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Single-chain folding of amphiphilic copolymers in water via intramolecular hydrophobic interaction and unfolding triggered by cyclodextrin

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ABSTRACT

Poly(ethylene glycol) methyl ether acrylate (PEGMEA) is copolymerized with 2-(ferrocenecarboxylate ethyl) methacrylate (EMA-Fc) and 4-(propoxy urethane ethyl acrylate) azobenzene (EMA-Azob), respectively. The nanoparticles can be obtained via the single-chain folding of these amphiphilic copolymers with hydrophilic poly(ethylene glycol) (PEG) side chains and hydrophobic ferrocene (or azobenzene) pendant groups in dilute aqueous solution via intramolecular hydrophobic interaction. After the addition of cyclodextrin, the inclusion complex can be formed between cyclodextrin and ferrocene (or azobenzene) pendant groups, which makes the amphiphilic copolymers hydrophilic and triggers the chain unfolding of the nanoparticles in aqueous system. Such kind of process has potential application in the fields of drug delivery systems and their controlled release, sensors, controllable catalysis, mimicry of biomacromolecules, as well as other fields.

1. Introduction

Polymer nanoparticles via single-chain folding and intramolecular crosslinking in dilute solution have become an appealing research area, which allows the facile preparation of the nanoparticles in 5–20 nm and has potential applications in the field of nanomedicine, catalysis, sensors, as well as mimicry of biomacromolecules [1–9]. Diverse crosslinking strategies, including covalent bonding [10–16], dynamic covalent bonding [17–19], and non-covalent interaction [20–27], have been adopted to achieve single-chain folding. Especially, the single-chain polymer nanoparticles (SCPNs) via intramolecular supramolecular interaction possess the virtues of stimuli-responsiveness and can respond to the external stimuli (such as pH, light, redox, temperature, electrochemistry, and so forth). Upon the external stimuli, the polymer chains can change their structure and morphology. The hydrophobic interaction is a useful method to prepare supramolecular nanoparticles. Akashi et al. [28,29] reported that amphiphilic copolymers of poly(γ-glutamic acid)-*graft*-L-phenylalanine (γ-PGA-Phe) with various lengths of γ-PGA chains plus hydrophobic Phe side chains can be self-assembled into the nanoparticles in aqueous media. Sawamoto et al. [30] reported the single-chain folding of amphiphilic methacrylate copolymers in water and the folding-unfolding transition on addition of methanol or by elevated temperature. The hydrophobic nanospace in these nanoparticles is the potential space for drug loading. With rapid growing in fabricating nanoparticles with stimuli-responsiveness via non-covalent interaction, the new types of synthetic methods and triggers for stimuli-responsiveness are necessary to achieve intramolecular collapsing.

In present study, poly(ethylene glycol) methyl ether acrylate (PEGMEA) is copolymerized with 2-(ferrocenecarboxylate ethyl) methacrylate (EMA-Fc) and 4-(propoxy urethane ethyl acrylate) azobenzene (EMA-Azob), respectively. These amphiphilic copolymers can undergo single-chain folding in dilute aqueous solution via intramolecular hydrophobic interaction and form single-chain nanoparticles, which can form host-guest complex with

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cyclodextrin and trigger the unfolding of the chain again. Such kind of nanoparticles have potential applications in the fields of drug delivery systems and their controlled release, sensors, controllable catalysis, mimicry of biomacromolecules, as well as other fields.

2. Experimental

2.1. Materials

2-Hydroxyethyl methacrylate, ferrocenecarboxylic acid, 3-bromo-1-propanol, α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), 4-hydroxyazobenzene, dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP) were obtained from Energy Chem. Co.. 2-Isocyanatoethyl acrylate was obtained from J & K Chem. Co.. PEGMEA was obtained from Sigma-Aldrich Co.. N, N-dimethyl formamide (DMF), azobisisobutyronitrile (AIBN), dichloromethane, sodium sulfate, and other chemicals were all analytical grade and purchased from Shanghai Chem. Reagent Co.. AIBN was recrystallized from ethanol. All other reagents were used without further purification. 3-Benzylsulfanylthiocarbonylsufanylpropionic acid was synthesized according to the method in literature [31].

2.2. Synthesis of EMA-Fc

2-Hydroxyethyl methacrylate (1.43 g, 11 mmol), ferrocenecarboxylic acid (2.3 g, 10 mmol), DCC (4.12 g, 20 mmol), and DMAP (0.12 g, 1 mmol) were dissolved in 100 mL dry CH_2Cl_2 and stirred for 24 h at room temperate. The resulted mixture was filtered and the organic phase was washed with 100 mL water. After the organic layer was dried with Na_2SO_4, the product was purified by column chromatography (CH_2Cl_2/petroleum ether, 3/1, v/v) yield 2.46 g solid (yield: 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (s, 1H), 5.62 (s, 1H), 4.83 (s, 2H), 4.46 (s, 3H), 4.42 (s, 2H), 4.21 (s, 4H), 1.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.54, 167.19, 136.02, 126.10, 71.48, 70.62, 70.22, 69.81, 62.69, 61.99, 18.33. FTIR (cm^{-1}): 3109 (Ar-C-H), 2984-2790 (−CH_2-), 1700 (C=O), 1636 (C=C). LC-MS (ESI+) *m/z* calculated for $C_{17}H_{18}FeO_4$ $(M + Na)^+$ 365.00, observed 365.00.

2.3. Synthesis of EMA-Azob

4-Hydroxyazobenzene (1.98 g, 10 mmol) and K_2CO_3 (3 g, 21.7 mmol) were suspended in 30 mL dry DMF, and heated to 75 °C, then 3-bromo-1-propanol (1.52 g, 11 mmol) was added dropwise to the mixture and stirred for 6 h. The resulted mixture was poured into 200 mL water and then extracted with 3 × 50 mL CH_2Cl_2. After the organic layer was dried with Na_2SO_4, the product was purified by column chromatography (EtOAc/CH_2Cl_2, 1/6, v/v) to yield 2.1 g orange solid (yield: 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.85 (m, 4H), 7.54–7.47 (m, 2H), 7.47–7.40 (m, 1H), 7.06–6.99 (m, 2H), 4.21 (t, J = 6.0 Hz, 2H), 3.90 (t, J = 5.9 Hz, 2H), 2.15–2.04 (m, 2H), 1.72 (s, 1H).

4-(3-Hydroxypropyloxy) azobenzene (1.28 g, 5 mmol), 2-isocyanatoethyl acrylate (0.8 g, 5.6 mmol), and two drops of dibutyltin dilaurate (DBTL) were dissolved in 50 mL dry THF. The mixture was stirred for 24 h and then the solvent was evaporated under reduced pressure. The product was purified by column chromatography (EtOAc:CH_2Cl_2, 1:10) to yield 1.82 g orange solid (yield: 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93–7.85 (m, 4H), 7.50 (t, J = 7.4 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 6.43 (d, J = 17.3 Hz, 1H), 6.12 (dd, J = 17.3, 10.4 Hz, 1H), 5.86 (d, J = 10.4 Hz, 1H), 5.02 (s, 1H), 4.29 (t, J = 6.1 Hz, 2H), 4.25 (t, J = 5.2 Hz, 2H), 4.12 (t, J = 6.1 Hz, 2H), 3.50 (dd, J = 10.7, 5.4 Hz, 2H), 2.27–1.94 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.08, 161.28, 156.38, 152.75, 147.04, 131.50, 130.40, 129.05, 127.95, 124.76, 122.56, 114.70, 64.71, 63.56, 61.74, 40.19, 28.94.

2.4. Synthesis of poly(2-(ferrocenecarboxylate ethyl) methacrylate-co-poly(ethylene glycol) methyl ether acrylate) (P(EMA-Fc-co-PEGMEA))

PEGMEA (0.96 g, 2.08 mmol), EMA-Fc (0.342 g, 1 mmol), 3-benzylsulfanylthiocarbonylsufanylpropionic acid (5 mg, 0.023 mmol), and AIBN (1 mg, 0.006 mmol) were dissolved in 2 mL DMF and the solution was degassed by bubbling nitrogen for 30 min and then placed in oil at 75 °C for 48 h. Subsequently, the mixture of the polymerization was dialyzed with water and then treated with freeze-drying (0.83 g, yield: 64%).

2.5. Synthesis of poly(4-(propoxy urethane ethyl acrylate) azobenzene-co- poly(ethylene glycol) methyl ether acrylate) (P(EMA-Azob-co-PEGMEA))

PEGMEA (0.96 g, 2.08 mmol), EMA-Azob (0.397 g, 1 mmol), 3-benzylsulfanylthiocarbonylsufanylpropionic acid (5 mg, 0.023 mmol), and AIBN (1 mg, 0.006 mmol) were dissolved in 2 mL DMF and the solution was degassed by bubbling nitrogen for 30 min and then placed in oil at 75 °C for 48 h. Subsequently, the mixture of the polymerization was dialyzed with water and then treated with freeze-drying (0.92 g, yield: 68%).

2.6. Characterization

^{1}H NMR, ^{13}C NMR, and NOESY NMR measurements were carried out on a Bruker AMX 300 spectrometer, DMSO-d_6, $CDCl_3$, and D_2O as the solvent respectively. FTIR analysis of the samples was carried out on a thermo Bruker EQUINOXSS/HYPERION2000 spectrometer. Mass measurement was performed on a Shimadzu Prominance-LCMS 2020 equipped with a SPD-20A photodetector (200–800 nm) and an MS spectrometer (MS, 2020; *m/z* range: 10–2000; ionization modes: ESI+). GPC measurement was performed on a Waters Alliance HPLC system, THF as the solvent and polystyrene as the standard. The apparent molecular weight of the polymers was calculated relative to linear polystyrene standard. TEM measurement of the samples was performed on Hitachi H-600, operating with an acceleration voltage of 150 KV. TEM samples were prepared by placing one drop of nanoparticle solution on a 200 mesh carbon-coated copper grid. The average particle size of the nanoparticles was also determined on DLS (Malvern Autosizer 4700), equipped with a solid-state laser (ILT 5500 QSL, output power 100 mW at λ = 532 nm) as light source. The solution was filtered through a 0.45 μm filter before DLS measurement. The height and size distribution of the nanoparticles were determined by tapping-mode AFM (SPA-300HV, Seiko Instruments Inc.). The standard silicon tips were used. The samples were prepared by drop-casting 10 μL solution of the nanoparticles (c = 0.01 mg/mL) on silicon wafer and dried at ambient temperature.

3. Results and discussion

3.1. Synthesis of P(EMA-Fc-co-PEGMEA)

Firstly, EMA-Fc was synthesized via esterification reaction between 2-hydroxyethyl methacrylate and ferrocenecarboxylic acid (DCC as the dehydrating agent and DMAP as the catalyst), as shown in Fig. 1(a). Its structure can be confirmed by ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectra (Figs. S1–S4 in Supplementary data (SD)). P(EMA-Fc-co-PEGMEA) was synthesized via reversible addition fragmentation chain transfer (RAFT) polymerization, AIBN as the initiator, 3-benzylsulfanylthiocarbonylsufanylpropionic acid as the chain transfer agent. Fig. 1(b) shows the synthetic route to P(EMA-Fc-co-PEGMEA). P1 and P2, two kinds of P(EMA-Fc-co-PEGMEA),