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Doxorubucin loaded pH-responsive chitosan-poly(acrylamide-maleic acid) composite hydrogel for anticancer targeting

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Highlights

- Chitosan/poly(acrylamide-co-maleic acid).
- It loaded by high efficiency.
- pH sensitive doxorubicin release.

Abstract

A pH responsive superadsorbent composite hydrogel, chitosan-poly(acrylamide-maleic acid)(Ch-p(Ac-Ma)), were synthesized, characterized and loaded by Doxorubucin (Dox), anti-cancer drug. Chitosan solution was modified by blending biocompatible chitosan and poly(acrylamide-co-maleic acid) in the polymerization medium. This new composite hydrogel had a high loading capacity for Dox (~90%). Some chemical characteristics of the prepared composite hydrogel were investigated by swelling test, SEM, FTIR, XRD. The drug release study confirmed the pH-responsive delivery ofdoxorubucin. The composite hydrogel was loaded by high efficiency and the release experiments exhibited that Dox is released more at pH 4.5 compared with pH 7.4 at 37°C. The biocompatibility of the prepared composite hydrogel was demonstrated via XTT assay in MCF-7 cells. The Dox loaded composite showed a controlled release, especially at acidic region. The Ch-p(Ac-Ma) exhibited a good biocompatibility against breast cancer cells (MCF 7) and dose dependent drug delivery behavior. Also, we employed molecular docking and density functional theory analysis to investigate the inhibitory activity, reactivity, and stability of Doxorubucin and target protein HER2 ((Pdb ID: 7JXH). The interaction between Doxorubucin and target protein HER2 ((Pdb ID: 7JXH) was investigated in the light of Molecular Docking calculations.

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Keywords

Chitosan; Breast cancer cell; Doxorubucin; Drug delivery; Molecular docking

1. Introduction

Stimulus-responsive polymers have emerged as a promising technique for delivering drugs to treat a wide range of disorders, particularly cancer. These polymeric carrier systems, also known as "smart drug delivery systems," are engineered to react to certain physical or biological cues, such as pH, temperature, redox potential, enzymes, light, and ultrasound, resulting in triggered release [1,2]. These custom nanocarriers can also improve the qualities of conventional chemotherapeutics in terms of solubility, bioavailability, and extended circulation time, as well as selectively release bioactive chemicals at the targeted location of action. In aqueous liquids, these

polymeric structures behave like a hydrogel. Hydrogels are hydrophilic, three-dimensional polymeric networks made up mostly of homopolymers or copolymers that can hold a considerable amount of fluid [3,4].

Composite hydrogels are particles that have the properties of both hydrogels and nanomaterials. They are similar to hydrogels in that they have a high water content, a tunable structure, and are biocompatible, and they, like nanomaterials, have a high surface area for bioconjugation, a long circulating half-life, and a tunable size [5]. these characteristics, as well as their ability to design stimuli responsive nanocarriers, makes them ideal candidates for improving chemotherapeutic delivery efficiency [6]. These composite hydrogels are made up of smart or stimulus sensitive (responsive) polymers that go through a phase transition in aqueous solution in response to tiny changes in external parameters like temperature, pH, ionic strength, electric or magnetic field, and so on. Polymers sensitive to pH are the most useful of these because, in the human body, these physicochemical parameters (pH) change in different body compartments under pathological conditions (pH difference between normal and pathologic tissue), acting as triggering agents [7]. Because of its unique characteristics such as biodegradability, biocompatibility, mucoadhesiveness, non-toxicity, and specialized biological activities, chitosan (CS), a natural polymer, has been widely used for hydrogel creation. Because of the abundance of amino and hydroxyl functional groups along the CS chain, it can react with crosslinking agents in situ to generate custom hydrogels [8], [9], [10].

In the current study, chitosan based drug delivery agent was modified with monomers (acrylamide-maleic acid). The purpose of this modification was to provide pH sensivity to composite hydrogel. By modification composite got advanced chemical properties to release Dox at lower pH values but not at pH 7.4. This study investigated in vitro release of Dox at different pHs by using new synthesized composite. Before *in vitro* release studies scanning electron microscopy (SEM), Fourier transform infrared (FTIR-ATR) and X-ray diffraction (XRD), swellin test were used for physical characterization of composite material. Based on the foregoing, we present for the first time the composite composed of cationic polymer chitosan and anionic co-polymer poly(acrylamide-maleic acid) and used for Dox release studies. Also, to investigate the inhibitory potential, reactivity, and stability of the Dox and other HER2 ((Pdb ID: 7JXH↗) inhibitors utilizing molecular docking and density functional theory analysis.

2. Materails and methods

2.1. Materials

Maleic acid (MA) and Acrylamide (AA), ammonium peroxodisulfate APS (H8N2O8S2), 4-(2-pyridylazo), N,N'-methylenebisacrylamide, N,N,N',N'-tetramethylethylenediamine (TEMED), and lysozyme powder (from chicken egg white) were obtained from Sigma-Aldrich (Steinheim, Germany). Chitosan (Mw 150,000Da 85% deacetylated) used by Akkaya etal. 2008 [11] and Doxorubucin HCl purchased from Merck. All other chemicals were of analytical-grade purity.

2.2. Synthesis of Ch-p(Ac-Ma)

5.0g of chitosan in acetic acid (1 percent v/v) was stirred for 15min to prepare the adsorbent (chitosan/poly(acrylamide–co-maleic acid). Maleic acid (10mL 0.135g maleic acid) and acrylamide (20mL 1.5g acrylamide) monomer solutions were added to the chitosan solution and stirred for 4h. Following the addition of N, N'-methylenebisacrylamide (2mL) and ammonium persulfate (10mL) to the suspension, N, N, N', N'-tetramethylethylenediamine (200L) was added to the polymerization medium. The composite hydrogel was washed with distilled water after the polymerization process was completed. After grinding, the Ch-p(Ac-Ma) composites were dried at room temperature and stored in polypropylene containers.

2.3. Chemical characterization of Ch-p(Ac-Ma) and dox-Ch-p(Ac-Ma)

2.3.1. Swelling ratio

To investigate swelling behavior, 1.0g of dry Ch-p(Ac-Ma) composite was immersed in different pH values (4.5 and 7.4) and held at a constant temperature of 37±0.5°C. Swollen composites were removed and weighed on a regular basis with an electronic balance. The dry to swollen sample weight ratio was calculated.

$$\textit{Swelling ratio}\ (\textit{percent}) = [(Wf - Wo)/Wo]\,x100 \quad (1)$$

Equation 1 was used to compute the water content of the swollen composite.

The weights of the composite before and after swelling are represented by Wo and Wf, respectively.

2.3.2. Scanning electron microscopy (SEM)

The surface morphology of the composite was examined using scanning electron microscopy (SEM). SEM was obtained by model of TESCAN MIRA3 XMU. The composite material was coated with a thin layer of gold under reduced pressure and its SEM images were taken.

2.3.3. Attenuated total reflection fourier transforminfrared (ATR FT-IR)