Polydopamine-Based Materials as Carriers for Drug Delivery

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Abstract. Polydopamine (PDA)–based material with tailored structures and properties are of particular interests due to their multifunctions and potential applications as new colloidal structures in diverse field. The past several years has witnessed a rapid increase of research concerning the new fabrication strategies, functionalization and applications of PDA-based materials in drug delivery. In this review, the very recent progress of PDA-based materials as carriers for drug delivery are summarized.

Introduction

In the late decades, polymer capsules have attracted great interest for drug delivery. To achieve controlled drug release, polymer capsules should be functionalized with various functional moieties, such as targeting ligands [1, 2], and require triggered release mechanisms to respond to intracellular stimuli, for instance, pH [3], redox reactions [4], and enzymes [5]. Dopamine (3,4-dihydroxyphenylethylamine, DA), which was inspired by the composition of adhesive proteins in mussels, has been demonstrated to be an effective adhesive that can be attached to almost all material surfaces (metals, oxides, ceramics [6], polymers [7], carbon nanotubes [8], magnetite nanoparticles (NPs) [9], and even Teflon [10]), and auto-polymerized to form PDA coating in alkaline aqueous media. The process of preparing PDA is simple, less labour intensive, and the physicochemical properties can be well controlled by further chemical modification. Furthermore, PDA shows excellent biocompatibility and low cytotoxicity, making it a versatile platform for bioapplications. The aim of the review is to outline the development of PDA-based capsules and NPS for drug delivery application.

PDA Capsules and NPs as Carriers for Drug Delivery

PDA capsules carriers can increase drug bioavailability, and facilitate targeted delivery. Toxicity of the PDA is an important property when they are planned to be used as drug delivery vehicles. Studies have demonstrated that PDA did not hinder the viability or proliferation of many kinds of mammalian cells such as fibroblasts, osteoblasts, neurons, endothelial cells [11], and colon cancer LIM1215 cells [12]. In vivo study showed that Ag @ PDA NCs were stable within cells of the liver and spleen for at least six weeks, and Ag @ PDA NCs did not show notable histological toxicity to main organs of mice in a long time [13]. These results can all improve the intracellular delivery capacity and biocompatibility of NPs for drug delivery.

To achieve controlled and targeted drug release, polymer capsules should be functionalized with various functional moieties like targeting ligands, and require triggered release mechanisms to respond to intracellular stimuli, such as pH, redox

reactions and enzymes. The pH-triggered release strategy is of particular interest for intracellular delivery, as carriers are subject to acidification when internalized from the slightly alkaline extracellular conditions into an acidic environment inside endosomal and lysosomal compartments. Carous et al. conjugated the anticancer drug doxorubicin (Dox) to PMA_{SH} with a pH cleavable hydrazone bond, and then immobilized in PDA capsules via robust thiol-catechol reactions between the polymer-drug conjugate and capsule walls. The loaded Dox showed limited release at physiological pH but release at endosomal/lysosomal pH. Cell viability assays showed that Dox-loaded PDA capsules enhanced the efficacy of eradicating HeLa cancer cells [14]. Fu *et al*. reported a controlled release system using PDA coated mesoporous SiO_2 NPs as pH-sensitive nanocarriers. Brifly, Dox was loaded into mesoporous SiO_2 NPs with a large pore diameter, which were subsequently modified with PDA coating. Using PDA coating as the gatekeepers, the drug molecules were blocked in mesoporous SiO_2 NPs at neutral pH and released at lower pH [15].

Degradation of the capsules is an important property for drug delivery. Based on this, Carous group synthesized of DA-modified poly(L-glutamic acid) (PGA) conjugates (PGA_{PDA}) for the continuous assembly of biodegradable capsules which assembled onto sacrifice SiO_2 particles. The degradability of capsules was relevant to the percentage of DA within the films [16]. However, some drugs have been degraded before their performance. For PDA capsule can shield the drug from degradation, Carous group used DMDES emulsions as soft templates for the preparation of PDA capsules. Fe_3O_4 NPs, CdSe/CdS and hydrophobic anticancer drug (thiocoraline) were preloaded during the formation of emulsion droplets, and remained encapsulated in the final PDA capsules after the removal of templates [17].

Mei and coworkers developed DTX-loaded formulations using PDA-modified NPs synthesized using D-a-tocopherol polyethylene glycol 1000 succinate-poly(lactide) (pD-TPGS-PLA/NPs). To target liver cancer cells, galactosamine was conjugated on the prepared NPs (Gal-pD-TPGS-PLA/NPs) to enhance the delivery of DTX via ligand-mediated endocytosis. The size and morphology of pD-TPGS-PLA/NPs and Gal-pD-TPGS-PLA/NPs changed obviously compared with TPGS-PLA/NPs. In vitro studies showed that TPGS-PLA/NPs, pD-TPGS-PLA/NPs and Gal-pD-TPGS-PLA/NPs had similar release profiles of DTX. Both confocal laser scanning microscopy and flow cytometric results showed that coumarin 6-loaded Gal-pD-TPGS-PLA/NPs had the highest cellular uptake efficiency in liver cancer cell line HepG2. Moreover, DTX-loaded Gal-pD-TPGS-PLA/NPs inhibited the growth of HepG2 cells more potently than TPGS-PLA/NPs and pD-TPGS-PLA/NPs. The in vivo biodistribution experiments show that the Gal-pD-TPGS-PLA/NPs were specifically targeted to the tumor. Furthermore, the in vivo anti-tumor effects study showed that injecting DTX-loaded Gal-pD-TPGS-PLA/NPs reduced the tumor size most significantly on hepatoma-bearing nude mice [18]. Yeo *et al*. functionalized poly(lactic-co-glycolic acid) (PLGA) NPs with folate, Arg-Gly-Asp, and poly(carboxybetaine methacrylate) as surface modifiers, which showed no cytotoxicity [19].

One major focus of antitumor drug delivery is the development of suitable carriers for therapeutic molecules. Superparamagnetic iron oxide nanoparticles are promising magnetic drug carriers as they are biocompatible, biodegradable, readily tunable, superparamagnetic, and, thus, controllable by an external magnetic field. Dong et al. demonstrate a PDA-functionalized superparamagnetic magnetite nanocrystal clusters for antitumor drug delivery. Firstly, an oil-phase evaporation-induced self-assembly strategy was introduced to fabricate magnetite nanocrystal clusters (MNCs), which

have the advantage of increased magnetization through a synergistic effect. Secondly, the surface functionalization of the MNCs with PDA was demonstrated. Thirdly, the antitumor drug epirubicin was attached to the surface of MNC@PDA, and its applicability for use as a magnetically guided carrier for antitumor drug delivery was demonstrated. The achieved MNC@PDA exhibits superparamagnetic characteristics, improved magnetization behavior under an external magnetic field, well-controlled loading, and pH-responsive properties [20].

Inspired by the natural binding ability of PDA with iron ion, a simple and versatile synthesis strategy was developed to prepare biodegradable coordination polymer (CP) encapsulated PDA nanocomplex (PDA@CPx, x = 3, 6, 9). Lu *et al*. found that the PDA@CP_3 can serve as a T1/T2 dual mode contrast agent (DMCA) for magnetic resonance imaging (MRI), which possesses high longitudinal (r_1=7.524 $mM^{-1}s^{-1}$) and transverse (r_2=45.92 $mM^{-1}s^{-1}$) relaxivities. In this system, DOX loaded PDAs@CP_3 nanocomplex was able to not only destroy the tumor directly by heat, but also stimulate the chemotherapy by enabling NIR-responsive on demand delivery of DOX [21]. Photodynamic therapy (PDT), using a combination of chemical photosensitizers (PS) and light, has been successfully applied as a noninvasive therapeutic procedure to treat tumors. However, most current clinically used PS have suffered from the instability in physiological conditions which lead to low photodynamic therapy efficacy. Herein, PDA conjugated with Chlorin e6 (PDA-Ce6) was designed as a nanotherapeutic agent to achieve simultaneous photodynamic/photothermal therapy (PDT/PTT). Compared to the free Ce6, the PDA-Ce6 nanosphere exhibited significantly higher PDT efficacy against tumor cells, because of the enhanced cellular uptake and subsequently greater reactive oxygen species (ROS) production upon laser irradiation at 670 nm. Meanwhile, the PDA-Ce6 nanosphere could be also used as a photoabsorbing agent for PTT, because of the excellent photothermal conversion ability of PDA nanoparticle under laser irradiation at 808 nm. Moreover, PDA-Ce6 had low dark toxicity, while excellent phototoxicity under the combination laser irradiation [22].

Conclusions and Outlook

The as-prepared capsules and core-shell structures have shown their great promise of applications in many areas of science and technologies. In particular, recent efforts have been made on the capsules prepared by new method and those with sophisticated structures for biomedical applications, including but not limited to drug carriers.

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