used as received.

### 2.2. Synthesis of BMS-HBPE

Briefly, the BMS substrates were immersed in a 2 mg/ml Tris–HCl (pH = 9, 0.05 M) solution of dopamine for 48 h in the dark. At the end of the reaction, the substrates were removed and rinsed with copious amount of deionized water, ethyl alcohol, followed by drying under reduced pressure. The dopamine-immobilized surface was referred to as the BMS-PDA surface. BMS-PDA was immersed in a large amount of 6% GA aqueous solution under stirring for 12 h to obtain the BMS-GA. The BMS-TPM was prepared by immersed in 2.3 mg/mL of TPM aqueous solution under stirring for 24 h. The BMS-HBPE was prepared by placing BMS-TPM, p-toluene sulfonic acid and into 50 mL toluene, with stirring at 150 °C for 6 h (the Molar ratio of DMPA and Trizma is 9:1).

### 2.3. Surface-initiated ATRP (SI-ATRP) of DMAPS using BMS-HBPE-Br as initiator

The BMS-HBPE substrates were immersed in 20 mL of anhydrous dichloromethane solution, containing 1.0 mL (7.2 mmol) of TEA. After 30 min of degassing with argon, BIBB (0.89 mL, 7.2 mmol) was added dropwise via a syringe. The reaction was allowed to proceed under an argon atmosphere at room temperature with continuous stirring for 24 h. The resulting surface was rinsed with copious amounts of dichloromethane, acetone, ethanol, and finally deionized water, followed by drying under reduced pressure. For the preparation of PDMAPS brushes on the BMS-HBPE-Br surface, the reaction was carried out using CuBr (0.057 g), bpy (0.125 g), DMAPS (2.36 g) in 7.5 mL of methanol under an argon atmosphere at room temperature with continuous stirring for 12 h. Then, BMS-HBPE-PDMAPS was washed thoroughly with methanol and water to ensure the complete removal of the physically adsorbed reactants. The synthetic route for the BMS-HBPE-PDMAPS is described in Schemes 1A and B.

### 2.4. Surface characterization

Attenuated total reflection Fourier-transform infrared spectra (ATR-FTIR) were recorded on a Nicolet NEXUS670 infrared spectrometer. The XPS measurements were performed on a Thermo ESCALAB 250 with an Al Ka ($h\nu$ = 1486.6 eV). Static water contact angles were measured using the sessile drop method with a 3 μL water droplet and a telescopic goniometer (Rame-Hart, Inc., Mountain Lake, NJ). The surface morphology of stents was observed with a scanning electronic microscope (SEM, JEOL 6300, Japan).