European Polymer Journal 85 (2016) 519–531

Contents lists available at ScienceDirect

European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

Macromolecular Nanotechnology

Controlled magnetite nanoclustering in the presence of glycidyl-functionalized thermo-responsive poly(*N*-isopropylacrylamide)

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ARTICLE INFO

Article history:
Received 6 June 2016
Received in revised form 30 October 2016
Accepted 1 November 2016
Available online 9 November 2016

Keywords:
Magnetite
Nanoparticle
Nanocluster
Poly(*N*-isopropylacrylamide)
Thermo-responsive

ABSTRACT

Glycidyl-functionalized poly(*N*-isopropylacrylamide) (PNIPAAm), synthesized *via* a reversible addition-fragmentation transfer polymerization (RAFT), was used for controlling degree of nanoclustering of magnetite nanoparticle (MNP). The polymer was grafted onto MNP *via* the ring-opening reaction between glycidyl groups at the PNIPAAm chain terminal and amino groups on the MNP surface to obtain thermo-responsive MNP nanocluster. Hydrodynamic size (D_h) and colloidal stability of the nanocluster, corresponding to the degree of nanoclustering reaction, can be regulated either by adjusting the ratio of MNP to the polymer in the reaction or by introducing glycidyl groups to the polymers. The size of the nanocluster ranged between 20 and 150 nm in diameter with about 10–120 particles/cluster. Thermogravimetric analysis (TGA) and vibrating sample magnetometry (VSM) were used to confirm the presence of the polymer in the nanocluster. A study showing indomethacin controlled release of these MNP nanoclusters was also performed. This stable nanocluster with magnetically guidable properties might be potentially used for entrapment of other bio-entities or therapeutic drugs with temperature-responsive properties for controlled release applications.

1. Introduction

In recent years, much attention has been paid in the study in magnetite nanoparticle (MNP) particularly in developing facile and efficient synthetic approaches to control its size, magnetic properties and chemical reactivity. Because of its high surface area-to-volume ratio, many attempts have been made in conjugating bioentities such as deoxyribonucleic acid (DNA) [1,2], peptide nucleic acid (PNA) [3,4], protein [5,6], amino acid [7] and antibodies [8,9], on the surface for potential uses in biomedical applications. Due to strong inter-particle attractive interactions such as Van der Waals force and magnetic force, they tended to agglomerate to form uncontrollable aggregate, resulting in the loss in nanoscale-related properties [10] and thus limiting its biomedical applications [11]. Coating the particle with long chain polymer is one of a promising approach to prevent the particle aggregation through a steric stabilization mechanism, resulting in improvement in stability and dispersibility in the media. In addition, the polymer coated on the particle surface also served as a platform for conjugation with functional biomolecules [12,13].

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http://dx.doi.org/10.1016/j.eurpolymj.2016.11.002
0014-3057/

Many applications, such as controlled drug delivery and magnetic separation of cells and antibodies, take advantages of magnetically guidable properties of MNP. In these applications, drug-conjugated or bioentity-conjugated MNP should have good magnetic responsiveness, so that they can rapidly respond to an external magnetic field. One of the promising approaches in enhancing magnetic responsiveness of MNP without the formation of macroscopic particle aggregation was to assemble them into the form of nanocluster. MNP nanocluster is composed of many interconnected single particles of ≈3–20 nm in size and minor amount of organic components [14]. Unlike micron-sized particles, formation of MNP nanocluster significantly increased magnetic responsiveness [15,16] as opposed to individual MNP and also maintained its dispersibility and stability in the media [17,18]. Importantly, its superparamagnetic properties should also be maintained as long as individual MNP core can be distinguished from each other after nanocluster formation, meaning that there was no one polycrystalline particle but a nanocluster with distinguishable particles smaller than 20 nm [19]. Controlling the degree of MNP nanoclustering with reasonable size will result in the nanocluster with good magnetic responsiveness, good dispersibility and stability in the media. Many approaches have been investigated in controlling the formation of MNP nanocluster such as physical or physicochemical interaction between pre-synthesized MNP and polymer particle [16,20], *in-situ* polymerization of monomers in the presence of MNP [21–23] and *in-situ* precipitation of MNP in the presence of polymer microsphere [24,25].

The study in the synthesis of MNP nanocluster coated with responsive polymers was rather limited [26,27]. In this work, preparation of MNP nanocluster coated with poly(*N*-isopropylacrylamide) (PNIPAAm) is presented. PNIPAAm functionalized with glycidyl methacrylate (GMA) was first synthesized *via* Reversible Addition Fragmentation Chain Transfer (RAFT) polymerization and then grafted onto MNP surface. RAFT polymerization, one of several types of controlled radical polymerization (CRP) techniques, was used in this work because it can produce polymers with controllable molecular weights and narrow polydispersity indices (PDIs) and can be performed under mild condition reactions in various reaction systems without using metal catalysts [28]. PNIPAAm is the most studied thermo-responsive polymer owing to its physiologically relevant transition temperature and relative insensitivity to pH and salt content [29]. It has a lower critical solution temperature (LCST) at 32 °C, which is close to that of human body [30]. Below its LCST, PNIPAAm is well soluble in water due to the formation of hydrogen bonding of the chains with water molecules, resulting in the formation of a swollen state. When increasing the temperature above its LCST, PNIPAAm deswells to a collapsed state due to the formation of hydrogen bondings among the polymer chains. This process is generally reversible, making the polymer to behave as an on-off system when the temperature is changed across the LCST. Syntheses of the copolymers containing PNIPAAm have been widely reported [31–35]. However, the studies in surface modification of MNP with PNIPAAm-containing copolymers are rather limited [36,37].

In this report, PNIPAAm was first synthesized *via* RAFT polymerization, followed by the functionalization with GMA units at the chain terminal. The chemical structures and functional groups of the synthesized PNIPAAm were characterized *via* proton nuclear magnetic resonance spectroscopy (^{1}H NMR) and fourier transform infrared spectroscopy (FTIR), respectively. It was then grafted to MNP through the ring-opening reaction of the glycidyl groups at the chain terminal with amino groups grafted on MNP surface and essentially induced the formation of MNP nanocluster. Transmission electron microscopy (TEM) was conducted to determine the nanocluster size and photocorrelation spectroscopy (PCS) was performed to determine hydrodynamic size (D_h) and LCST of the nanoclusters. The effects of MNP-to-polymer ratio used in the reactions and the number of GMA units in the polymer on D_h and colloidal stability of the nanocluster were also investigated. Magnetic properties of the nanoclusters were investigated *via* vibrating sample magnetometry (VSM). The composition of MNP-polymer nanocluster was also determined *via* thermogravimetric analysis (TGA). In addition, a case study showing the drug controlled release application of these MNP nanoclusters was also investigated (see Fig. 1).

2. Experimental

2.1. Materials

Unless otherwise stated, all reagents were used without further purification: iron (III) acetylacetonate ($Fe(acac)_3$) (Acros, 99.9%), benzyl alcohol (Unilab, 98%), oleic acid (Fluka), triethylamine (Carto Erba, 97%), 3-aminopropyl triethoxysilane (APS) (Acros, 99%), glycidyl methacrylate (GMA) (Sigma-Aldrich, 97%), 2,2′-azobis (2-methylpropionitrile) (AIBN) (Sigma-Aldrich, 98%), *S*-(thiobenzoyl)thioglycolic acid (Sigma-Aldrich, 99%). *N*-isopropylacrylamide (NIPAAm) (Acros, 99%) was recrystallized twice in hexane before polymerization.

2.2. Synthesis

2.2.1. Synthesis of PNIPAAm macro RAFT agents

In a round bottom flask, NIPAAm (10 g, 88.370 mmol), S-(thiobenzoyl) thioglycolic acid RAFT agent (0.0924 g, 0.435 mmol) and an AIBN initiator (0.0182 g, 0.110 mmol) were dissolved in 50 mL of 1,4-dioxane under N_2 atmosphere with stirring for 30 min. RAFT polymerization of PNIPAAm was allowed for 48 h at 60 °C to achieve 60% monomer conversion. The mixture was then diluted with 1,4-dioxane to 100 mL and cooled to room temperature. The polymer was then purified by