Facile synthesis of polymeric fluorescent organic nanoparticles based on the self-polymerization of dopamine for biological imaging

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Abstract

Polymeric fluorescent organic nanoparticles (**polymer-FONs**) have raised considerable research attention for biomedical applications owing to their advantages as compared with **fluorescent inorganic nanoparticles** and small organic molecules. In this study, we presented an efficient, facile and environment-friendly strategy to produce polymer-FONs, which relied on the self-polymerization of dopamine and polyethyleneimine (PEI) in rather mild conditions. To obtain the final polymer-FONs, aldehyde group-containing copolymers (named as poly(UA-co-PEGMA)) were synthesized by reversible addition–fragmentation chain-transfer polymerization using polyethylene glycol methyl ether methacrylate (PEGMA) and 1-undecen-10-al (UA) as monomers. The dopamine was conjugated onto poly(UA-co-PEGMA) through a multicomponent reaction between UA and dopamine to obtain poly(UA-co-PEGMA)-DA, which was further utilized for preparation of **polymer-FONs** through self-polymerization of dopamine and PEI. ¹H nuclear magnetic resonance, Fourier transform infrared spectroscopy, transmission electron microscopy and fluorescence spectroscopy were employed to characterize the structure, morphology, compositions and optical properties of these polymer-FONs. Cell viability and cell uptake behavior results suggested that these polymer-FONs possess good biocompatibility and can be potentially utilized for biomedical applications. More importantly, the method can be also applied to fabricate many other multifunctional polymer-FONs with great potential for biomedical applications.

Key words: Polymeric fluorescent organic nanoparticles, biological imaging, dopamine, self-polymerization, biocompatibility

Introduction

In recent years, fluorescent nanomaterials have attracted considerable research attention as their outstanding properties and performances, such as quantum effect, high specific surface areas, small size, fluorescence, multifunctional potential and so on.[1-4] Therefore, they have been widely applied in communication[5-7], storage[8], biomedical imaging[9, 10], diagnosis[11-13] and theranostics[14-16]. Among all these applications, biological imaging has played an important role and greatly promoted the development of fluorescent nanomaterials. Biological imaging can be used to monitor the biological processes and obtain the information of tumor growth and metastasis, development of infectious diseases and expression of certain genes, and improve the veracity and **decrease** the operation simultaneously.[17] Fluorescent nanomaterials can be divided into three parts: inorganic, organic and traditional fluorescent proteins. Traditional fluorescent proteins, for example green fluorescent protein series, red fluorescent proteins and independent light-emitting proteins, are poor in stability and membrane penetration.[18] The synthesis of these fluorescent proteins is also tedious and expensive. **Fluorescent inorganic nanomaterials**, including semiconductor quantum dots[19, 20], carbon quantum dots[21-24], silicon quantum dots[25], upconversion nanoparticles[26] and metal nanoclusters[27], Ln ions doped luminescent nanomaterials[28, 29] **were** perplexed by their toxicity and poor degradability. Therefore, some efforts in searching new methods should be done to deal with such dilemma.

Besides the highlights of biocompatibility, fluorescent organic nanomaterials (FONs) have advantages over **fluorescent inorganic nanomaterials** in the designability of structure and functions.[30-32] Zhou et al. created six new dyes adopted 2, 2'-bipyridyl as electron acceptor and six other conjugated compounds as electron donors, which were promising in cell imaging as low toxicity[33]. **Jang et al.** prepared conjugated polymer dots using poly (diphenylacetylene) derivatives and commercial conjugated polymers following specific molecular design rules[34]. However, planar conjugated organic dyes involved in the aggregation-caused quenching effect (ACQ). Tang et al. discovered aggregation-induced emission materials can still keep high fluorescence in high concentration or solid state and are promising for bio-probes[35-38]. Meanwhile, it was largely limited by complex and multi-step experimental procedure, high cost and hydrophobic nature[39]. Therefore, it is desirable to develop green, efficient and economical methods in the synthesis of FONs. Dopamine (DA), an important molecule in mussel inspired chemistry, has been widely applied in catalysis[40],

adsorption[41-43], antiseptic, surface modification, functional materials for controlled drug delivery and photothermal treatment[44-49], energy storage and conversion[50-52] as it occurred self-polymerization under alkaline condition[53-56]. In recent years, some fluorescent polydopamine (PDA) compounds, including PDA-based FONs[57], fluorescent PDA capsules[58] and fluorescent PDA-polyethyleneimine (PEI) copolymers[59, 60], were reported successively. However, it is still challengeable to control their chemical compositions and functional groups of these PDA based FONs.

In this contribution, a novel strategy has been developed to fabricate PDA based FONs through the combination of reversible addition-fragmentation chain transfer polymerization (RAFT) polymerization and self-polymerization of dopamine and PEI in rather mild conditions. First, the copolymers poly(PEGMA-co-UA) were prepared from RAFT polymerization using polyethylene glycol methyl ether methacrylate (PEGMA) and 1-undecen-10-al (UA) as monomers. Then dopamine was conjugated on poly(UA-co-PEGMA) through mercaptoacetic acid locking imine (MALI) reaction. The final polymer-FONs were formed by the self-polymerization of PEI and poly(UA-co-PEGMA)-DA. For verifying their potential biomedical applications, the biocompatibility and cell uptake behavior of polymer-FONs are also studied.

2. Experimental

2.1 Materials and measurements

All of the chemical agents and solvents were used as received. Mercaptoacetic acid (MC), UA, 2, 2-Azobis (2-methylpropionitrile) (AIBN) and PEGMA were purchased from Aladdin (Shanghai, China). Dopamine hydrochloride (DA) was purchased from Sangon Biotech. Co., Ltd (Shanghai, China). Chain transfer agent was prepared as our previous report[61]. Other chemical agents were commercially available and of analytical grade. Deionized water (D.I. water) was used in the experiment. UV-Vis spectra were recorded on an ultraviolet and visible spectrophotometer (Beijing Purkinje General Instrument Co., China). Fluorescence spectra were measured on a Hitachi FS F-4500 spectrometer with a slit width of 5 nm for both excitation and emission. The ^1H nuclear magnetic resonance (NMR) spectrum was recorded on a Bruker Avance-400 spectrometer with D_2O and CDCl_3 as the solvent. Transmission electron microscopy (TEM) images were recorded on a Hitachi 7650B microscope operated at 80 kV; the TEM specimens were obtained by placing a drop of ethanol nanoparticle suspension on a carbon-coated copper grid. The Fourier transform infrared (FT-IR) spectra

were recorded in a transmission mode on a Nicolet 5700 spectrometer (Waltham, MA, USA). The size distribution of polymer-FONs in water was determined by a Nano Zeta Potential and Submicron Particle Size Analyzer (Beckman Coulter Delsa).

2.2 Preparation of the poly(UA-co-PEGMA)

The synthesis of poly(UA-co-PEGMA) was shown in **Scheme 1** in detail. RAFT polymerization was carried out using AIBN as the initiator, UA and PEGMA as the monomers. Briefly, 504.84 mg UA, 712 mg PEGMA, 12.173 mg AIBN and 9.7 mg CTA were dissolved in 5 mL ethyl acetate and then added into schlenk flask. The reaction systems were tightly sealed and then purged with dry N₂ for 30 min to remove the oxygen. Then, the schlenk flask was immersed in an oil bath at 65 °C. After 20 h, schlenk flask was moved into ice bath. Finally, the mixture was dialyzed for 24 h to remove the solvent and monomer before drying in vacuum oven.

Scheme 1 Synthesis route of poly(UA-co-PEGMA).

2.3 Preparation of poly(UA-co-PEGMA)-DA

Poly(UA-co-PEGMA)-DA was synthesized via the MALI reaction (**Scheme 2**). Besides mild reaction conditions, MALI reaction possesses the superiority of high efficient and environmental friendliness with water as the only byproduct. **In brief**, 500 mg poly(UA-co-PEGMA), 260 mg MC, 250 mg DA, and 5 mL dimethyl formamide were put into 10 mL round-bottom flask, then keep the mixture for 2 h at room temperature. Finally, the mixture **was dialyzed** for 24 h and **dried** in vacuum oven.

Scheme 2 The preparation of poly(UA-co-PEGMA)-DA via MALI reaction.

2.4 Preparation of polymer-FONs

The procedure for preparation of polymer-FONs was displayed in **Scheme 3**. In brief, 500 mg poly(UA-co-PEGMA)-DA copolymers were dissolved into 3 mL deionized water at room temperature before adding PEI (150 mg). The solution was kept 2 h under ambient temperature. Then, it can be got the target products, polymer-FONs were purified through dialysis in porous cellulose bag and drying in vacuum oven at 40 °C for 24 h.

Scheme 3 The preparation of polymer-FONs in a gentle and efficient method.

2.5 Cytotoxicity of Polymer-FONs

The cell viability of polymer-FONs on human lung adenocarcinoma epithelial (A549) cells was determined by cell counting kit-8 (CCK-8) assay based on our previous reports.[62] The detailed experimental procedure can be found in the supporting information.

2.6 Confocal microscopic imaging of cells using polymer-FONs

The detailed information was provided in the supporting information.

3. Results and discussion

The ^1H NMR spectra of polymer-FONs and intermediate products were characterized to supply

structural information. The monomers involved in the RAFT polymerization were UA and PEGMA which possessed characteristic peaks of proton. As shown in **Fig. 1A**, an obvious signal peak at 9.72 ppm (a) was observed. It can be contributed to $-CHO$ of UA. Meanwhile, the triplet peak located at 3.66 ppm (c) just corresponded to the signal peaks of methylene in PEGMA. The peak of b was from $CDCl_3$. So, it can conclude the RAFT polymerization of UA and PEGMA had succeeded. Compared with **Fig. 1A**, another peak at 6.7~6.5 ppm was found in **Fig. 1B**. It should be derived from the aromatic ring of DA. However, the peak at 9.72 ppm was disappeared in **Fig. 1B** as the influence of DA and MC. Thus, DA has conjugated with UA through MALI reaction. D_2O was chosen as solvent in the characterization of polymer-FONs. PEI is an important multi-amino compound, which is widely used in biomedicine. As shown in **Fig. 1C**, the characteristic peak of b-PEI (2.2~1.9 ppm) was clearly detected, indicating the existence of PEI in polymer-FONs. Therefore, it suggested that polymer-FONs have been prepared as designed.

Fig. 1 Characterization of polymer-FONs and the intermediate 1H NMR (400 MHz).

The TEM **images** provided the size and morphology information about these polymer-FONs. As shown in **Fig. 2**, polymer-FONs were rather uniform and monodispersed. Overall, the surface was a bit rough but round. Under high magnification, it can accurately identify that these polymer-FONs were with an average diameter of about 50 nm. As shown in **Fig. S1**, the dynamic light scattering (DLS) experiment has been carried out to determine the size distribution of PDA based FONs in PBS. The results showed the size distribution was about 57.4 ± 23.7 nm with a polydispersity index (PDI) of 0.206. As the forming mechanism, it can be supposed to the chain entanglement as the forces between the hydrophilic segments and hydrophobic blocks. The optical properties of polymer-FONs were

evaluated by UV-Vis spectroscopy and fluorescence spectroscopy. First, UV-visible spectroscopy was used to offer specific data to confirm the functional groups and composition of polymer-FONs. As shown in **Fig. S2**, the peak at 277 nm was obviously observed. In view of the rough composition, the peak is probably derived from the transition of $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ in C=O and C=N. The above results indicated that Schiff base may exist in polymer-FONs and it could contribute to the fluorescence of the resultant FONs.

Fig. 2 TEM images of polymer-FONs with different magnificants, scale bar = 100 nm (A), and 50 nm (B).

Due to the complexity of **compositions**, FT-IR data **were** further applied. As shown in **Fig. 3**, the peaks at 2868, 2720, 1732, 1465, 1298, 1250 and 1114 cm^{-1} observed in poly(UA-co-PEGMA), which can be attributed to $-\text{CH}_2$, C=O (HC=O), C=O ($-\text{COOH}$), σ as ($-\text{CH}_2-$), C-O ($-\text{COO}-$), C-O ($-\text{COOH}$), C-O (C-O-C), respectively. After introducing dopamine and PEI, the peak in 2720 cm^{-1} disappeared, **suggesting that** aldehyde group involved in the reaction of MALI. In addition, the peaks near 1600 cm^{-1} **were** appeared in polymer-FONs, which may be from N-H and C-H in benzene ring. The peak at 1110 cm^{-1} evidently changed stronger than poly(UA-co-PEGMA), and it can be assigned to the C-N in PEI. Therefore, all of the above results indicated that polymer-FONs have been successfully synthesized.

Fig. 3 The FT-IR spectra of poly(UA-co-PEGMA) and polymer-FONs.

The XPS survey scan ranging from 0 to 1200 eV was carried out to determine the elements in

polymer-FONs. As shown in **Fig. 4A**, three characteristic peaks at 284.6, 397.8 and 531 eV can be observed, which can be attributed to C, N and O, respectively. The high nitrogen content in the sample of polymer-FONs suggested that PEI was successfully connected with DA. In addition, the individual elements of polymer-FONs were further displayed in **Fig. 4B-E**, the peak at 161.7 eV can be attributed to emergence of S, which could be observed in polymer-FONs, indicating DA was successfully conjugated with poly(UA-co-PEGMA) via MALI reaction. Based on XPS analysis, we can draw the conclusion that PDA based polymer-FONs were successfully synthesized.

Fig. 4 XPS spectra of polymer-FONs. (A) Survey scan ranging from 0 to 1200 eV, (B) C1s region, (C) N1s region, (D) O1s region and (E) S2p region.

Fluorescence spectra of polymer-FONs were shown in **Fig. 5**. It can be seen that the emission wavelengths were gradually increased when the excitation wavelengths were increased from 340 to 410 nm. Based on the excitation spectra, the optimal excitation wavelength was located at 375 nm. The maximum emission wavelength of polymer-FONs was 505 nm under the optimal excitation wavelength (375 nm). The fluorescent results are well consistent with the optical images in the insets of **Fig. 5**. Uniform and green fluorescence can be observed when water suspensions of polymer-FONs were irradiated with UV lamp at 365 nm (Right bottle in insets). **Fig. 5B** shows the effect of pH values on the fluorescent properties of polymer-FONs. It can be seen that the emission peak of polymer-FONs has not obviously changed in different pH solution.

Fig. 5 FL spectra of polymer-FONs (A) and the influence of pH to the fluorescence intensity (B). Optical image of aqueous solution of polymer-FONs were also shown in A, under natural light (left), and UV lamp ($\lambda = 365$ nm) (right).

The photostability and quantum yield (QY) were also important to evaluate their performance in cell imaging. Herein, we further investigated the photostability and QY of **polymer-FONs** before the utilization in cell imaging. As displayed in **Fig. 6**, the fluorescence intensity of polymer-FONs just had slight decrease after continuous irradiation for 1 h under the ultraviolet lamp at 365 nm. Besides, QY was also conducted and the fluorescence QY of polymer based FONs were reached up to 15.1%. Considering their excellent biocompatibility and fluorescence properties, thus **polymer-FONs** are promising for cell imaging application.

Fig. 6 Photostability of polymer-FONs in aqueous solution. The water suspensions of polymer FONs were continuously irradiated by UV lamp at 365 nm for 1 h. The fluorescent intensity values before and after irradiation were measured

CCK-8 assay was carried to quantitatively evaluate the cytotoxicity of polymer-FONs. It was

obvious that the viability of cells did not decline after incubated with different concentrations of polymer-FONs for 24 h (**Fig. 7**). Even the concentration of polymer-FONs was as high as $100 \mu\text{g mL}^{-1}$, the cell survival rate was still above $98.75 \pm 0.008\%$. Therefore, polymer-FONs owned favorable biocompatibility. Meanwhile, it can be demonstrated that the cell experiment had a good reliability. As the outstanding properties, for example, high fluorescent intensity, good water-solubility and simple preparation, polymer-FONs have broad application prospects in biomedicine fields.

Fig. 7 Cell viability of polymer-FONs with A549 cells (the concentrations of polymer-FONs are ranged from 20-100 $\mu\text{g mL}^{-1}$).

To evaluate the potential biomedical applications of polymer-FONs, their cell uptake behavior was investigated by CLSM. A549 cells were seeded in culture with $20 \mu\text{g mL}^{-1}$ of polymer-FONs. After 3 h, the cell uptake of polymer-FONs was clearly observed in **Fig. 6**. Fluorescence signal was visible in cytoplasm when cells were irradiated with 405 nm laser. Meanwhile, the center locations of cells are absent of fluorescence signals. It suggested the polymer-FONs were uptake by cells through non-specific endocytosis and mainly accumulated in cytoplasm. The above speculation was further confirmed by the emerged image in **Fig. 6C**, which clearly showed that these polymer-FONs can be internalized by cells but cannot enter cell nuclei. Considered the facile and designability preparation procedure, high water dispersibility and good biocompatibility, these polymer-FONs should be of great potential for various biomedical applications.

Fig. 8 CLSM images of A549 cells when they were incubated with $20\ \mu\text{g mL}^{-1}$ of polymer-FONs for 3 h. (A) excited with 405 nm laser, (B) bright field, (C) merge image of A and B. Scale bar = 20 μm .

4. Conclusion

In summary, polymer-FONs were designed and prepared combining RAFT polymerization and self-polymerization of DA and PEI. The prepared polymer-FONs were characterized by ^1H NMR, TEM, FT-IR, and fluorescence spectroscopy. All of these characterization results demonstrated that these polymer-FONs possess high water dispersibility, strong fluorescence and desirable biocompatibility, making them very promising candidates for biological imaging applications. More importantly, the chemical compositions and functional groups of these polymer-FONs could be well adjusted through RAFT polymerization owing to its well monomer adaptability. It is therefore the method described in this work may potentially be utilized for fabrication of many other multifunctional polymer-FONs while combination of RAFT polymerization and self-polymerization of dopamine.

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Graphic abstract

Polymeric fluorescent nanoparticles were fabricated via a novel strategy that combines the RAFT polymerization, multicomponent reaction and self-polymerization of dopamine.