Biomaterials 127 (2017) 97–106

Contents lists available at ScienceDirect

Biomaterials

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

Surface engineering of semiconducting polymer nanoparticles for amplified photoacoustic imaging

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ARTICLE INFO

Article history:
Received 31 January 2017
Received in revised form
3 March 2017
Accepted 3 March 2017
Available online 6 March 2017

Keywords:
Semiconducting polymer nanoparticles
Photoacoustic imaging
Surface engineering
Tumor imaging

ABSTRACT

Despite the deeper tissue penetration of photoacoustic (PA) imaging, its sensitivity is generally lower than optical imaging. This fact partially restricts the applications of PA imaging and greatly stimulates the development of sensitive PA imaging agents. We herein report that the surface coating of semiconducting polymer nanoparticles (SPNs) with the silica layer can simultaneously amplify fluorescence and PA brightness while maintaining their photothermal conversion efficiency nearly unchanged. As compared with the bare SPNs, the silica-coated SPNs (SPNs-SiO_2) have higher photothermal heating rate in the initial stage of laser irradiation due to the higher interfacial thermal conductance between the silica layer and water relative to that between the SP and water. Such an interfacial effect consequently results in sharp temperature increase and in turn amplified PA brightness for SPNs-SiO_2. By conjugating poly(ethylene glycol) (PEG) and cyclic-RGD onto SPNs-SiO_2, targeted PA imaging of tumor in living mice is demonstrated after systemic administration, showing a high signal to background ratio. Our study provides a surface engineering approach to amplify the PA signals of organic nanoparticles for molecular imaging.

1. Introduction

Photoacoustic (PA) imaging as a hybrid non-ionizing imaging modality that measures the conversion of photon energy into acoustic pressure waves, which provides deep tissue penetration as compared with optical imaging due to the minimized scattering of acoustic waves relative to light [1,2]. PA imaging has been not only used to understand fundamental biology such as imaging of diseases biomarkers [3,4], brain function [5] and angiogenesis [6], but also involved in preclinical and clinical studies such as cancer diagnostics [7,8], guided sentinel lymph node biopsy [9], brain imaging [10] and dosimetry in thermal therapy [11]. However, as PA signals are mainly determined by the absorption and photothermal conversion of imaging agents, the sensitivity of PA imaging is generally lower than optical imaging [12]. To advance the applications of PA imaging in life science, imaging agents with high PA brightness are highly desired, which can also minimize the dosage required for *in vivo* studies and in turn alleviate the potential issue of toxicity.

Semiconducting polymer nanoparticles (SPNs) have recently been used for PA imaging in addition to small-molecule organic dyes [13,14], fluorescent proteins [15,16], gold nanoparticles [17], carbon nanotubes [18–21], two-dimensional materials [22–24], up-conversion nanoparticles [25] and porphysomes [26–28]. SPNs are made from semiconducting polymers (SP) with π-electron delocalized backbones, which have proved as versatile photonic nanomaterials for a variety of molecular imaging and theranostic applications [29–39]. In particular, SPNs have been developed into smart activatable probes for *in vivo* PA imaging of tumor [40], reactive oxygen species [41] and pH [42]. SPNs often have higher photostability and PA brightness as compared with other PA agents such as carbon nanotubes and gold nanorods [41,43]. These intrinsic merits in conjunction with their organic and biologically benign ingredients place SPNs at the forefront of PA imaging.

To improve the sensitivity of SPNs for PA imaging, we not only investigated the relationship between the structure and PA properties of SPs [44] but also proposed an intraparticle engineering approach [45]. As compared with massive screening of SPs, the intraparticle doping approach is a more facile way that avoids time-consuming synthesis. The doping approach incorporates a secondary component into SPNs that serves as the electron acceptor to

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http://dx.doi.org/10.1016/j.biomaterials.2017.03.003
0142-9612/

create photoinduced electron transfer (PET) (Fig. 1a), that promotes nonradiative decay, quenches the fluorescence and converts this part of photon energy into extra heat, ultimately augmenting PA signals. In addition, such enhancement in heat generation increases maximum photothermal temperature and thus benefits photothermal therapy [45]. However, this approach can only be applied to fluorescent SPNs, and after doping, SPNs are no longer light-emitting, which comprises the capability for complementary fluorescence imaging. Moreover, other materials such as layered MoS_2 nanosheets [46] and reduced graphene oxide coated gold nanorods [47] have been reported to have amplified signals for sensitive PA imaging.

In this study, we report a general surface engineering approach to develop multilayered SPNs with simultaneously amplified fluorescence and PA brightness for *in vivo* imaging. The multilayered SPN contains a hydrophobic SP core coated with an optically inner silica shell (Fig. 1a). Note that although silica-coated nanoparticles composed of small-molecule dyes have been reported [48], the effect of silica on the PA properties has yet to be revealed. We synthesized silica-coated SPNs (SPNs-SiO_2) and compared their optical, photothermal and PA properties with the uncoated SPNs. To demonstrate the generality of this approach, both nonfluorescent (SP1) and fluorescent (SP2) polymers were tested. We found that SPNs-SiO_2 had higher PA brightness than the uncoated SPNs. We thus carried out the finite element analysis (FEA) simulation to reveal the underlying mechanism involved. The results revealed that the photothermal heating rate of SPN-SiO_2 is faster than that of the uncoated SPNs due to the higher heat interfacial conductance for the interface between the silica layer and water as compared with that between the SP core and water. Such an interfacial effect eventually led to the higher PA signals for SPN-SiO_2 relative to that for the uncoated SPNs. To demonstrate the proof-of-concept imaging application, SPNs-SiO_2 were conjugated with peptide and applied for PA imaging of tumor in living mice.

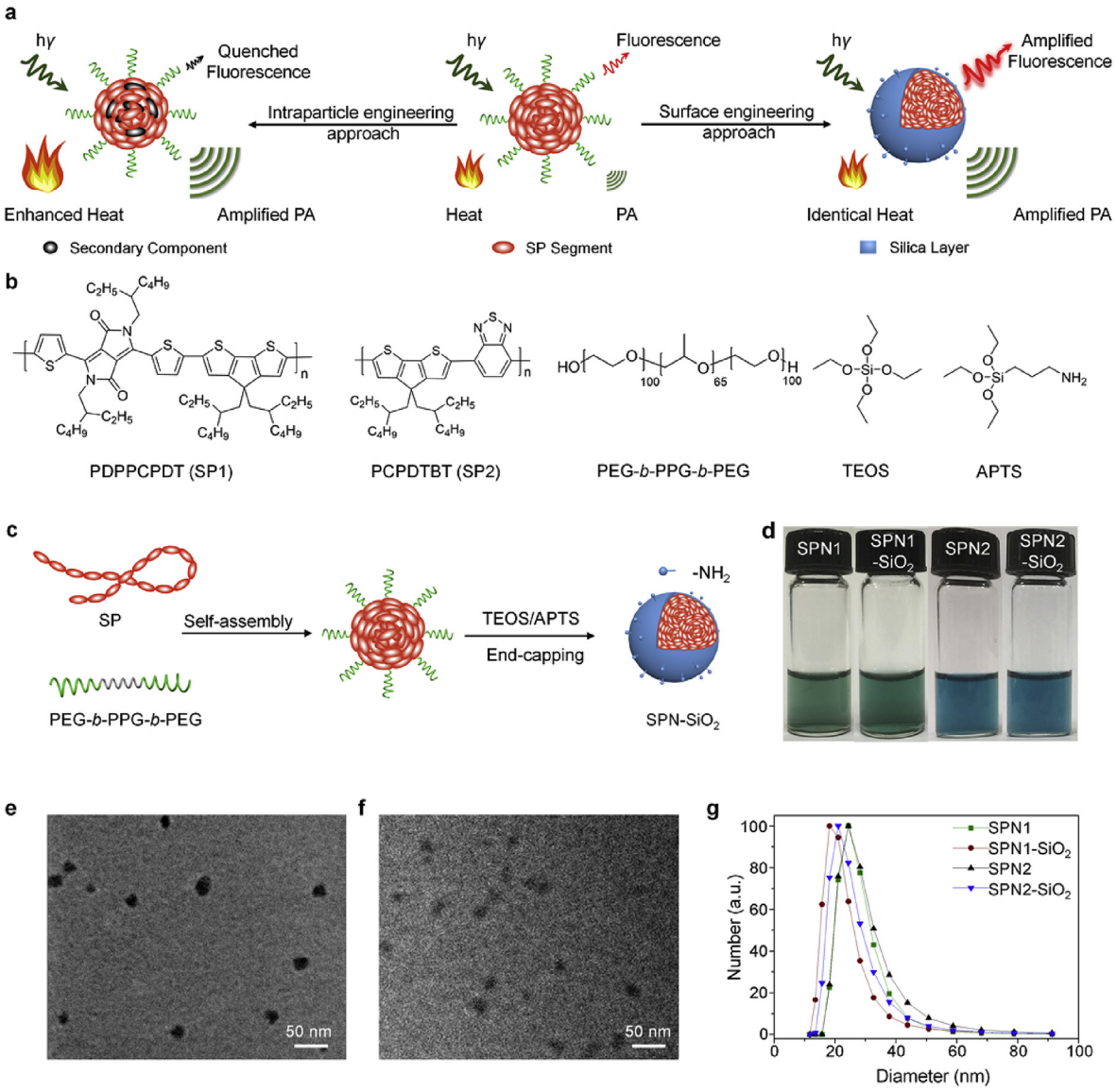

Fig. 1. Synthesis and characterization of SPNs. (**a**) Schematic illustration of intraparticle engineering and surface engineering approaches for amplified PA imaging. (**b**) Chemical structures of reagents used for preparation of SPNs, including PDPPCPDT, PCPDTBT, PEG-*b*-PPG-*b*-PEG, TEOS, and APTS. (**c**) Schematic illustration of the preparation of SPN-SiO_2. (**d**) Photography of the solutions of SPNs. [SPN] = 20 μg mL^{-1}. Representative TEM images of SPN1 (**e**) and SPN1-SiO_2 (**f**). (**g**) Representative DLS profiles of SPNs in PBS.