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Fabrication of Rod-like Nanocapsules based on Polylactide and 3,4-Dihydroxyphenylnalanine for Drug Delivery System

Dongjian Shi, Lei Zhang, Jiali Shen, Xiaojie Li, Mingqing Chen, and Mitsuru Akashi

3,4-Dihydroxyphenylalanine (DOPA) has the property of self-polymerization to form PDOPA polymer with crosslinking structure, and coating on the surfaces of the diverse substrates at alkaline pH values. In this study, rod-like nanocapsules were facilely fabricated based on bio-based polymer by taking advantage of the DOPA properties. Block-like poly(lactide)-b-amidated poly(3,4-dihydroxyphenylalanine) (PLA-b-APDOPA) copolymer was firstly synthesized through amidation reaction with the pre-prepared functional PLA and APDOPA. The DOPA compound and obtained PLA-b-APDOPA copolymer were orderly coated on the silica nanorods to get PLA-b-APDOPA/PDOPA nanocapsules. Afterwards, the PLA-b-APDOPA/PDOPA nanocapsules were formed by removal of the silica template. The structure of the copolymer was confirmed by $^1$H NMR spectrum. The formed nanorods and nanocapsules were observed by SEM and TEM. The structure and amount of the coated layers were determined by XPS and TGA. The results showed the roughness surface of the nanorods after coated polymers and the formation of the thin PDOPA layer and thick PLA-b-APDOPA layer on the silica surface. Moreover, the formed nanocapsules had well biocompatibility. A model drug was successfully entrapped into the capsules, and could be slowly released from the nanocapsules in vitro depending on the pH buffers. The obtained rod-like nanocapsules could be used as carriers for the biomedical fields.

Introduction

Spherical nanoparticles (NPs) with multi-functionalities have been developed as nano-carriers for sustained release, molecular targeting, and environmental responsiveness in the biomedical fields, due to their high drug loading and cellular uptake efficacies. Bio-inspired from virus with characteristic rod-like shape for efficiently entering cells, rod-like nanoparticles have been developed and also confirmed to have more excellent cellular uptake efficacy than spherical nanoparticles. Therefore, various rod-like nanoparticles have been prepared by liposomes, peptide, polylactide (PLA), chitosan, and other polymers. Among them, PLA has attracted considerable attention, due to they are synthesized from renewable resources and are nontoxic after biodegradation for various applications in the industry, agriculture, and biomedical fields. Up to now, particularly, hollow PLA nanomaterial surfaces can be generally achieved by two methods. The one is surface-initiated ring-opening polymerization (si-ROP) of lactide after preliminary surface modification of the nanomaterials. Mrózcyński et al. reported magnetic-PLA core-shell nanoparticles through a chemical linkage by si-ROP of lactide. Priftis group employed the “grafting from” technique to polymerize lactide on the surface of the carbon nanotube. Another method is that covering PLA coating on the nanomaterial surfaces by spin coating. However, the first process was relatively complicated and resulted in low inducing amount of PLA. The latter process might exist weak stick between PLA and templates. Therefore, a primary adhesive coating is advised to be covered on the one hand and connected the PLA on the other hand.

3,4-Dihydroxyphenylalanine (DOPA) and dopamine, the biomolecules that contain the catechol and amine functional groups, are found as an amino acid in the proteins of diverse animal species. Messersmith and other researchers demonstrated the PDOPA coating on the surfaces of the diverse substrates, such as metals, metal oxides, ceramics, synthetic polymers, and a wide range of other hydrophilic and hydrophobic materials by self-polymerization of DOPA at alkaline pH values. The PDOPA coating obtained from this methodology is very thin, approximately several nanometers. This thin PDOPA layer will provide important insights into their safety and efficacy as protein and drug carriers, due to DOPA is an amino acid resource. Accordingly, DOPA is indeed the molecule that could anchor to the materials to be adhesive covered on the template surface and connected the PLA polymer. Moreover, the formed crosslinking PDOPA layer could keep the...
particles stable, even after etching the nano-template. Therefore, by introducing the

![Diagram of PL-b-APDOPA/PDOPA nanocapsules](image)

**Scheme 1.** Synthetic illustration of PL-b-APDOPA/PDOPA nanocapsules

DOPA chains into the PLA polymer, the obtained PLA-PDOPA might be coated on the surface of the silica particles by one step.

It was well documented that silica nanoparticles are not immunogenic or toxic both in vivo and in vitro test[20]. Rod-like silica nanoparticles are of special interest because of their hydrophilic nature, easy colloidal suspension formation, easy removing by HF, surface functionalization. Modified silica nanorods have demonstrated potential applications for biomedicine, bioseparation and biocatalysis. Moreover, the silica nanorods had been found to have the ability of excellent cellular uptake efficacy and rapid clearance from urine.[6,30] Thus, silica nanorods are the suitable templates for preparation the high performance of hollow nanorods. However, there is no report to prepare PLA-PDOPA copolymer and further to fabricate the rod-like nanocapsules using silica nanorods as template.

Therefore, herein, we synthesized block-like poly(lactide)-b-amidated poly(3,4-dihydroxyphenylalanine) (PL-b-APDOPA) through amidation reaction between pre-prepared PLA and APDOPA. Then, DOPA and PL-b-APDOPA orderly adhesive coated on the surface of the silica nanorods. Subsequently, the PL-b-APDOPA/PDOPA nanocapsules were fabricated by removal of the silica template (Scheme 1). A model drug, Ibuprofen, was successfully entrapped into the capsules. The drug-loaded capsules showed a slow drug release behavior in vitro.

**Experimental Section**

**Materials**

Lactide was purchased from Tokyo Chemical Industrial Co., LTD and recrystallized from ethyl acetate, and then dried in vacuo at room temperature for 24 h. 3,4-Dihydroxyphenylalanine (DOPA, 99%), Boc-t-butoxycarbonyl (99%), tert-butyl(dimethyl)silyl chloride (TBDMs, 97%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 99%), tetrabutyl ammoniumfluoride (TBAF, 99%), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 99%), hydroxybenzotriazole (HOBT, 99%), and Ibuprofen were obtained from Aladdin Reagent Co., Ltd. (Shanghai, China) and used without purification. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was purchased from Life Technologies co., LTD. Methanol, succinic anhydride, acetonitrile, ethanol, chloroform, dichloromethane (DCM), polyvinylpyrrolidone (PVP, 98%), potassium bisulfate, sodium citrate dehydrate, amino propanol, ammonium hydroxide, dicumyl peroxide, hydrofluoric acid (HF) and triethylamine (TEA) were bought from sinopharm Chemical Industrial Co. Ltd and used as received. Dulbeco’s modified eagle medium (DMEM), fetal bovine serum (FBS) and penicillin-streptomycin (P/S) were purchased from Gibco. NIH/3T3 cells were purchased from Biomedical Co., Ltd., China.

**Synthesis of APDOPA(TBDMS)₂**

Synthesis of APDOPA(TBDMS)₂ was according to the previous reports[31]. Firstly, 3.0 g DOPA was added into a stirred solution of TBDMS (6.28 g) in anhydrous acetonitrile. The colorless suspension was cooled in an ice bath for 10 min and addition of DCM (6.5 mL) was subsequently dropped into the above solution. After further reacted in the ice bath for 4 h, it was stirred at room temperature for an additional 20 h. A colorless solid DOPA(TBDMS)₂ was obtained by evaporating the solvent in vacuo, washed with chloroform, and further purified with methanol/acetonitrile by three dissolving/precipitation cycles. The yield was about 40%.

**H NMR (CDCl₃):** 0.18 (m, 12H), 1.03 (s, 9H), 2.90 (m, 2H), 3.90 (m, 1H), 6.65–6.80 (m, 3H). M_{w}/M_{n}: 1.24.

Then, 2.12 g of DOPA(TBDMS)₂ was added into 50 mL DCM containing 1.91 g of EDC, 2.73 g of HOBT and 10 mL TEA, and the mixture was kept at room temperature for 24 h. APDOPA(TBDMS)₂ was obtained by extraction with DCM for three times and dried in vacuo. **H NMR (CDCl₃):** 0.18 (m, 12H), 1.03 (s, 9H), 2.90 (m, 2H), 3.90 (m, 1H), 6.65–6.80 (m, 3H). M_{w}/M_{n}: 1.24.

**Synthesis of H₂N-PLA-COOH**

Amino propanol (20 mmol) and Boc-t-butoxycarbonyl (22 mmol) were dissolved in chloroform, and then the mixture was placed at room temperature for 24 h. After the reaction finished, Boc-amino propanol was obtained by washing with potassium bisulfate, deionizing water for several times, and then drying in vacuo at room temperature. Then, L-lactide (3 g) was dissolved in 2 mL dimethylenzene containing 9 mg of stannous octoate. The Boc-amino propanol (185 mg) was added into the above mixed solution, and the reaction was heated to 160 °C and kept for 12 h[32]. Once the polymerization finished, the reaction mixture was cooled to room temperature and resulted a solid. Boc-HN-PLA was finally purified by dissolving in chloroform and precipitated in an excess of diethyl ether for three times, and dried under vacuum. Boc-HN-PLA (1 g) and succinic anhydride (0.25 g) were added into a flask and reacted for 6 h under 160 °C. The product H₂N-PLA-COOH was purified by dissolving in chloroform and precipitated in diethyl ether, and then dried at room temperature under a vacuum. M_{w}/M_{n}: 4000, and M_{w}/M_{n}: 1.18.

**Synthesis of PLA-b-APDOPA block-like copolymer**

H₂N-PLA-COOH (1.5 g) and APDOPA(TBDMS)₂ (0.23 g) was dissolved in methanol. Two solutions were mixed and reacted at 25 °C for 24 h, in the presence of EDC and HOBT as catalysts. Block-like (PLA-b-APDOPA)x (abbreviated as PLA-b-APDOPA) polymer was obtained by using TBAF to remove the TBDMS groups, and then was further purified by dissolving in acetone to remove the unreacted PLA and dialysis in ethanol to remove APDOPA.

**Synthesis of rod-like silica**
Polyvinylpyrrolidone (30 g) was dissolved in n-amyl alcohol (300 mL) by sonication for 2 h. Then, ethanol (30 mL), ultrapure water (8.4 mL), and 0.18 mol/L sodium citrate dehydrate (2 mL) were added into PVP solution. After the mixture formation, TEOS (3 mL) and ammonium hydroxide (6.75 mL) were added into the mixture and reacted for 12 h at room temperature. The precipitate nanorods were collected by centrifuging and washing with ethanol and water for three times.

Polymer coating on silica nanorods

Firstly, 40 mg of the silica nanorods were dispersed in 40 mL Tris buffer (pH=8.5). DOPA (80 mg) was added and continuously stirring at room temperature for 24 h to form PDOPA polymer layer. The PDOPA coated silica nanorods (PDOPA@SiO₂) were centrifuged, followed by washing with water. PLA-b-APDOPA/PDOPA@SiO₂ nanorods were fabricated by coating PLA-b-APDOPA on the surface of the PDOPA@SiO₂ nanorods, which were the same process as the PDOPA@SiO₂ nanorods.

Preparation of PLA-b-APDOPA/PDOPA nanocapsules

PLA-b-APDOPA/PDOPA capsules were obtained after removing the template particles using 2 M HI/8 M NH₄F solution at pH 5. The PLA-b-APDOPA/PDOPA@SiO₂ nanorods (20 mg) were added into 10 mL of Tris buffer (pH=5) aqueous solution, and the mixture stirred at room temperature for 12 h. The nanoparticles were collected by centrifugation and then dispersed in water (10 mL) for three times and then dried at room temperature under a vacuum to obtain the PLA-b-APDOPA/PDOPA nanocapsules.

In vitro cell cytotoxicity of the nanocapsules

In this experiment, positive group, sample group, and negative group were designed. NIH/3T3 cells were firstly placed into a plastic dish with 3.5 cm diameter (5×10⁴ cells/well) in complete DMEM (with 10% FBS) and incubated at 37 °C in a 5% CO₂ incubator for 24 h. Then, 10 μL DMSO and PLA-b-APDOPA/PDOPA nanocapsules suspension added into the 90 μL culture medium, respectively, and these two mixtures were centrifuged and washed with PBS (pH 7.4) at a constant temperature of 37 °C. At regular intervals, 100μL solution was taken out for UV absorption measurement at a wavelength of 264 nm.

In Vitro Drug Release

Ibuprofen-encapsulated nanocapsules were dispersed in 5mL PBS (pH 7.4) at a constant temperature of 37 °C. At regular intervals, 100μL solution was taken out for UV absorption measurement at a wavelength of 264 nm, and an equal volume of blank PBS was added.

Characterization

Fourier transform infrared (FTIR) spectra were recorded with a Nicolet iSS5 infrared spectrometer (Thermo Fisher Scientific) in the range of 400–4000 cm⁻¹ with a resolution of 4 cm⁻¹. ¹H NMR spectra were recorded on a AVANCE III HD 400MHz spectrometer(Switzerland) in CDCl₃. The purified and dried samples were subjected to thermo gravimetric analysis (TGA) under air using a Mettler Toledo TGA instrument at a heating rate of 20 °C·min⁻¹ from 50 to 600 °C under oxygen. Transmission electron microscopy (TEM) image were taken with JEM-2100 field emission microscope. For the TEM observations, samples were dispersed in deionized water and then dried on a holey carbon film Cu grid. Scanning electron microscopy (SEM) image was taken with Hitachi S-4800 electron microscope. For the SEM observations, samples were dispersed in deionized water and then dried on silicon slice. Fluorescent microscopy image was taken with a Fluorescent microscopy (Nikon 80i). X-ray photoelectron spectroscopy (XPS) was carried out using an energy analysis instrument (Thermo ESCALAB 250) with an Al Ka X-ray source and ultrahigh vacuum (~10^-10 mbar).

Drug encapsulating into the nanocapsules

A certain amount of nanocapsules was added into 2 mL ibuprofen/ethanol solution (2 mg/mL) for 24 h. Then, the ibuprofen-encapsulated nanocapsules were centrifuged, dried by lyophilization and kept for further study. The supernatant of the ibuprofen solution after separated the nanocapsules was collected to determine the encapsulation efficiency by UV spectroscopy at a wavelength of 264 nm.

Encapsulation Efficiency = (C_{ibuprofen} × C_{free}/C_{total}\cdot ibuprofen)×100%

Encapsulation Content = (C_{total}\cdot ibuprofen - C_{free}\cdot ibuprofen)/W_{nanocapsules}×100%

Scheme 2. Schematic representation for the synthesis process of (PLA-b-APDOPA)x (abbreviated as PLA-b-APDOPA)
The PLA-b-APDOPA copolymer was further coated on the surface of the PDOPA@SiO₂ nanorods in the pH 8.5 buffer solution. The diameter of the obtained PLA-b-APDOPA/PDOPA@SiO₂ nanorods was slightly bigger (about 210 nm) than that of the PDOPA@SiO₂ nanorods, as shown in Fig. 2c. Moreover, the surface of the PLA-b-APDOPA/PDOPA@SiO₂ nanorods was also roughness. Previous studies have successfully proved that nano-scale with rough surface had excellent cellular uptake efficacy. Thus, the PLA-b-APDOPA/PDOPA@SiO₂ nanorods might enhance the cellular uptake.

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Coating on the SiO$_2$ nanorods with PDOPA and PLA-b-APDOPA was further confirmed by XPS spectra of the resulting SiO$_2$, PDOPA@SiO$_2$, and PLA-b-APDOPA/PDOPA@SiO$_2$ nanorods. In the XPS spectrum of the SiO$_2$ nanorods (Fig. 4a), the SiO$_2$ nanorod surfaces showed Si2p (~102 eV), C1s (285 eV), and O1s (532 eV) peaks. The O1s, Si2p peaks corresponded to the SiO$_2$ surfaces showed Si2p (~102 eV), C1s (285 eV), and O 1s (532 eV) peaks, remaining in the XPS spectrum of the PLA-b-APDOPA/PDOPA@SiO$_2$ nanorods. In the XPS spectrum of the SiO$_2$ nanorods (Fig. 4a), the SiO$_2$ nanorod surfaces showed Si2p (~102 eV), C1s (285 eV), and O1s (532 eV) peaks. The O1s, Si2p peaks corresponded to the SiO$_2$ nanorod and the C1s peak might belong to the remaining stabilizer. After the coating of PDOPA, the intensity of C1s increased (Fig. 4b). Particularly, a new N1s peak at 399 eV appeared, which belonged to the characteristic component of PDOPA. However, the Si2p peak still existed, which indicated that PDOPA layer was very thin (same to the result from TGA curve in Fig. 3) and the coating of PDOPA on the silica surface was incomplete (also confirmed by SEM image in Fig. 2b). However, after the coating of PLA-b-APDOPA on the surface of the PDOPA@SiO$_2$ nanorods, there were only two peaks, i.e., the C1s and O1s peaks, remaining in the XPS spectrum of the PLA-b-APDOPA/PDOPA@SiO$_2$ nanorods (Fig. 4c). The peak intensities of C1s and O1s increased significantly, while the Si2p and N1s peaks disappeared. These results indicated that the surface component of the resulting nanorods was PLA polymer chains and the PLA layer were relatively thick. SEM and TGA measurements also indicated the thick coating layer and large coating amount (55.3% in Fig. 3) of the PLA-b-APDOPA copolymer on the silica nanorods.

**Formation of the PLA-b-APDOPA/PDOPA nanocapsules**

By dispersing the PLA-b-APDOPA/PDOPA@SiO$_2$ nanorods in HF/NH$_4$F (pH = 5), the silica template was etched from the core, and the hollow PLA-b-APDOPA/PDOPA nanocapsules were then produced. Fig. 2d shows the morphology of the PLA-b-APDOPA/PDOPA nanocapsules. The core of the nanorods became white from the image, suggesting the capsules formation. Moreover, after removal of the silica nanorods, the length of the nanocapsules became shorten, from average 1.5 μm to 500 nm, whereas the diameter of the nanocapsules was broaden from 200 nm to 350 nm, compared with the PLA-b-APDOPA/PDOPA@SiO$_2$ nanorods. These size changes were possibly due to the change of osmotic pressure between the inner and outer of the capsules by a lack of supporting template and for keeping the lowest surface energy of the nanocapsules. Moreover, it was the crosslinking bond in the self-polymerized PDOPA layer that kept the rod-like shape of the nanocapsules to avoid dissociation during the process of silica removing.

**Cytotoxicity studies of the PLA-b-APDOPA/PDOPA nanocapsules**

The cytotoxicity of the PLA-b-APDOPA/PDOPA nanocapsules was estimated using NIH/3T3 cells as the model cells by MTT assay method, and the results are shown in Fig. 5a. By changing the concentration of PLA-b-APDOPA/PDOPA nanocapsules from 0.5 to 2 mg/mL, the cell viability for the nanocapsules was about 88% independently on the nanocapsule concentration. Thus, these PLA-b-APDOPA/PDOPA nanocapsules exhibited negligible cytotoxicity to the cells.

Moreover, the morphology of the cell growth was also observed by fluorescence microscopy. Fig. 5b shows the NIH/3T3 cell adhesion on the PLA-b-APDOPA/PDOPA nanocapsules. It is clear that NIH/3T3 cells showed well adhered and proliferated on PLA-b-APDOPA/PDOPA, indicating the well cell biocompatibility of the PLA-b-APDOPA/PDOPA nanocapsules.

**Drug encapsulating and in vitro release**

Ibuprofen, as a model hydrophobic drug, was easily encapsulated into the PLA-b-APDOPA/PDOPA nanocapsules, due to non-covalent interactions such as the hydrophobic interactions, π-π interactions and hydrogen bond interactions. The drug encapsulation content and encapsulation efficiency were measured to be about 12% and 48%, respectively.
In vitro drug release of ibuprofen from the PLA-b-APDOPA/PDOPA nanocapsules was performed at 37 °C in different buffer solutions (pH 7.4 and pH 5.8). As shown in Fig. 6, there was no dramatic burst release of ibuprofen appeared in pH 7.4 and pH 5.8 buffer solutions. The release rate of ibuprofen in pH 7.4 buffer was much higher than that in pH 5.8 buffer, and about 60% and 10% of ibuprofen released from the nanocapsules within 500 min. The slow release rate might distribute to the crosslinking of the nanocapsules. The difference in drug release behavior between pH 7.4 and pH 5.8 was probably due to the following two reasons. Firstly, ibuprofen is more soluble in neutral and basic solutions than in acidic solution, resulting in it could come out of the capsules and dissolve in the buffer solution at pH 7.4. Secondly, the interactions of hydrogen bond interactions between ibuprofen and nanocapsules at pH 7.4 might be weaker, compared to the interactions at pH 5.8, due to the partly oxidation of DOPA. Moreover, both ibuprofen and DOPA molecular chains contain the carboxyl groups, and the electrostatic repulsive force between the ibuprofen and nanocapsules increased in pH 7.4 buffer solution.

Thus, ibuprofen could be controlled release from the PLA-b-APDOPA/PDOPA nanocapsules depending on the pH condition. Since there are multifunctional groups such as carboxyl, amine and catechol groups in DOPA, DOPA might have the strong interaction with various drugs (or cells). Thus, different drugs might showed different release behaviour, which was depending on the drugs solubility in pH buffers and the interactions between the drugs and the nanocapsules. Thus, we are now further intensively studying the encapsulation and release mechanism of the various drugs in the PLA-b-APDOPA/PDOPA nanocapsules.

Fig. 6 Drug release from the encapsulated PLA-b-APDOPA/PDOPA nanocapsules in pH 7.4 and pH 5.8

Conclusions

Block-like PLA and APDOPA copolymer was synthesized through amidation reaction between pre-prepared functional PLA and APDOPA. DOPA and the obtained PLA-b-APDOPA copolymer could be adhesive coated on the surface of the silica nanorods. SEM images showed the formed nanorods with roughness surface. XPS and TGA results indicated the formation of the thin PDOPA layer and thick PLA-b-APDOPA layer on the silica surface. The PLA-b-APDOPA/PDOPA nanocapsules were formed by removal of the silica template. The nanocapsules had hollow structure and well biocompatibility. Moreover, a model drug was successfully entrapped into the capsules, and could be slowly released from the nanocapsules in vitro depending on the pH buffers. The obtained rod-like nanocapsules has the potential application to be as carriers for the biomedical fields through oral taking or injection, according to the drug property.

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Notes and references

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Rod-like nanocapsules were facilely fabricated based on bio-based polymer by taking advantage of the DOPA properties. The obtained nanocapsules showed rough surfaces and high drug-loading efficacy. The drug could be further released depending on different pH buffer solutions.