International Journal of Biological Macromolecules 124 (2019) 1220–1229

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: http://www.elsevier.com/locate/ijbiomac

Anionic carboxymethylagarose-based pH-responsive smart superabsorbent hydrogels for controlled release of anticancer drug

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ARTICLE INFO

Article history:
Received 24 July 2018
Received in revised form 29 November 2018
Accepted 2 December 2018
Available online 04 December 2018

Keywords:
Carboxymethylagarose
Functional polymers
Drug delivery

ABSTRACT

Herein, we demonstrate the preparation of superabsorbent hydrogel (CMA-g-PAm) materials using anionic and cold water soluble carboxymethyagarose (CMA, a seaweed polysaccharide-based derivative) with polyacrylamide (PAm) through rapid microwave assisted grafting technique. The successful fabrication of CMA-g-PAm was verified by FT-IR, SEM, XRD, TGA and CHN analyzer. Effects of initiator, crosslinker, and monomer on the swelling behavior and grafting parameters have been thoroughly investigated. Moreover, the swelling behavior of the resulting hydrogels was systematically studied, and the results suggested they exhibit excellent pH and salt responsive behavior. The drug delivery application of thus fabricated hydrogel was further evaluated using doxorubicin (Dox) as a model drug to explore its possible applications. Release study results revealed that Dox release was significantly accelerated with decrease in pH from 7.4 to 5.0. Toxicity assays confirmed that the blank hydrogels had negligible toxicity to normal cells (VERO), whereas the Dox-loaded hydrogels remained high in cytotoxicity for A549 and Hep-G2 cancer cells. All of these attributes implied that the new proposed hydrogel (HK11) serves as potential drug delivery platforms for cancer therapy.

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1. Introduction

Controlled release drug delivery is a modish approach of treating infirmity in which the emphasis is given to utilize a drug delivery system that provides sustained release of the drug. While it is hard to tailor the drug release in an on-demand and predictable manner, a large percentage of poorly soluble drugs are especially problematic in the progress of controlled release dosage formulations [1]. On the contrary, the development of new drug molecule is expensive and time-consuming. To address these issues, the introduction of another polymer (such as a rigid synthetic polymer) to form an interpenetrating network or hydrogel is a feasible approach to reinforce the drug molecules. However, the selection of suitable biocompatible and biodegradable materials for achieving desired drug release profile at the target site has been a challenging task. Anthracycline antibiotics, particularly doxorubicin (Dox) ranks among the widely used anticancer drug due to its high antitumor activity [2]. It exerts its cytotoxic activity by inhibiting DNA and RNA biosynthesis within cancer cells. The use of Dox and its derivatives causes dilated cardiomyopathy and congestive heart failure due to the accumulation of the drug and Dox-induced cardio toxicity. Coupling anticancer drugs to synthetic polymers is a promising approach to improve the efficacy and reduce the side effects of these drugs. Till date, several drug delivery systems including polymer-drug conjugates, liposomes, nanoparticles, hydrogels and polymeric micelles have been developed to overcome these deleterious side effects [3].

Superabsorbent hydrogels are loosely cross-linked hydrophilic polymers that can absorb, swell and retain aqueous solutions up to hundred times their weight [4]. The absorption of a significant amount of water by hydrogels is attributed to the presence of a large number of hydrophilic groups on the polymer chains such as —NH_2, —OH, —COOH, —SO_3H, etc. along with capillary action and osmotic pressure [5]. The sensitivity of hydrogels to a large number of chemical and physical factors like temperature, light, electrical voltage, pH, ionic strength, biological, and chemical agents make them suitable for a broad range of applications [6]. Recently, biopolymers based hydrogels have sparked particular interest for synthesizing novel drug delivery vehicles owing to their environmental responsiveness, outstanding biocompatibility, adjustable mechanical properties, easy manipulation of the swelling level and, thereby, solute permeability [7]. Because of significant variations in physiological pH at various body sites in normal as well as pathological conditions, pH-responsive polymeric networks have been extensively studied as self-regulated devices for drug delivery [8,9]. Till date, many natural polymers have been used to synthesize pH-

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https://doi.org/10.1016/j.ijbiomac.2018.12.045
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