Colloids and Surfaces B: Biointerfaces 116 (2014) 359–364

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

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

Hyaluronated nanoparticles with pH- and enzyme-responsive drug release properties

Seong Won Kim [a], Kyung Taek Oh [b], Yu Seok Youn [c], Eun Seong Lee [a,*]

[a] Department of Biotechnology, The Catholic University of Korea, 43-1 Yeokgok 2-dong, Wonmi-gu, Bucheon, Gyeonggi-do 420-743, Republic of Korea
[b] College of Pharmacy, Chung-Ang University, 221 Heukseok-dong, Dongjak-gu, Seoul 155-756, Republic of Korea
[c] School of Pharmacy, Sungkyunkwan University, 300 Chonchon-dong, Jangan-ku, Suwon, Gyeonggi-do 440-746, Republic of Korea

ARTICLE INFO

Article history:
Received 14 August 2013
Received in revised form 9 January 2014
Accepted 13 January 2014
Available online 23 January 2014

Keywords:
pH-responsive nanoparticle
Hyaluronidase-responsive nanoparticle
3-(diethylamino)propylamine
Hyaluronic acid

ABSTRACT

In this study, we report the development of a novel pH-responsive nanoparticle composed of hyaluronic acid (HA) grafted with functional 3-diethylaminopropyl (DEAP) groups (HA-*g*-DEAP). The pH-responsive nanoparticles were fabricated by a self-assembled arrangement of a hydrophilic block (HA) and a hydrophobic block (non-protonated DEAP) of HA-*g*-DEAP at pH 7.4. HA-*g*-DEAP was prepared by a simple conjugation of the carboxylic acid groups of HA and the free amine groups of DEAP. The HA-*g*-DEAP nanoparticles displayed pH-dependent changes in their physicochemical properties. We observed nanoparticle destabilization because of the protonation of DEAP when the pH of the solution decreased to 5.0. This phenomenon resulted in the release of the encapsulated content (model drug, doxorubicin: DOX) from the nanoparticle core. In addition, the degradation of HA by hyaluronidase (Hyal) significantly accelerated the DOX release rate, which may allow for increased drug release in diseased cells with acidic endosomal pH (~pH 5.0) in the presence of Hyal. Overall, a significant improvement in the drug release rate was evident when this nanoparticle system was stimulated by both an acidic pH and specific enzymes.

1. Introduction

The field of nanomedicine and nanoscience has developed through interacting and communicating with the field of chemistry [1–3]. It has been suggested that the progress of next-generation nanomedicine includes access to various chemical methods capable of constructing functional drug carriers [1–8]. Chemical coupling methods of polymers, functional moieties or drugs have usually provided efficient drug delivery techniques associated with the amelioration of drug side effects [4–8]. In particular, there has been increasing interest in the design and development of a novel drug delivery vehicle using various chemical coupling procedures with stimuli-responsive chemicals [1–8].

Several examples involve the exploitation of physical stimuli (such as pH and temperature) [4–6,9] or biological stimuli (enzymes) responsive chemicals [10,11]. The drug delivery vehicles constructed with these chemicals have demonstrated their pharmaceutical potential; the vehicles respond to internal or external stimuli and release their encapsulated contents or the compounds linked to their core or on their surface [12,13]. Such multifunctional systems represent cutting-edge therapeutic approaches that are capable for both drug targeting and therapy.

In this study, we report novel hyaluronated stimuli-responsive nanoparticles that have programmed drug release behaviors. Unlike the vast majority of stimuli-responsive nanovehicles, our nanoparticles were fabricated after a facile polymer synthesis process. We grafted 3-diethylaminopropyl (DEAP) to the carboxylic acid groups of hyaluronic acid (HA) using *N,N′*-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (NHS) (Fig. 1a). HA grafted with DEAP (HA-*g*-DEAP) self-organized in an aqueous solution, with HA blocks on the hydrophilic shell and non-protonated DEAP (at pH 7.4) blocks in the hydrophobic inner core. The pK_b of DEAP ranged from 7.0 to 6.0 according to the type of backbone polymer or the degree of DEAP conjugation [4,14–16]. Several studies have reported that the protonation of a DEAP block at an acidic pH decreases its hydrophobicity [14–16] and destabilizes the nanoparticle core that contains the DEAP blocks. This property of DEAP may effectively enable a pH-controlled release of a drug that is trapped in the nanoparticle core. Moreover, HA, the backbone polysaccharide, has been frequently utilized as a specific ligand for CD44 receptors on cells and can efficiently degrade in hyaluronidase (Hyal)-rich endosomes [17,18]. It has been shown that drug release from

* Corresponding author. Tel.: +82 2 2164 4921; fax: +82 2 2164 4865.
E-mail address: eslee@catholic.ac.kr (E.S. Lee).

0927-7765/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.colsurfb.2014.01.017

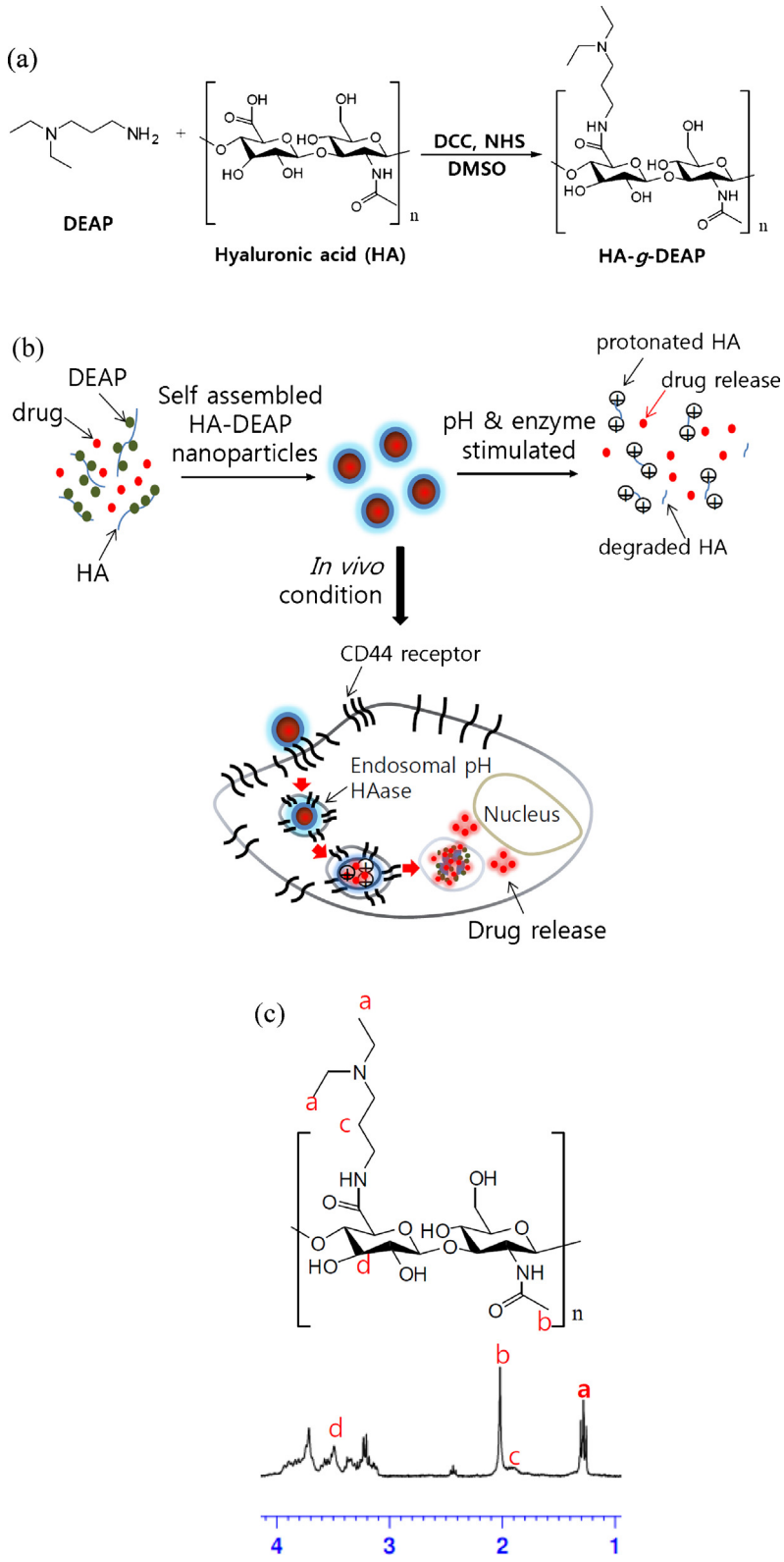

Fig. 1. (a) The synthesis scheme of HA-*g*-DEAP. (b) Schematic concept for a proposed hyaluronated pH-responsive nanoparticle. (c) ^{1}H NMR peak of HA-*g*-DEAP.

this nanoparticle system can be stimulated in the endosomes by both an acidic pH (~5.0) [19] as well as Hyal during the endocytic pathway of nanoparticles (Fig. 1b). In this study, we specifically investigated the stimuli-response properties and drug release profile of HA-*g*-DEAP nanoparticles to evaluate their pharmaceutical potential.

2. Materials and methods

2.1. Materials

Hyaluronate (HA, Mw = 4 kDa) was kindly provided by Bioland Company (Cheonan, Korea). *N*-hydroxysuccinimide (NHS),