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Regular Article

Poly(HEMA-*co*-HEMA-PFPA): Synthesis and preparation of stable micelles encapsulating imaging nanoparticles

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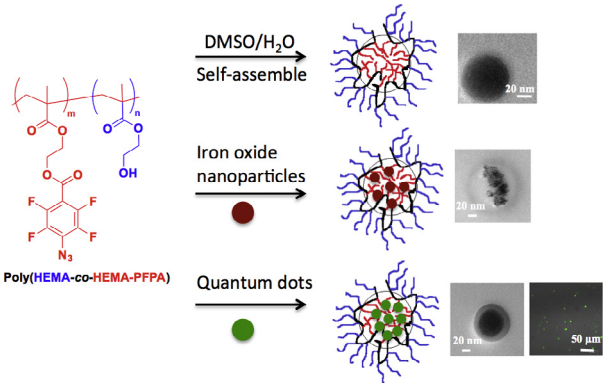
GRAPHICAL ABSTRACT



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ABSTRACT

We report the preparation of stable micelles from random copolymers of 2-hydroxyethyl methacrylate (HEMA) and perfluorophenyl azide (PFPA)-derivatized HEMA (HEMA-PFPA). The copolymers were synthesized by RAFT polymerization at room temperature under mild conditions without affecting the azide functionality. Upon addition of water to the copolymer solution in DMSO, the random copolymers self-assembled into micelles even at the percentage of HEMA-PFPA as low as 4.5%. The size of the micelles can be controlled by the molecular weight and the concentration of the copolymer, and the percentage of HEMA-PFPA in the copolymer. In addition, iron oxide nanoparticles and quantum dots were successfully encapsulated into the micelles with high encapsulation efficiency (~80%). These nanoparticles, which were hydrophobic and formed agglomerates in water, became fully dispersed after encapsulating into the micelles. The micelles were stable and the size remained unchanged for at least 6 months.

1. Introduction

Polymer micelles have been a topic of intense studies since their first discovery [1,2]. They are usually synthesized from amphiphilic block copolymers that self-assemble in the aqueous medium, where the hydrophobic block forms the core structure and the

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hydrophilic block forms the protecting corona. Like other types of micelles, polymer micelles are capable of encapsulating hydrophobic molecules such as non-polar drugs inside the core. This configuration enables the dispersion of non-polar substances that are otherwise insoluble in aqueous media, thus eliminating the additional synthetic effort to make the water-soluble version of the drug. The micelles also serve to protect the encapsulated substance and delay its interactions with the exterior environment, thus increasing its stability. In addition, the structure, composition, chemical functionality, and molecular weight of the polymer can be precisely controlled, and therefore the property, size and encapsulation capacity of the micelles can be tailored to suit specific applications. Polymer micelles have therefore been extensively investigated as vehicles for drug delivery. In addition, a targeting group can be introduced at the surface of the micelle for the targeted delivery.

Inorganic nanoparticles such as iron oxide nanoparticles and quantum dots (QDs) have been increasingly used in biomedical applications due to their unique optical, magnetic, and electronic properties. For example, magnetic iron oxide nanoparticles, such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), are used in magnetic targeting, *in vitro* purification, *in vivo* imaging, and thermal therapy [3]. A major issue with these nanomaterials is particle agglomeration, resulting from large specific surface area and high surface energy. To overcome this issue, various approaches have been developed to lower the surface energy of nanoparticles, including passivation of particle surface using appropriate ligands by either physisorption or chemisorption, and the introduction of a protecting shell such as silica or a polymer [3]. Amphiphilic polymers are excellent stabilizing agents for nanoparticles [4,5]. In this so-called steric stabilization, the non-polar block of the polymer anchors on the nanoparticle surface whereas the polar block serves as a steric barrier preventing particles from agglomeration. A practical method that has been developed to encapsulate nanoparticles inside micelles is flash nanoprecipitation, where an amphiphilic block copolymer and nanoparticles are mixed in a solvent that can disperse both materials. Water is then added to the dispersion, resulting in the formation of micelles that encapsulate the hydrophobic nanoparticles inside the cores [6,7].

Micelles can also be formed from random copolymers. Compared with block copolymers, random copolymers are more difficult to form micelles due to the higher entropic energy required to organize random copolymers into micellar structures. On the other hand, random copolymers are relatively easier to synthesize, for example, by conventional free radical polymerization from large selections of monomers without the need for complex chemical derivatization or stringent polymerization conditions. There are a number of examples where micelles are prepared from random copolymers [8–16]. The control over the self-assembly of random copolymers is usually through the hydrophobic-hydrophilic balance, while in block copolymers, it is governed by the nonpolar and polar chain length [16]. The common preparation method follows the protocol developed by Eisenberg et al. where micelles are formed by slowly adding water into the polymer solution [17]. Mechanism study by Li and coworkers suggests that the micelles form by stepwise aggregation of the polymer chains [12]. Upon the addition of water, the most hydrophobic chains aggregate first, leading to the formation of the micellar core structure. As the percentage of water increases, chains with lower hydrophobicity would start to aggregate as well. This process continues until all polymer chains have aggregated and colloidal spheres are formed. Fluorinated copolymers have shown to be an excellent choice for this purpose owing to the hydrophobic and the fluorophilic effects which effectively promote the copolymer aggregation to form stable micelles [18–22].

Poly(2-hydroxyethyl methacrylate) (PHEMA) was first synthesized and made into contact lenses in 1960 [23]. PHEMA is biocompatible and has excellent antifouling properties [24,25]. By preventing protein adsorption, the circulation lifetime of the micelles increases [2]. Micelles made from PHEMA have found wide uses in biomedical applications such as drug delivery [26], gene delivery [27], and biosensor [28]. Critical to these applications is the ability of the micelles to withstand the environmental challenge including the biological milieu. A stable colloid system is also important in designing an effective delivery system where a targeting molecule needs to be further introduced by chemical functionalization of the micellar surface [29].

Here, we report the synthesis of a new random copolymer consisting of HEMA and HEMA-PFPA (perfluorophenyl azide), and the formation of micelles based on this copolymer. The formation of micelles from random copolymers requires a balance between the hydrophobic and hydrophilic contents in the copolymer to promote self-assembly. It has been shown that PFPA is fairly hydrophobic and possess π-π stacking ability [4,30–32]. We therefore hypothesize that the copolymer of PHEMA and HEMA-PFPA would be able to self-assemble into micelles even at lower content of PFPA. Also, PFPAs have been used as an efficient photocoupling agent for surface functionalization and nanomaterial conjugation [33–36], and react readily with dipolarophiles and electrophiles without the use of any metal catalysts [37–40]. Thus, the PFPA can serve as the conjugation point for further functionalization of the copolymer and the micelle. In this article, we describe the synthesis of the random copolymer, poly(HEMA-*co*-HEMA-PFPA), by RAFT polymerization, and the formation of micelles by a simple precipitation method. Copolymers of different compositions were prepared by varying the mole ratio of HEMA and HEMA-PFPA in the feed, and the micelle formation and micellar structures were studied and characterized. The micelles were further used to encapsulate iron oxide nanoparticles and QDs to generate nanoparticle-encapsulated micelles.

2. Experimental section

2.1. Materials

Benzoyl peroxide (BPO, 98%), cadmium oxide (99.5%), chloroform, 2-cyano-2-propyl benzodithioate (CPBD, >97%), *N*,*N*-dimethylaniline (DMA), 4-dimethylaminopyridine (DMAP), dibenzyl ether (98%), dichloromethane (DCM), dimethylsulfoxide (DMSO, HPLC grade), diethyl ether, ethanol (200-proof), ethyl acetate, *N*-ethyl-*N*-(3-dimethylaminopropyl)carbodiimide (EDAC) hydrochloride, 1,2-hexadecanediol (85%), hexanes, 2-hydroxyethyl methacrylate (HEMA, 97%), hydrochloric acid, methanol, 1-octadecene (90%), octadecylamine (90%), oleic acid (90%), oleylamine (70%), selenium (99.5%), silica gel, sodium bicarbonate, sodium chloride, sodium hydroxide, sodium sulfate, stearic acid (95%), sulfur (99.5%), toluene, *p*-toluenesulfonic acid (TsOH) monohydrate, tri-*n*-butylphosphine (99%), tributylphosphine oxide, and zinc oxide (99%) were purchased from Sigma-Aldrich. Water used was from a Milli-Q water ultrapure water purification system. Methyl pentaflurobenzoate ($\geq$97%) and sodium azide were purchased from TCI America (Portland, OR). Iron (III) acetylacetonate was purchased from Acros Organics (Fair Lawn, NJ). Methylene chloride was dried over calcium hydride, and was distilled before use. Regenerated cellulose dialysis tubing with molecular weight cut-off at 12,000–14,000 was purchased from Fisher Scientific. HEMA was purified following a reported method with a slight modification [41]. Briefly, HEMA was distilled under reduced pressure at 70 °C, and water was then added at 1:4 v/v HEMA/water. The mixture was washed with hexanes 3–5 times to remove the