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Antibacterial poly (3,4-ethylenedioxythiophene):poly(styrene-sulfonate)/agarose nanocomposite hydrogels with thermo-processability and self-healing

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ABSTRACT

Recently, Near-infrared (NIR)-induced photothermal killing of pathogenic bacteria has received considerable attention due to the increase in antibiotic resistant bacteria. In this paper, we report a simple aqueous solution-based strategy to construct an effective photothermal nanocomposite composed of poly(3,4-ethylenedioxythiophene):poly(styrene-sulfonate) (PEDOT:PSS) and agarose with thermo-processability, light triggered self-healing, and excellent antibacterial activity. Our experiments revealed that PEDOT:PSS/agarose was easily coated on both a 2D glass substrate and 3D cotton structure. Additionally, PEDOT:PSS/agarose can be designed into free-standing objects of diverse shape as well as restored through an NIR light-induced self-healing effect after damage. Taking advantage of strong NIR light absorption, PEDOT:PSS/agarose exhibited a sharp temperature increase of 24.5 °C during NIR exposure for 100 s. More importantly, we demonstrated that the temperature increase on PEDOT:PSS/agarose *via* photothermal conversion resulted in the rapid and effective killing of nearly 100% of the pathogenic bacteria within 2 min of NIR irradiation.

1. Introduction

It is becoming increasingly difficult to combat bacterial infection due to the emergence of multidrug resistant strains of bacteria, which leads to serious problems such as failure of medical devices and threats to global public health (Arciola, Campoccia, Speziale, Montanaro, & Costerton, 2012; Hall-Stoodley, Costerton, & Stoodley, 2004; Kim et al., 2015; Neoh, Li, Kang, Chiong, & Tambyah, 2017; Wei, Tang, Yu, & Chen, 2017). This has led to over 13 million deaths worldwide per year from infectious diseases (Song & Jang, 2014). A traditional antibiotics-based chemotherapy has several intrinsic limitations including solubility, overdosing, and systemic toxicity (Jeong, Sharker, In, & Park, 2015; Li et al., 2018; Zhang, Xia, Chen, Chen, & Wu, 2017). These current treatments are slow and destroy the bacteria chemically through lysis of pathogenic bacteria originating from interference with the normal metabolic process. Furthermore, antibiotic-resistant bacteria have been observed almost immediately after a new class of antibiotics are marketed (Molton, Tambyah, Ang, Ling, & Fisher, 2013; Zipperer et al., 2016). Thus, innovative antibacterial materials that are able to address microbial resistance as well as rapidly destroy pathogenic bacteria are in high demand.

Recently, near-infrared (NIR) laser-induced photothermal therapy has proven to be a versatile, powerful tool to combat cancer and bacterial infection (Chen, Fang, Tang, & Zheng, 2012; Chen, Tang, Tang, & Li, 2017; Chen et al., 2016; Wang et al., 2017; Wu, Deokar, Liao, Shih, & Ling, 2013; Yang et al., 2011; Zhang et al., 2018). NIR irradiation in the range of 700 – 1100 nm has a particularly large advantage in biological applications because it is deeply penetrable into tissues and is nearly harmless to living tissues, while ultraviolet (UV) is not (Boas, Elwell, Ferrari, & Taga, 2014; Ferrari & Quaresima, 2012; Manley, 2014). For selective and rapid hyper-thermal killing of pathogenic bacteria, the key component is a photothermal agent that can absorb NIR light (at

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the range of 650–900 nm) and emit photothermal heat through a non-radiative mechanism. Therefore, a number of inorganic gold-based nanostructures have been extensively studied as potential photothermal killing agents (Chen et al., 2017; Jiang & Teng, 2017; Khantamat et al., 2015; Ran et al., 2017). In spite of their viability, the use of inorganic nanomaterials may be limited in future clinical applications since they are non-biodegradable, causing cytotoxic effects such as induction of oxidative stress (Hsiao et al., 2015; Jia et al., 2009; Lal, Clare, & Halas, 2008; Norman, Stone, Gole, Murphy, & Sabo-Attwood, 2008).

Hydrogels, which consist of physically or chemically cross-linked polymer chains, are soft materials with a high water content (Kim et al., 2016; Ko, Kim, Kim, Yamauchi et al., 2017; Thoniyot, Tan, Karim, Young, & Loh, 2015; Xing et al., 2016; You et al., 2015). A number of hydrogels are biocompatible and can be tailored to possess mechanical properties matching those of natural tissues and thus have been extensively utilized in a variety of applications including wound healing, surface coatings for implants, and antibacterial agents (Dhandayuthapani, Yoshida, Maekawa, & Kumar, 2011; Goldberg, Langer, & Jia, 2007; Spencer et al., 2017; Veiga & Schneider, 2013). Carefully designed photothermal agent-incorporated hydrogels can be promising antibacterial materials and coatings due to their ease of formation and the possibility for tailoring their physicochemical properties (size, surface chemistry, porosity, shape, stability, *etc.*) and photothermal performance.

In this study, the goal of this study is to present an antibacterial all-organic nanocomposite hydrogel composed of poly(3,4-ethylenedioxythiophene):poly(styrene-sulfonate) (PEDOT:PSS) and agarose with thermo-processability and self-healing ability. PEDOT:PSS, an aqueous-based conductive polymer nanoparticles with strong NIR absorbance, has recently emerged as a new NIR photothermal therapy (PTT) agent due to its water-dispersibility, high photothermal conversion efficiency, excellent photostability, and good biocompatibility (Jeong et al., 2015; Khan & Narula, 2016; Ko, Kim, Kim, & You, 2017; You et al., 2013). Agarose, one of the main polysaccharide components of agar, serves as the hydrogel backbone for antibacterial nanocomposite hydrogels. This physical agarose hydrogel can exhibit reversible sol-gel transition upon heating and cooling, originating from reversible cross-linking *via* hydrogen bonding, which enables to control size and shape and possess the self-healing performance (Hur et al., 2014; Park, Chae, Kim, & Hur, 2016; Wu et al., 2017). Because agarose gelation requires only a single component agarose without catalyst, agarose gel can be prepared more simply and rapidly than other gels by guar gum, celluloses, and other biopolymer materials. Based on these advantages of agarose, we have selected the agarose for preparation of functional hydrogel with photothermal properties. Recently, the fabrication of electroconductive hybrid microspheres has been reported by using PEDOT:PSS/agarose/polyvinyl alcohol(PVA)/Fe_3O_4 composite through microfluidic channel (Lee, Choi, Cho, & Yim, 2016). In contrast to previous study focusing on the electrical conductivity and magnetic property of hybrid microspheres, we describe here a simple aqueous solution-based strategy to construct spin-coatable, free-standing PEDOT:PSS/agarose composite hydrogel with excellent hemocompatibility and then demonstrated the potential bactericidal activities of PEDOT:PSS/agarose against pathogenic bacteria. In detail, by combining desirable properties of PEDOT:PSS and agarose hydrogel without any additives, we demonstrated that PEDOT:PSS/agarose all-organic nanocomposite hydrogel exhibited a rapid thermal response to NIR laser irradiation, resulting in complete bacterial death after 2 min irradiation, as well as possessing thermoplasticity and NIR light-assisted self-healing properties. We are not aware of studies investigating the use of PEDOT:PSS/agarose nanocomposite hydrogels for photothermal-based antibacterial activity. This conducting nanocomposite hydrogel with unique properties may find broad utility in future bioapplications, especially in photothermal therapy in pathogenic bacteria and cancer treatment, on-demand drug release systems responsive to electric field, light, and temperature, biomimetic devices such as artificial muscles, and organic bioelectronics devices.

2. Experimental section

2.1. Materials

Poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) was purchased from Sigma-Aldrich and used without further purification. Agarose powder (MW: 120,000; sulfates content: < 0.10%) was purchased from Genomic Base. *tert*-Butyl alcohol and ethanol were purchased from Duksan Pure Chemicals Company Co., Ltd. (Korea). Phosphate buffered saline (PBS) was purchased from Life Technologies.

2.2. Preparation of agarose and PEDOT:PSS/agarose composite hydrogel

In general, 3 wt% agarose was mixed with DI water and the mixture was heated by a microwave oven to prepare a completely dissolved agarose precursor solution. To fabricate the PEDOT:PSS/agarose composite hydrogel, PEDOT:PSS (solid content: 1 wt%) solution was added to the agarose precursor solution with varying PEDOT:PSS concentrations (5, 10, 20, 40 v/v%). After the solution was thoroughly vortexed for two minutes, the mixture was poured onto a plastic petri dish and allowed to cool to room temperature. After gelation, the hydrogel was carefully peeled from the petri dish. The shape and size of the PEDOT:PSS/agarose composite hydrogel were easily adjusted with diverse molds. In addition, the PEDOT:PSS/agarose precursor solution was evenly coated on glass substrates and 3D cotton surfaces using spin-coating (500 rpm, 30 s) and dipping (2 min) methods, respectively.

2.3. Characterization of agarose and PEDOT:PSS/agarose composite hydrogel

The Fourier Transform infrared spectroscopy (FT-IR) measurements were recorded on FT-IR spectrophotometer (Spectrum One System, Perkin-Elmer) by dried samples. The morphologies of agarose and PEDOT:PSS/agarose composite aerogels were observed *via* field emission scanning electron microscopy (FE-SEM, Hitachi, model S-4200, Carl Zeiss, model Merlin). To prepare the SEM samples, the agarose and PEDOT:PSS/agarose composite hydrogel was converted to an aerogel *via* solvent exchange (water-ethanol-*t*-butyl alcohol) followed by freeze-drying (Kim et al., 2017). For this, 50 ml of water/ethanol and ethanol/*t*-butyl alcohol (75/25, 50/50, 25/75, 0/100) were exchanged at 30 min intervals, and 100% of the ethanol and *t*-butyl alcohol was used twice. The elemental analysis was performed using energy dispersive spectrometry (EDS).

The tests for swelling, porosity, and degradation properties of the prepared hydrogels were carried out by a gravimetric method (McBath & Shipp, 2010; Rennerfeldt, Renth, Talata, Gehrke, & Detamore, 2013; Sornkamnerd, Okajima, & Kaneko, 2017). The vacuum-dried agarose and PEDOT:PSS/agarose composite gels (diameter: 30 mm) were weighed and immersed in water for 3 days to calculate the swelling. For the porosity test, the freeze-dried samples were weighed and immersed in absolute ethanol for 1 day. The residual water or ethanol on the surface of swollen gel was removed before weighing. The swelling and porosity properties were calculated using Eqs. (1) and (2), respectively:

$$\text{Swelling} \quad (\%) = \frac{W_s - W_d}{W_d} \times 100 \tag{1}$$

$$\text{Porosity} \quad (\%) = \frac{W_s - W_d}{\rho V} \times 100 \tag{2}$$

where W_s is the weight of swollen gel, W_d is the weight of dry gel, ρ is the density of absolute ethanol and V is the volume of swollen gel. The degradation test of the hydrogels was performed by immersing in PBS buffer for 10 days. The degree of degradation was calculated using Eq.