Reactive and Functional Polymers 116 (2017) 24–30

Contents lists available at ScienceDirect

Reactive and Functional Polymers

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

Facile preparation of pH/reduction dual-responsive prodrug microspheres with high drug content for tumor intracellular triggered release of DOX

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ARTICLE INFO

Keywords:
Prodrug microspheres
High drug content
pH/reduction dual-responsive
Tumor intracellular triggered release
Doxorubicin

ABSTRACT

To integrate the two advantages of upregulated stability during blood circulation and site-specific drug release in cancer cells, pH/reduction dual-responsive prodrug microspheres with high drug content were designed by conjugating doxorubicin (DOX) onto aldehyde-functionalized disulfide-crosslinked copolymer microspheres via acid-labile imine linkage, where the copolymer microspheres were synthesized by facile emulsion copolymerization of poly(ethylene glycol) methyl ether methacrylate (PEGMA) and 4-formylphenyl acrylate (FPA) with *N*,*N*-bis(acryloyl)cystamine (BACy) as crosslinker. Their particle size and average hydrodynamic diameter were 150 nm and 205 nm respectively, with high DOX content of 44.4%. The DOX release ratio reached 73% within 60 h and the prodrug microspheres decrosslinked into water soluble copolymers within 72 h in the simulated tumor microenvironment (pH 5.0 with 10 mM GSH), while only 16% of DOX was released in physiological medium (pH 7.4 with 10 μM GSH), demonstrating their good tumor intracellular triggered release performance. Furthermore, the disintegration of the copolymer microspheres into water soluble copolymers in simulated tumor microenvironment would favor the metabolism of drug carriers. The MTT assay demonstrated that the prodrug microspheres exhibited the enhanced inhibitory efficiency against HepG2 cells in comparison with free DOX, while the bare polymer microspheres were cytocompatible.

1. Introduction

Cancer has currently surpassed heart disease as the top killer of human and now chemotherapy becomes as one of the most used clinical approaches to treat cancer, especially after surgical operation. Unfortunately, the cancer patients suffer from severe toxic and side effects of chemotherapeutics due to their non-selectivity [1]. In order to improve the anticancer efficacy, smart drug delivery system (DDS) has been widely studied to reduce the side effects and improve the bioavailability of anticancer chemotherapeutics [2], by means of triggered release anticancer drugs responding to tumor intracellular stimuli, such as pH [3] and reductant level [4]. In such case, the drug release in physiological medium would be suppressed to reduce the toxic and side effects on normal tissues.

Compared with the common DDSs in which anticancer drugs are usually loaded or encapsulated via a weak interaction (for examples, electrostatic interaction, hydrogen bond, or hydrophobic interaction), polymer prodrugs, in which one or more drug(s) are covalently attached to the functional groups of the polymer via a weak covalent bond directly or through a spacer, should be a more efficient strategy [5]. On the basis of the intracellular differences in the biophysical and biochemical indexes of normal and tumor cells, pH and glutathione (GSH) level have been intensely investigated as switch to trigger the release of anticancer chemotherapeutics from prodrugs in the last decade. For pH-triggered prodrugs, the anticancer drugs are usually conjugated onto the nano-vehicles via acid-labile imine or hydrazone linkage [6], which could be cleaved off to release drugs in tumor intracellular acidic media. As for the reduction-triggering mode [7], the prodrugs could release the derivative of anticancer drugs [8], due to that the drug is conjugated via the bioreducible disulfide bond.

Comparatively speaking, the disulfide bond might be more suitable crosslinking structure to control the disintegration of the nano-prodrugs and drug diffusion subsequently. For examples, Zhao and Liu fabricated core-shell-corona micelles by self-assembly of triblock copolymer and shell-crosslinking with disulfide bond as promising tumor microenvironment-responsive nano-vehicles for doxorubicin (DOX) by GSH triggering [9]. Polymer nanoparticles or nanohydrogels have attracted more and more interest owing to their facile preparation in comparison with polymer micelles. Zhou et al. designed monodisperse biodegradable PEGylated pH and reduction dual-stimuli sensitive poly

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http://dx.doi.org/10.1016/j.reactfunctpolym.2017.05.002
Received 22 November 2016; Received in revised form 29 March 2017; Accepted 4 May 2017
Available online 04 May 2017
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[methacrylic acid-*co*-poly(ethylene glycol) methyl ether methacrylate-*co*-*N*,*N*-bis(acryloyl)cystamine] nanohydrogels via one-step distillation precipitation polymerization as DDS for DOX [10]. Jia et al. synthesized fluorescent poly(methacrylic acid-*co*-poly(ethylene glycol) methyl ether methacrylate-*co*-N′-rhodamine B-acrylhydrazine) nanoparticles as potential theranostic nanoplatform via facile distillation precipitation copolymerization with bio-reducible disulfide-containing crosslinker, after DOX loading via electrostatic interaction [11]. Pan et al. fabricated folate-conjugated poly(N-(2-hydroxypropyl)methacrylamide-*co*-methacrylic acid) nanohydrogels for targeted delivery of DOX, via distillation-precipitation polymerization and subsequent folate modification [12].

Most recently, Zhang et al. established pH and reduction dual-sensitive prodrug nanogel to integrate the two advantages of upregulated stability during blood circulation and selective release of drug in cancer cells, by simultaneously conjugating DOX via acid sensitive hydrazone bond and cross-linking with reduction responsive disulfide containing linkage in the core through one step "click chemistry" crosslinking of diblock copolymer (methoxy poly(ethylene glycol)-*b*-poly(γ-propargyl-L-glutamate)) with 2-azidoethyl disulfide into core-crosslinked micelles [13].

In the present work, a facile strategy has been developed for the fabrication of the pH/reduction dual-responsive prodrug microspheres, by conjugating DOX via acid-labile imine linkage onto PEGylated copolymer microspheres prepared by emulsion copolymerization of polyethylene glycol methyl ether methacrylate (PEGMA) and 4-formylphenyl acrylate (FPA) with *N*,*N*-bis(acryloyl)cystamine (BACy) as crosslinker (Scheme 1). The in vitro release experiments showed that the accumulative release ratios were 73.3% and 16.6% in the simulated tumor and physiological media respectively, indicating the tumor intracellular triggered release of DOX from the proposed prodrug microspheres.

2. Experimental

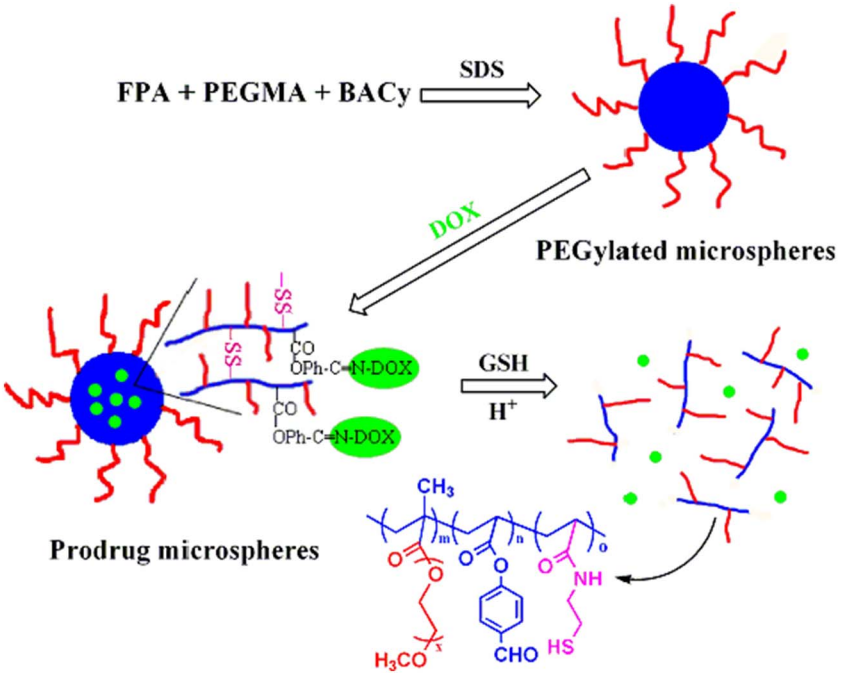
2.1. Materials and reagents

p-Hydroxybenzaldehyde (AR, 98%) was purchased from Tianjin Chemical Reagent Co., Tianjin, China. Acryloyl chloride (96%) was purchased from Tianjin Heowns Company. Triethylamine (99%) was purchased from Alfa Aesar and dried by CaH_2. Poly(ethylene glycol) methyl ether methacrylate (PEGMA, M_n = 475, 98%) was purchased from Sigma Aldrich and purified with alkaline aluminum oxide column to remove inhibitor before use. Sodium dodecyl sulfate (SDS, CP) was purchased from Shanghai Shiyi chemical reagents Ltd. Ammonium persulphate (APS, 98%) was purchased from Kelong Chemical Reagent Factory. Glutathione (GSH, 97%) and cystamine dihydrochloride (96%) were obtained from Tianjin Heowns Biochemical technology Co, Tianjin, China. Doxorubicin hydrochloride (DOX·HCl, 99.4%) was obtained from Beijing Huafeng Lianbo Technology Co., Ltd., Beijing, China. Tetrahydrofuran (THF, 99%, Tianjin Kermel Chemical Reagent Co., Ltd) was dried by CaH_2 and distilled prior to use. *N*,*N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and other reagents were achieved from Tianjin Chemical Reagent II Co. and used without further purification. Deionized water was used throughout.

2.2. Synthesis of PEGylated polymer microspheres

4-Formylphenyl acrylate (FPA) was synthesized by esterification reaction of phenolic hydroxyl with acyl chloride, as reported previously [14]. Typically, a solution of acryloyl chloride (4.5 mL) in 10 mL anhydrous tetrahydrofuran was added dropwise at −5 °C into a solution of *p*-hydroxybenzaldehyde (2 g, 0.016 mol) and dried triethylamine (4.5 mL) in 25 mL of anhydrous THF with stirring, the reaction was continued 10 h at room temperature. Then the product was filtered and evaporated under vacuum. The residual organic layer was purified by passing a silica gel column chromatography (eluant: petroleum ether/ethyl acetate = 8:1 v/v). Finally, the product was concentrated and dried in vacuum. (^{1}H NMR spectrum (400 MHz, $CDCl_3$) (Fig. S1): δ 6.08(H_e,1H), 6.36(H_d,1H), 6.66(H_f,1H), 7.33(H_b,1H), 7.93(H_c,1H), 10.0(−CHO,1H); yield: 75%).

BACy was synthesized according to the reported procedure [15,16]. Cystamine dihydrochloride (5.630 g, 0.025 mol) was dissolved in 25 mL deionized water. Then the solution was added into a 250 mL three-necked round bottom flask equipped with a magnetic stirrer. A solution of acryloyl chloride (4.526 g, 0.050 mol) in 5 mL dichloromethane and a NaOH aqueous solution (8.0 g in 10 mL water) were added simultaneously and slowly to the flask within 1 h in ice bath.



Scheme 1. Schematic illustration of the preparation of prodrug microspheres, their disintegration and DOX release in tumor microenvironment.

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