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Featured Letter

# Polyurethane tethering natural antibacterial substances for catheter applications

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ABSTRACT

Antibacterial central venous catheters (CVC) have been in great demand in recent years. However, biomedical polyurethane (PU), the most used polymer for CVC extrusion, lacks antibacterial properties, surface coating after catheter extrusion or additives is generally required for fabricating antibacterial CVC. To develop antibacterial PU for CVC extrusion, a natural derived substance, benzoic acid, was thus grafted onto a PU with pendant alkynyl groups successfully through Cu(I)-catalyzed azide-alkyne cycloaddition click reaction in this research. The synthesized PU tethering benzoic acid (PUB) was fabricated into catheter which displays a suitable strength for CVC application. PUB tethering benzoic acid over 2 mmol/g has proved good antibacterial properties against *Escherichia coli* and *Staphylococcus aureus* based on a bacterial colony forming units test, and bone mesenchymal stem cells proliferation on PUB also demonstrate good cell compatibilities, suggesting PUB a promising polymer for CVC extrusion.



## 1. Introduction

A central venous catheter (CVC) is widely used in clinic to administer medication or fluids, obtain blood tests and measure venous pressure. Bloodstream infections associated with CVC are very common and serious problems with high morbidity and mortality, causing an increase in health care costs and hospital stay [1,2].

Polyurethane (PU) elastomer is the dominated and irreplaceable material used for CVC due to its elasticity, blood compatibility and biocompatibility [3]. Since PU has poor antibacterial properties, treatments have been performed to prevent bacterial adhesion and/or kill the bacterial adhered on their surface, including the incorporation of zwitterionic chains or bactericides silver in bulk, and the surface coating of biomimetic components and the surface patterning of a nano structure [4–7]. In general, those methods require additional steps following the extrusion and the final CVC products show potential toxicity from residual antibacterial reagents. Therefore, it's promising to develop novel PU without further antibacterial treatment for biomedical application.

Benzoic acid, a natural acid from plant, is a popular food preservative. This relatively nontoxic compound inhibits the growth of mold, yeast and bacteria, and can be excreted as hippuric acid from human body, showing its potential applications in medicines [8,9]. However, few works have been reported on the introduction of benzoic acid into biomaterials for antibacterial applications until now.

The aim of this work is to fabricate the blood compatible and antibacterial PU *via* incorporating benzoic acid into PU chains without sacrificing the mechanical and processing properties. The relevant properties were investigated to measure its potential applications for CVC.

## 2. Materials and methods

Polyurethane with propynyl pendent group (PUp, 0.58 mmol/g propynyl) was prepared by our laboratory according to the reference [10]. *N*, *N*-dimethylformamide anhydrous dimethylacetamide, copper sulfate pentahydrate, sodium ascorbate and 4-azidobenzoic acid were bought from Maclin Co. Ltd (Shanghai, China). Phosphate buffer saline (PBS), Dulbecco's Modified Eagle Medium (DMEM) and fetal bovine serum (FBS) were from Gibco (Shanghai, China). Luria Bertani (LB) medium was from Qiyun Co. Ltd (Guangzhou, China). Cell-counting kit-8 (CCK-8) was from Donjindo Co. Ltd (Shanghai, China).

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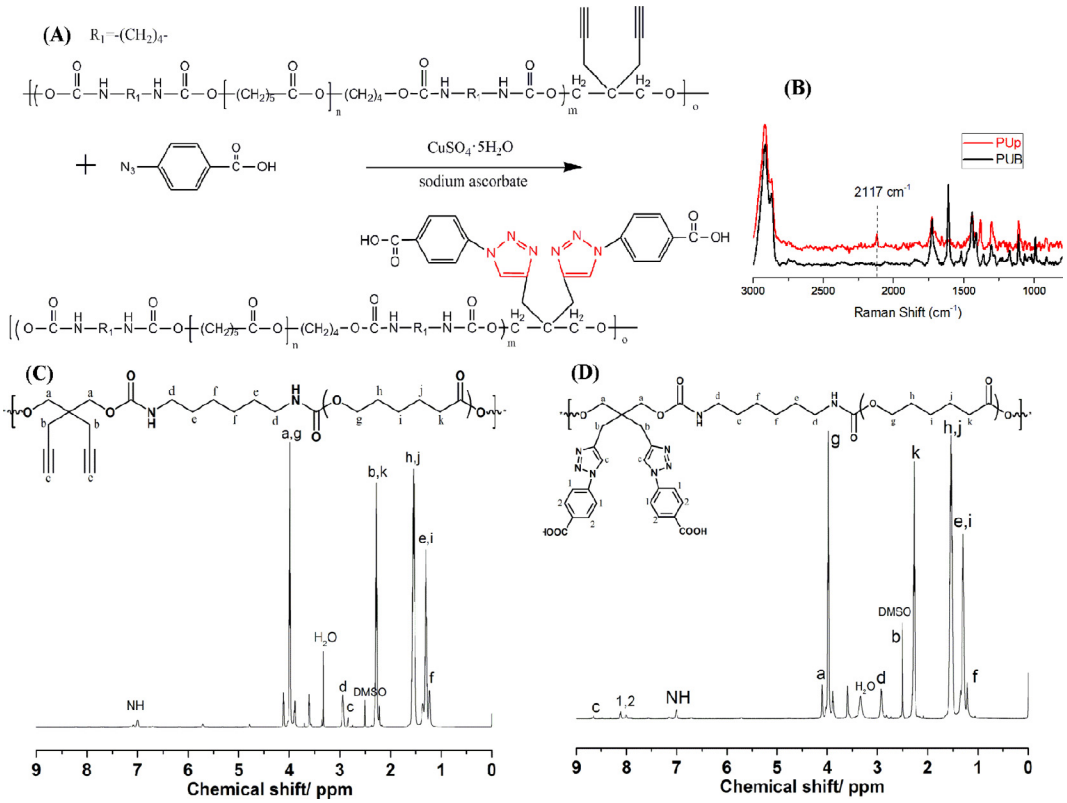


**Fig. 1.** Scheme of PUB CuAAC click reaction (A), Raman (B) and $^1$H NMR (C, D) spectra of PUB.

**Table 1**
The water contact angle and weight increase percentage after water adsorption for the polyurethane tethering various amount of benzoic acid.

| Sample | Water contact angle (°) | Weight increase (%) |
|---|---|---|
| PUp | 78.5 ± 4.1 | 0.1321 ± 0.0024 |
| PUB1 | 70.6 ± 3.4 | 0.1421 ± 0.0041 |
| PUB2 | 68.3 ± 4.2 | 0.1456 ± 0.0027 |
| PUB3 | 65.7 ± 3.9 | 0.1465 ± 0.0028 |

PU bearing a pendant benzoic acid (PUB) was synthesized under argon atmosphere as follows: 23 mg (0.085 mmol) copper sulfate pentahydrate, 40 mg sodium ascorbate (0. 2 mmol), and 480 mg (2.9 mmol) of azido-benzoic acid were added into the solution containing 5 g PUp (2.9 mmol alkyne groups) at 40 °C for 8 h to perform the copper (I)-catalyzed Huisgen 1,3-dipolar alkyne-azide cycloaddition (CuAAC) click reaction. The final PUB were precipitated from diethyl ether, washed with distilled water ten times, and dried for further use. Three PUBs tethering various contents of benzoic acid (1, 2, 3 mmol/g) were synthesized and referred as PUB1, PUB2 and PUB3, respectively.

The Raman spectra were measured using Laser Confocal Micro-Raman Spectroscopy (LabRAM Aramis) equipped with a 633 nm HeNe laser. Proton nuclear magnetic resonance spectra ($^1$H NMR) were recorded on a Bruker 600 MHz spectrometer at room temperature using dimethylsulfoxide (DMSO-$d_6$) as solvents. Chemical shifts were reported in ppm from external tetramethylsilane. The water contact angle was determined through sessile drop method (1 μL droplet volume) with a water contact angle measurer (OCA15, DATAPHYSICS) at room temperature on membrane. Water adsorption ratio was measured by putting the sample in PBS for 24 h and then weighted to determine mass increase according to the

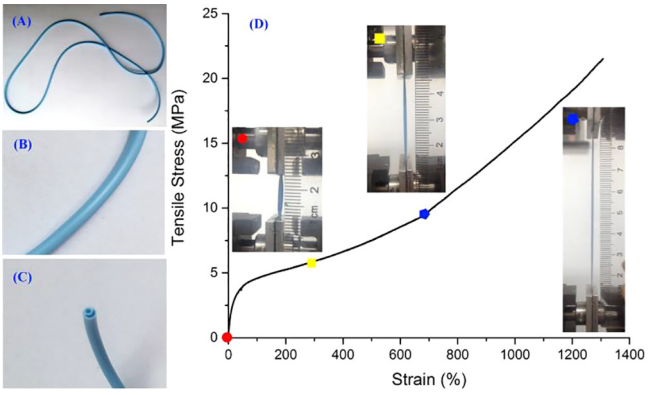


**Fig. 2.** Pictures of PUB tube and its tensile stress-strain curve.

equation: $(W_1\text{-}W_0)/W_0 \times 100\%$, where $W_0$ is the initial weight and $W_1$ is the weight after water adsorption. Tensile test were performed using an INSTRON 5967 at a crosshead speed of 5 mm/min. The calculated data are expressed as mean ± standard deviation by working out five parallel samples in each test.

PUB films (2.0 cm × 2.0 cm) sterilized by ultraviolet radiation for 30 min were separately put into 7 mL of LB liquid suspension containing gram-negative bacteria *Escherichia coli* (*E. coli*) and the cuvettes were then subjected to incubation in a shaking incubator at 37 °C for 24 h. Subsequently, the film was removed from the cuvettes, and the *E. coli* cells were detached from the film using 15 mL of 0.1% LB culture medium. Then 200 μL of the dilute solution was spread onto a LB solid culture medium and incubated at 37 °C for another 24 h. Each sample was tested three times.