Colloids and Surfaces B: Biointerfaces 173 (2019) 155–163

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

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

Fabricating cauliflower-like and dumbbell-like Janus particles: Loading and simultaneous release of DOX and ibuprofen

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ARTICLE INFO

Keywords:
Janus particles
Seeded emulsion polymerization
Phase-separation
Simultaneous
two drug release

ABSTRACT

Most recent studies on Janus particles have concentrated on amphiphilic Janus particles. Herein, a facile and efficient method based on polymerization-induced phase separation is presented to fabricate Janus particles with different morphologies. Theses novel hydrophilic Janus particles with two distinct hydrophilic domains have been prepared by combination of distillation precipitation polymerization (DPP) and seeded emulsion polymerization. Crosslinked poly(2-hydroxyehtyl methacrylate) (PHEMA) cores were synthesized via DPP and used as seed particles. Also, methacrylic acid (MAA) was used as second hydrophilic monomer. Effect of feeding approach, and reaction medium were investigated on the morphology of fabricated composite particles. Different morphologies such as cauliflower-like, dumbbell-like, and core-shell toward cauliflower-like structures were obtained by varying feeding approach and polymerization medium. The morphology of resultant particles was observed by means of FE-SEM and TEM images and their particle sizes were confirmed by DLS. Fabricated composite particles were used to simultaneously carry both DOX and ibuprofen. Drug release studies showed that Janus particles can be used in loading and release of two drugs simultaneously. However, release behaviors of DOX and ibuprofen were different at different pH values. Also, release behavior was significantly affected by the structure of composite particles.

1. Introduction

Janus particles are colloidal structures with asymmetrically-distributed physical and chemical properties through their surface or bulk [1]. Recently, they have attracted more attentions due to their potential applications in various fields such as stabilizing emulsions [2], compatibilizing blends [3], catalysts [4], delivering of chemical payloads such as drug delivery systems [5], etc. Synthesis of a Janus particle needs to create different chemical properties on each side of a particle where three main methods including self-assembly of block copolymers [6], masking [7] and phase separation of two different substances [8] because of a very powerful driving force have been used. Seeded Emulsion Polymerization is a very facile and efficient method based on phase separation to produce Janus particles. This method involves polymerization of secondary monomer within seed particles which leads to phase separation with reaction progression [9]. However, recent studies on Janus particles focused on amphiphilic Janus particles with distinct hydrophilic and hydrophobic domains [10] and there is a few works on fabrication of hydrophilic Janus particles with two distinct hydrophilic domains [5,8,11].

Janus particles can collect two completely different chemistry, hydrophobicity, polarity, functionality and surface charge because of their asymmetrical and unique structure. So, they are an attractive group of synthetic materials in biomedical applications. Existence of two distinct faces makes these particles attractive colloids that can be used to simultaneous detect and treat of cells [12]. These biocompatible Janus nanoparticles have a bipolar affinity to human cells which can carry a drug and detect the targeted cells at the same time [13].

Although intelligent drug delivery systems based on biocompatible and degradable polymers such as smart particles [14], micelles [15], dendrimers [16], and molecularly imprinted polymers (MIPs) [17] have been widely used in controlled release of different drugs, Janus particles have attracted much more attention in new smart drug release systems due to their unique dual properties. The presence of a second face in these particles lets different ligands to be attached on them as targeting or detection agents. Therefore, these particles will also be able to detect the cell in addition to successful delivery of the drug [18]. The second face can also be used for imaging [19]. Simultaneous drug delivery and cell detection make Janus particles super-smart and multifunctional particles.

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https://doi.org/10.1016/j.colsurfb.2018.09.068
Received 7 July 2018; Received in revised form 4 September 2018; Accepted 26 September 2018
Available online 29 September 2018

On the other hand, the cardiotoxicity of anticancer drugs such as doxorubicin (DOX) limits their usefulness. Nonsteroidal anti-inflammatory drugs such as ibuprofen are necessary to be used with cardiotoxicity drugs. Ibuprofen significantly increases survival for DOX because of its cyclooxygenase and neutrophil infiltration inhibiting effects [20]. This reveals the importance of co-delivery of two drugs such as DOX and ibuprofen. In addition, the surface charge of nanoparticles is an important factor in tumor therapy. Nanoparticles with positive charge lead to immune reactions; so, neutral and negatively-charged nanoparticles are better for clinical application [21].

Herein, Janus particles with dumbbell-like and cauliflower-like morphologies are prepared by seeded emulsion polymerization. The synthesized Janus particles are negatively charged. To synthesize such particles, cross-linked poly(2-hydroxyethyl methacrylate) (PHEMA) cores as hydrophilic seed particles are synthesized via distillation precipitation polymerization (DPP) and then, methacrylic acid (MAA) was used as second hydrophilic monomer. PMAA is a pH-sensitive polyelectrolyte with high tendency to DOX [22]. Additionally, effect of feeding method on the morphology of particles is studied using three different feeding approaches including adding one together feeding approach, rest approach, and continues feeding approach. To prove the ability of seeded emulsion polymerization to produce Janus particles, second stage of polymerization is performed using DPP too. The morphology of resultant particles is observed by field emission scanning electron microscope (FE-SEM) and transmission electron microscopy (TEM). Also, particle sizes and particle size distributions are measured by dynamic light scattering (DLS). Fabricated composite particles were successfully used to simultaneous delivery of DOX and ibuprofen. Finally, simultaneous release behaviors of drugs are investigated at different pH values.

2. Experimental section

2.1. Synthesis of monodispersed PHEMA microspheres by DPP

PHEMA cores were produced by DPP through a batch process as reported previously [23]. HEMA (1.44 mL, 11.85 mmol, 2.5 vol. % of reaction mixture), MBA (0.457 g, 20 mol. % of total monomer) and AIBN (0.024 g, 0.15 mmol, 1 mol. % of total monomers) were dissolved in acetonitrile (80 mL) in a 100-mL two-necked round-bottom flask attached to a fractionating column and a receiver. The reaction mixture was heated from 50 °C to boiling state (82 °C) within 15 min under a nitrogen atmosphere. After a few minutes, the solvent began to be distilled from medium and then, homogeneous colorless reaction mixture turned to milky white dispersion after about 15 min. The reaction was continued until 40 mL of acetonitrile was collected (around 1 h). The resultant PHEMA microspheres were separated and purified by repeating centrifugation (10,000 rpm for 15 min), decanting, and resuspending in acetonitrile with ultrasonic bath for three times. Finally, product was vacuum-dried at 35 °C for 24 h.

2.2. Preparation of Janus particles by seeded emulsion polymerization

A mixture of PHEMA microspheres (0.2 g), SDS (0.1 g), and deionized water (200 mL) was charged into a 250 mL two-necked round-bottom flask and homogenized by sonication. Then, KPS (1 mol. % of total monomers) as initiator was added. After adding methacrylic acid (1 g) and MBA (20 mol. % of total monomers), reaction was carried out under nitrogen atmosphere for 18 h at 70 °C. The resultant particles were separated and purified by repeating centrifugation (10,000 rpm for 15 min), decanting, and resuspending in water with ultrasonic for three times and product was dried in a vacuum oven at 35 °C for 24 h.

To study the effect of feeding approach on morphology of obtained particles, moreover adding one together, two other feeding approaches were also used. In rest approach, reaction mixture rested for 24 h at room temperature. Then, KPS was added and emulsion was stirred at 70 °C for 18 h. In continues feeding approach (a semi-batch process), seed particles were dissolved in 150 mL of deionized water (seed mixture) and SDS, monomer, MBA, and KPS were dissolved in 50 mL of deionized water (monomer emulsion). The seed mixture was charged into the reactor at 70 °C and monomer emulsion was added to seed mixture over 2 h by dosing pump. After the complete injection, polymerization was continued for 16 h under nitrogen atmosphere at 70 °C.

2.3. DPP of MAA in presence of PHEMA seed particles

MAA (1.28 mL), MBA (20 mol. % of total monomer), AIBN (1 mol. % of total monomers) and PHEMA (0.2 g) were dissolved in acetonitrile (80 mL) and DPP of MAA in presence of PHEMA seeds was performed as stated in Section 2.1.

2.4. Simultaneous loading of ibuprofen and DOX onto Janus nanoparticles

Different Janus particles (24 mg) were added to a solution (6 mL) of DOX (0.5 mg/mL) and ibuprofen (0.5 mg/mL) at pH = 8 which is near the isoelectric point of DOX [24]. At this pH, DOX can be loaded in neutral state. After 48 h in dark condition at 25 °C, drugs-loaded particles were collected by centrifugation (9000 rpm). The amounts of loaded drugs were determined by UV–vis absorptions according to calibration curves.

2.5. In vitro simultaneous release of drugs

The release of drugs from drugs-loaded Janus particles was performed at two pH values (5.3 and 7.4) at 37 °C. To this end, 4 mg of each sample was dispersed in 1 mL of PBS (pH = 5.3 and 7.4) and poured into cellulose dialysis bag (MWCO = 12,000). Dialysis bag was soaked in 100 mL of corresponding buffer under stirring for 48 h. At pre-determined time intervals, 1-mL of media was taken as sample and replaced with 1 mL of fresh PBS. The concentrations of drugs were measured by UV–vis absorption at 263 nm for ibuprofen and 480 nm for DOX.

3. Results and discussion

3.1. Synthesis and characterization of Janus particles

PHEMA seed particles synthesized by DPP are presented by FE-SEM image in Fig. S1. They are spherical and their surface is smooth. Number-average diameter (D_n), weight-average diameter (D_w) and polydispersity index (PDI) of PHEMA cores are calculated762.2 nm, 833.7 nm, and 1.09 respectively (Fig. S2) using Eqs. (1)–(3) [25]:

$$D_n = \frac{\sum_1^n n_i D_i}{\sum_1^n n_i} \quad (1)$$

$$D_w = \frac{\sum_1^n n_i D_i^4}{\sum_1^n n_i D_i^3} \quad (2)$$

$$PDI = \frac{D_w}{D_n} \quad (3)$$

Also, PHEMA seed particles are characterized by DLS in aqueous media. As shown in Fig. S1, particle size obtained from DLS is 1.8–2 times larger than size obtained from FE-SEM. This is attributed to swelling of particles in water because of hydrophilic nature of PHEMA. Additionally, low PDI value of 0.007 obtained from DLS coincides PDI value obtained from FE-SEM image and conclusively, synthesized seed particles are mostly monodispersed.

Synthesized PHEMA particles were used as seed particles in emulsion polymerization of MAA with different feeding approaches and morphology of obtained structures were investigated using different analysis methods. As shown in Fig. 1, cauliflower-like particles were