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Polyethylene Glycol-Modified Chitosan (Cs-PEG): A pH-Responsive Nanocarrier for Doxorubicin (DOX) delivery

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Abstract: The aim of this research was simple preparation of the modified chitosan by polyethylene glycol (Cs-PEG) through a green procedure. To achieve this goal, polyethylene glycol was grafted to the chitosan and made a hydrogel. In particular, chitosan, a natural polymer, stands out as a first-choice material for hydrogels elaboration in biomedical, cosmetic, and health related applications, owing to its interesting properties including biocompatibility, biodegradability, antimicrobial capacity, and mucoadhesivity. Moreover, chitosan also allows drugs to absorb easier through biological barriers. pH-Responsive nanoparticles are regarded as an ideal candidate for anticancer drug targets. The obtained nanomaterial was characterized by using different spectroscopic, microscopic and analytical methods. Various techniques and methods namely Fourier transform infrared (FTIR), field emission scanning electron microscopy (FESEM), ultraviolet-visible spectroscopy (UV-VIS) were utilized to identify the nanomaterial. Then, the doxorubicin (DOX) was loaded onto the Cs-PEG hydrogel, as a pH-responsive nanocarrier, for anticancer drug delivery. In conclusion, the efficiency of the drug load increases because of the hydrogel structure of the Cs-PEG and it can decrease the side effects of drugs including DOX.

Keywords: Biopolymeric Drug Carriers; Modified Chitosan; PEG; Drug Delivery; DOX

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1. Introduction

Chitosan is a linear polysaccharide with repeating unit β-(1→4) linked D-glucosamine and has a large number of amino and hydroxyl groups; this biopolymer is obtained by chitin deacetylation in large scales [1, 2]. Chitosan as a natural biopolymer can play a major role in drug delivery systems because of the biodegradability and biocompatibility properties. Moreover, a wide range of applications have been reported for the chitosan such as medicine, food packaging, cosmetics, water treatments, membranes and hydrogels [3-7].

To expedite chitosan for drug delivery systems, improving of its water solubility is necessary. To aim this goal, using polyethylene glycol (PEG) to increase the biocompatibility and water solubility is one of the ways reported in papers for modified chitosan [8].

Polyethylene glycol (PEG), is a polyether consisting of ethoxy units derived from ring opening polymerization of ethylene oxide [9]. Traditional PEG is a linear polymer with hydroxyl groups at both ends and it can easily conjugate with a functional group of nanoparticles; this process is called PEGylation. After PEGylation a hydrophilic protective layer is formed around the nanoparticles [10]. In drug delivery systems, PEG is used as a stealth material that enhances the half-life of drugs, reduce drug accumulation in clearance organs [11].

Nanomaterial can be defined as a material with size ranged between 1 to 100 nm. Nanotechnology by using nanostructures and nanophases at various fields can remove

the barrier of biological and physical science. Besides, it has shown the interesting capability in drug delivery systems and carriers. Nanostructures can stay in the blood circulatory system for a long period and enable the release of drugs as per the specified doses [12].

A pH-responsive nanomaterials can be defined as material that can respond to pH changes by swelling, degrading, shrinking or dissociating. This material can release their drug load in a pH-responsive method within the target in tissue or body organs. pH-Responsive nanoparticles are regarded as an ideal candidate for anticancer drug targets, for example it can be used for delivery of doxorubicin. The tumor microenvironment often exists at a lower pH (~ 5.7) than its surroundings (~ 6.8 – 7.0) due to localized acidosis [11].

Doxorubicin (DOX) is an anticancer drug that can be used for virulent lymphoma, leukemia and soft tissue sarcoma [13].

The aim of this research was simple preparation of the modified chitosan by polyethylene glycol (Cs-PEG) for making hydrogels. Hydrogels, an important class of soft materials, represent 3D polymeric networks designed for biomedical applications; specially, in drug delivery systems. Hydrogels are capable of trapping the large amount of water in their 3D network [14].

2. Experimental

2.1. Materials

All chemicals were purchased from Merck or Aldrich. Medium molecular weight chitosan, polyethylene glycol (MW 4000), acetic acid, doxorubicin (DOX), 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDC), reagent grade EtOH, acetone and deionized water was used for all experiments.

2.1.1. Preparation of Cs-PEG Hydrogel

0.5 g chitosan was dissolved in 50 ml acetic acid (1% V/V) in a 150 ml round bottom flask, stirring on a magnetic stirrer for 2 h at room temperature. Then, 0.5 g PEG was dissolved in 5 ml deionized water and added to Cs-acetic acid solution. The Cs-acetic acid-PEG solution was stirred on a magnetic stirrer for 24 h at room temperature. Then, 20 ml of ammonia solution (25%) was added to the Cs-PEG solution. After 24 h, the obtained hydrogel was filtered and washed with EtOH. Then, it was put in an oven (50 ˚C) for 5 h.

2.1.1.1 Encapsulation of Doxorubicin

For encapsulation of doxorubicin, it was needed to add 0.05 g EDC and 0.2 g of CS-PEG into 2 ml of different concentration of DOX including 2.5 μg/ml, 5.0 g/ml and 10.0 μg/ml of doxorubicin, it stirred for 24 h in room temperature.

3. Results and Discussion

3.1. Characterization of Cs-PEG

The obtained nanomaterial was characterized by using different spectroscopic, microscopic and analytical methods. Various techniques and methods namely Fourier transform infrared (FTIR), field emission scanning electron microscopy (FESEM) were utilized to identify the nanomaterial (**Figure 1 a, b**).

Fourier transform infrared (FTIR) was required to check the structure. Absorption peaks indicate the formation of bonds and structure (**Figure 1a**). Wide band at 3600-3200 cm^{-1} shows the OH and NH_2; the band 2888 cm^{-1} shows the vibration stretching of C–H bond. The characteristic peaks associated with PEG in CS-PEG at 1280, 947, and 842 cm^{-1} were significantly observed. The signal related to the amino group in 1635 cm^{-1} has significantly decreased compared to chitosan. This indicates that Cs-PEG nanoparticles were successfully linked.

FESEM picture of Cs-PEG shows the layered morphology of the Cs-PEG nanocarrier (**Figure 1b**).

Drug load efficiency (%) = $\frac{Amount\ of\ actual\ drug\ in\ the\ hydrogel}{Amount\ of\ drug\ added\ to\ hydrogel} \times 100$ (**Eq. 1**)

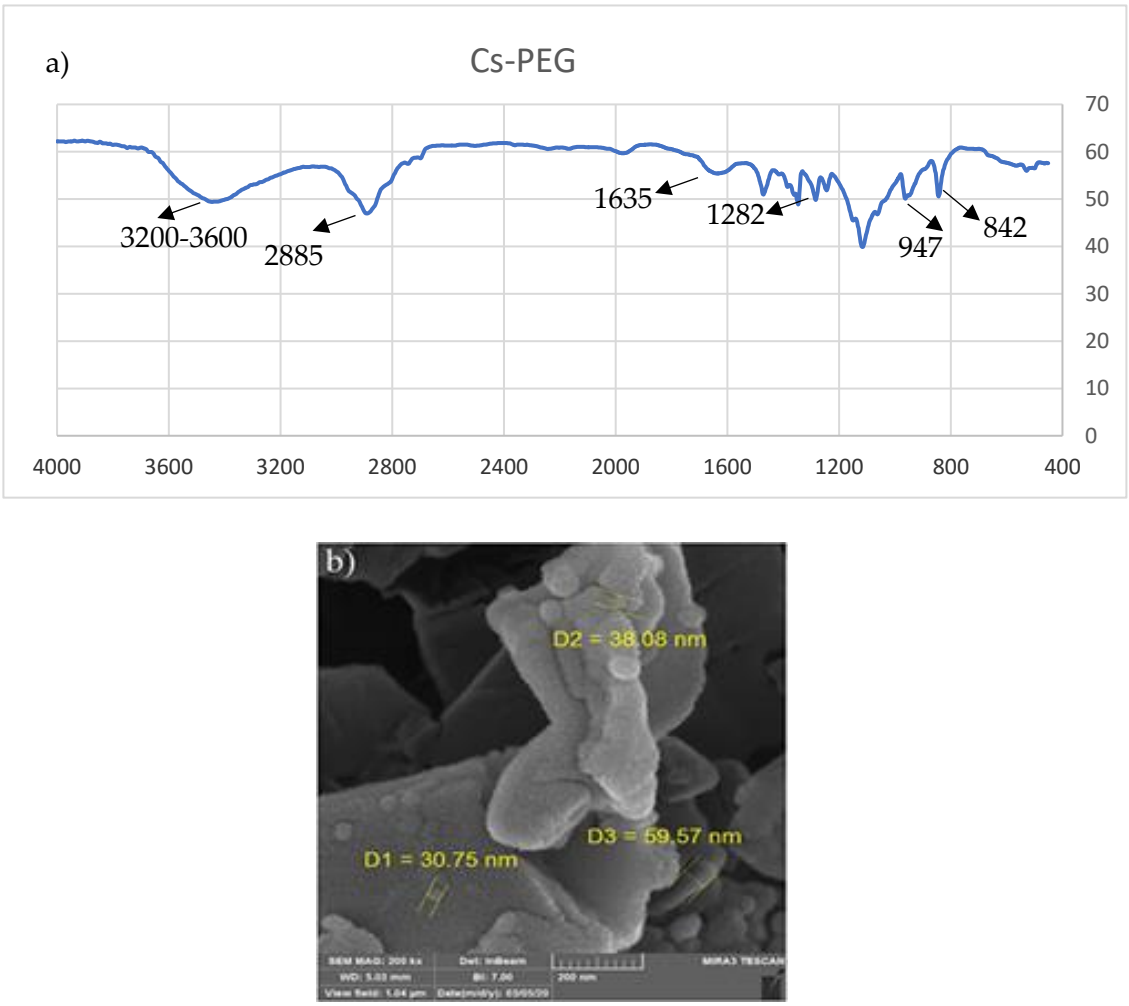

Figure 1. a) FTIR analysis of Cs-PEG; b) FESEM picture of Cs-PEG.

3.2. Analysis of DOX-Cs-PEG

Ultraviolet-Visible (UV-VIS) spectroscopy was used to check the loaded doxorubicin on Cs-PEG hydrogel. In **Figure 2**, the UV-VIS spectra of DOX master batch and filtrate solution after absorption on Cs-PEG have been demonstrated. The reduction of peaks between 400-500 shows that DOX successfully loaded on the Cs-PEG nanocarrier.

In vitro release profile shows the release rate of the pure DOX and DOX-Cs-PEG at pH 5.5 and 7.4 during 72 h. The release of the DOX at pH = 5.5 was better than the pH 7.4. Besides, the release rate of the DOX-Cs-PEG was better than the pure DOX; It indicates that the DOX loaded on Cs-PEG has had controlled release (**Figure 3**).

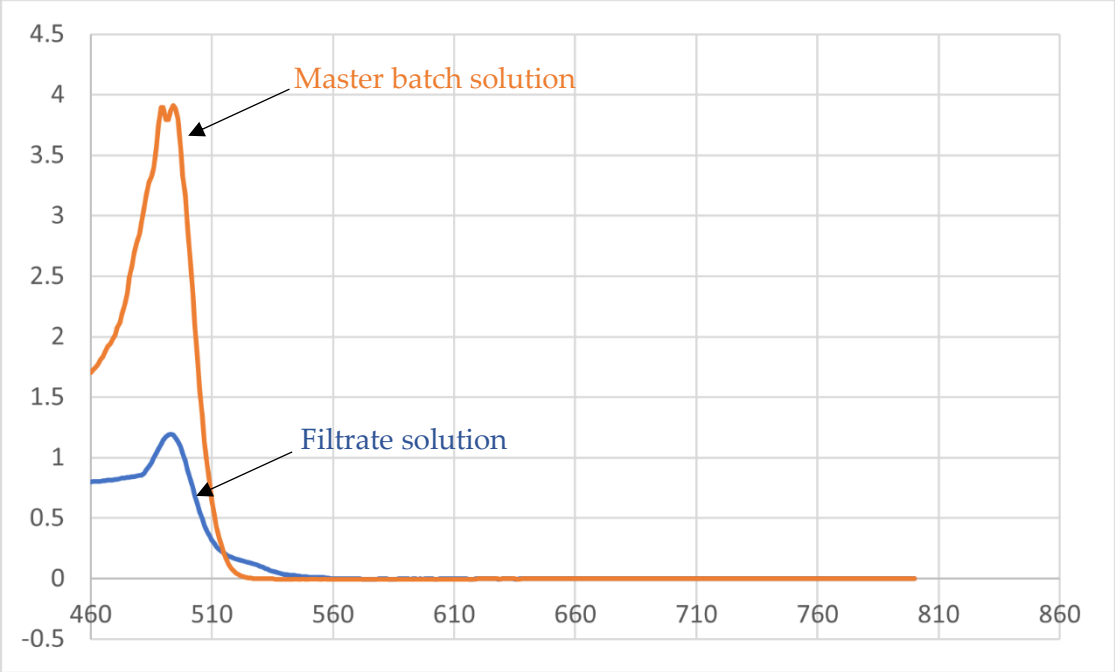

Figure 2. UV-VIS spectroscopy of DOX master batch (Orange) and filtrate solution after absorption on Cs-PEG the loaded doxorubicin (Blue) at 2.5 µg/ml concentration of DOX.

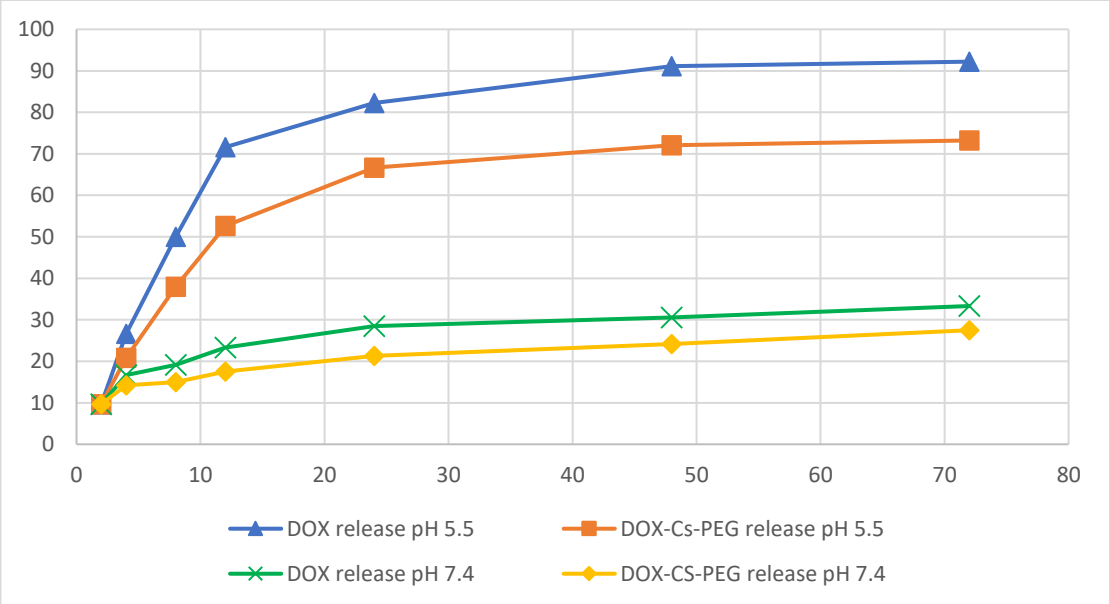

Figure 3. Dox release profile of DOX-Cs-PEG at pH 5.5 and 7.4.

4. Conclusion

The major goal of this research was simple preparation of the modified chitosan by polyethylene glycol (Cs-PEG) and local controlled delivery of doxorubicin by Cs-PEG nanocarrier. FTIR analysis shows that Cs-PEG nanocarriers were well prepared. Cs-PEG nanocarrier made a hydrogel, which is a suitable for doxorubicin drug loading and release. The UV-VIS indicates that by loading doxorubicin on Cs-PEG nanoparticles the efficiency of DOX release increases. These nanocarriers decrease the doxorubicin side effects and toxicity. It can be suggested that the Cs-PEG nanocarrier is a superior candidate for anticancer drug targeting.

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