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Preparation of polyoligo(ethyleneglycol) methacrylate decorated with pendant cholesterol moieties: Hydrogel and mesoglobule preparation and their use for entrapping lipophilic nanomaterials

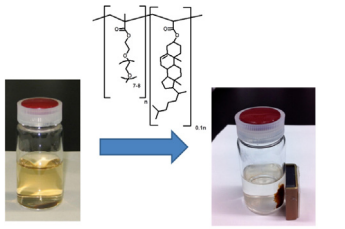
Frederic Delbecq [a,*], Kohsaku Kawakami [b]

[a] NIMS, National Institute for Material Science, 1-1, Namiki, Tsukuba, Ibaraki 305-0044, Japan
[b] Smart Biomaterials Group, Biomaterials Unit, Nano-Bio Field, MANA, National Institute for Materials Science, 1-1 Namiki, Tsukuba, Ibaraki 305-0044, Japan

HIGHLIGHTS

- Cholesterol-based hydrogel and water soluble mesoglobules were prepared.
- Physico-chemical analyses such as critical aggregation concentration were carried out.
- The ability for embedding hydrophobic nanomaterials was also tested.

GRAPHICAL ABSTRACT



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ABSTRACT

A long (oligoethyleneglycol) methacrylate and cholesteryl acrylate were polymerized together using two different free-radical polymerization conditions. A surfactant- and cross-linker-free emulsion polymerization afforded a white opaque hydrogel. By contrast, a polymerization performed in the presence of AIBN led to the formation of large water-soluble mesoglobules of associated polymer micelles that were stable at room temperature. Both of these materials were characterized by ^{1}H NMR and Fourier transform infrared (FT-IR) spectroscopies, and the morphology of the hydrogel was also observed by SEM. The swelling ratio of the gel was measured in water, and the fluorescence probing of the mesoglobules and the capacity for entrapping hydrophobic nanomaterials were studied using magnetic iron oxide nanoparticles.

1. Introduction

It is well known that modified poly(polyethylene glycol) methacrylate (POEGMA) exhibits different responsive properties as a smart biocompatible biomaterial. After atom transfer radical polymerization (ATRP) is employed to prepare copolymers of OEGMA that exhibit different pendant hydrophilic chain lengths, these temperature-responsive polymers have been used as models for fundamental investigation of their phase transition, which is characterized by the lower critical temperature (LCST) measured in water or in a buffer of interest [1,2]. The biocompatibility of POEGMA, which is superior to that of poly(*N*-isopropyl) acrylamide (PNIPAM), allowed most of the POEGMA-based materials to be used in many research fields, such as biomedical, biotechnology and nanotechnology [3–7]. The measured LCST values of these polymers vary with the side chain length of OEGMA and with the molecular weight of the synthesized polymers. This value can also be

* Corresponding author. Tel.: +81 29 854 7800.
E-mail addresses: Frederic.delbecq@gmail.com, DELBECQ.Frederic@nims.go.jp (F. Delbecq).

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modulated by copolymerization with a more hydrophobic monomer. The free-radical polymerization of OEGMA may lead to the formation of random copolymers. Therefore, POEGMA has been used for the preparation of nano or microspheres, such as micelles, vesicles, nanogel capsules, and core-shell particles with organic and inorganic cores [8]. In our study, we focused on the free radical polymerization of OEGMA (MW = 475) copolymerized with a synthesized cholesteryl acrylate using two different conditions for the free radical polymerization. We have chosen the cholesteryl pendant moiety due to its recognized biocompatibility and capacity to interact with cellular membranes.

Recently, modified polyelectrolytes or water-soluble polymers with pendant cholesteryl moieties have been studied [9–11]. In general, the resulting random polymers of water-soluble acrylamide monomers, which incorporated less than of 10% of the cholesteryl monomers in its backbone, exhibited a strong tendency for interpolymer chain association in water even at a very low concentration. The chains self-assemble into large structures called mesoglobules, which are stable at room temperature. In addition, these hydrophilic materials displayed a closed type multipolymer flower micelle structure with a number of hydrophobic microdomains in one polymer assembly. This type of material is also expected to entrap various types of hydrophobic species inside their cavities due to strong non-covalent hydrophobic and supramolecular interactions. For our purpose, magnetic iron oxide nanoparticles (MNPs) were easily prepared by co-precipitation mixing of the chemical precursors (i.e., Fe II and Fe III ions) in the presence of ammonia with excess oleic acid (OA) [12]. After extraction with toluene, the resulting oleic acid bilayer-coated MNPs were ready for surface modifications, such as ligand exchange followed by condensation with an amino silane. Recently, when polyacrylic acid (PAA) was used as a stabilizer, a generation of nonaggregated magnetic composite microspheres was prepared [13], and it has received much attention in the medical science field due to their multifunctional properties, such as surface effects, quantum size effects, macroscopic quantum tunneling effect and easy recovery, which is aided by a magnetic field to avoid centrifugation. In this work, we report the preparation of a physically cross-linked hydrogel and water-soluble mesoglobules, which were both loaded with OA-coated MNPs. The analysis of the composite materials was carried out using FT-IR and ^{1}H NMR spectroscopies, FE-SEM observation, UV emission of pyrene embedded in the mesoglobules and the measurement of the turbidity variation.

2. Experimental

2.1. Materials

Oligo(ethylene glycol) methacrylate (MW = 475) was purchased from Aldrich USA. The monomer was purified by filtration on Al_2O_3 (basic-type) column. Cholesterol, acryloyl chloride, azo bisisobutyronitrile (AIBN), oleic acid, pyrene and triethylamine (TEA) were purchased from TCI, Japan. The organic solvents were purchased from Wako Chemicals, Japan and the water used in the experiments was Millipore Milli-Q grade. Iron(II) sulfate heptahydrate, iron(III) chloride hexahydrate and potassium peroxodisulfate (KPS-$K_2S_2O_8$) were purchased from Nacalai Tesque Japan, Inc., Kyoto Japan.

2.2. Preparation of CholA monomer

To 50 mL of $CHCl_3$ were added 2.00 g (5.18 mmol) of cholesterol and 2.61 g (25.90 mmol) of TEA. The resulted solution was stirred and cooled with an ice bath, then followed by addition of 2.34 g (25.30 mmol) of acryloyl chloride drop wise. The solution was stirred at room temperature overnight. The organic layer was successively washed with deionized water, and 10% HCl aqueous solution before being dried on Na_2SO_4. The organic layer was evaporated in vacuum to afford yellow crude which is purified on silicagel with $CHCl_3$ as eluant. After evaporation of the filtrate, the resulted crude was recrystallized from ethanol to afford a white cream solid (m = 1.27 g; yield = 56%).

^{1}H NMR ($CDCl_3$): δ 0.66–2.08 (m, 41H); 2.35 (d, 2H, J = 8.0 Hz); 4.69 (m, 1H); 5.37 (s, 1H); 5.79 (d, 1H, J = 1.6 Hz); 6.09 (m, 1H); 6.35 (d, 1H, J = 15.6 Hz). M.p. 65 °C [14] found 64–66 °C. FT-IR (KBr, cm^{-1}): 2939; 1720; 1638.

2.3. Preparation of POEGMA–CholA copolymer hydrogel via surfactant-free radical polymerization

To 10 mL of deionized water were added 1.25 g (2.63 mmol) of OEGMA and 0.05 g (0.13 mmol) of CholA. Then the resulted suspension was subjected to ultrasound treatment until the cholesteryl acrylate completely dissolved in the solution. Argon was bubbled for 20 min and 0.10 g (0.37 mmol) of KPS was added to the liquid. The mixture was finally allowed to stir under inert atmosphere at 80 °C for 5 h to get a white hydrogel which was purified by dialysis using a Float-a-Lyzer G2 (volume 5 mL, MWO 100 kDa) device immersed for a week in 100 mL of water at room temperature.

2.4. Preparation of linear OEGMA–CholA copolymers

In 10 mL of inhibitor free THF were dissolved 2.50 g (5.26 mmol) of freshly purified OEGMA and 0.1 g (0.26 mmol) of CholA, followed by argon bubbling for 15 min. Then 0.06 g (0.365 mmol) of AIBN was added to the solution which was stirred refluxing under inert atmosphere for 24 h. The solvent was removed under reduced pressure to afford colored oil purified by dialysis in 100 mL of water. The same procedure was employed for preparing a second polymer containing 10% of the Chol A monomer.

2.5. Gel permeation chromatography (GPC)

The number average molecular weight (Mn) and dispersity DPI (=Mw/Mn) of the synthesized polymers P1 and P2 were determined by GPC analysis using a Tosoh HLC-8220 GPC with DMF as eluant at 30 °C (1 mL/min) and a Shodex GPC-101 with aqueous acetonitrile solution respectively calibrated with narrow polymethylacrylate (PMMA) and polystyrene (PS) standards.

2.6. Preparation of OA bilayer capped MNPs

For preparing the MNPs, we employed the method found in the literature [12]. In 50 mL of deionized water, 1.17 g (4.22 mmol) of $FeSO_4$, $7H_2O$ and 2.05 g (7.59 mmol) of $FeCl_3$, $6H_2O$ were vigorously stirred until a yellow orange solution was formed. Then, 12 mL of 25% ammonia aqueous solution was added, followed by addition of 0.5 mL of oleic acid. The resulting black dispersion was allowed to stir at 80 °C for 2 h. The generated MNPs were analyzed by TEM and XRD analysis and the results were conformed to the datas found in the literature [12] with MNPs displaying 9 nm in diameter.

2.7. Nuclear magnetic resonance (NMR) spectroscopy

^{1}H NMR analysis of monomers and polymers were conducted using a JEOL 400SS 400 MHz spectrometer equipped with auto sampler at room temperature. Measurements were performed in $CDCl_3$ containing some amount of trimethylsilane (0.1%) at 25 °C.