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Synthesis of Carboxymethyl Chitosan and Its Derivatives Using KI and/or Ultrasonication †

Mahsa Rajabi, Mohammad Dohendou and Mohammad G. Dekamin *

Pharmaceutical and Heterocyclic Compounds Research Laboratory, Department of Chemistry, Iran University of Science and Technology, Tehran 1684613114, Iran

* Correspondence: mdekamin@iust.ac.ir; Tel.: +98-21-77240284

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Abstract: Chitosan is a natural polysaccharide that is mainly obtained from the shell of marine crustaceans including crabs, lobsters, shrimps, etc. Chitosan has been widely used in biomedicine due to its special characteristics of low toxicity, biocompatibility, biodegradation, and low immunogenicity. However, owing to the limited solubility of CS in water, its water-soluble derivatives are preferred for the mentioned applications. Carboxymethyl chitosan (CMC) is one of the water-soluble derivatives of chitosan, which has antibacterial, anticancer, antitumor, antifungal, antioxidant properties, and is used in both drug delivery and enzyme delivery. This material is also utilized in tissue engineering, wound healing, and bioimaging. For these reasons, in this article, a different and novel method by using KI and/or ultrasonication is proposed.

Keywords: chitosan; carboxymethyl chitosan (CMC); ultrasonication

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1. Introduction

Nowadays, due to the dramatic growth in demands for improving and creating novel biocompatible and biodegradable functional materials, the use of natural biopolymers, such as chitosan, alginate, etc., is increasing [1–3]. Chitosan is found in the cell wall of crustacean marine animals and is also synthesized by deacetylation of chitin, the main polysaccharide essentially extracted from crustacean cuticles. Moreover, because of its numerous properties comprising nontoxicity, biodegradability, and biocompatibility it has been broadly employed in different fields of knowledge including tissue engineering [4–6], drug delivery [7,8], organocatalysis [9–11], and wound dressing [12]. One of the most important parameters in the usage of natural polymers in medicine is their solubility. Chitosan is insoluble in neutral water (pH ~7) since its amino groups (–NH2) remain unprotonated in neutral water [13]; therefore, producing a soluble derivative of chitosan, such as carboxymethyl chitosan (CMC), for better application, is crucial. Converting chitosan to CMC is one of the important methods for increasing the solubility of this natural polymer, which is performed by changing the polar properties of the polymer to a higher polarity. As a result, the CMC can be dissolved in water over a wide range of pH, which affords an expedient use of CMC in abundant applications [12]. Moreover, CMC has eligible properties, such as antimicrobial activity [14–16], biocompatibility [17,18], and low toxicity [19], which are crucial items in the field of medicine and drug delivery. In this article, we discuss two approaches to the synthesis of CMC by using KI and ultrasound radiation.

2. Materials and Methods

2.1. Materials

Chitosan, 100 mesh, magnesium hydroxycarbonate, and KI GR was purchased from Merk Company, monochloroacetic acid was supplied by the Sigma Company, ethyl alcohol (96%) and ethyl chloroacetate were provided from Riedel dehaen Company.

2.2. CM-Chitosan Preparation with KI

To synthesize CMC, magnesium hydroxycarbonate (0.4 g, 1.7 mmol) was dissolved in distilled water with a slight heating, then chitosan (0.2 g) was added gradually to the suspension. After that, potassium iodide (0.05 g, 0.3 mmol) was added to the solution and mixed for one hour. A mixture of monochloroacetic acid (0.38 g, 4 mmol) in IPA (2 mL) was added dropwise under stirring at 30 min, then the solution was mixed at room temperature for a further 4 h. To obtain the prepared CMC Na-salt, 10 mL ethanol was poured into the suspension, then mixed and filtered and dried under vacuum. The CMC Na-Salt (0.45 g) was suspended in 80% ethanoic aqueous solution (10 mL) and neutralized with hydrochloric acid (2 mL, 13%), after that the mixture was stirred for 30 min. The solid product (CMC) was filtered and rinsed with 80–90% ethanoic solution, to obtain neutral mother liquor, then the filtrate was placed in the vacuum oven to acquire the final dry product.

2.3. Preparation Et-CMC under Ultrasonication

To synthesize Et-CMC, chitosan (0.3 g) and chloroethyl acetate (2.2 mL) were mixed in a flask and stirred for one hour at room temperature. The mixture was placed in an ultrasonic bath for 4 times (10 min), 5 min interval each time, and then it was put into an oven for 1 h to dry the product, Et-CMC, completely (Figure 1).

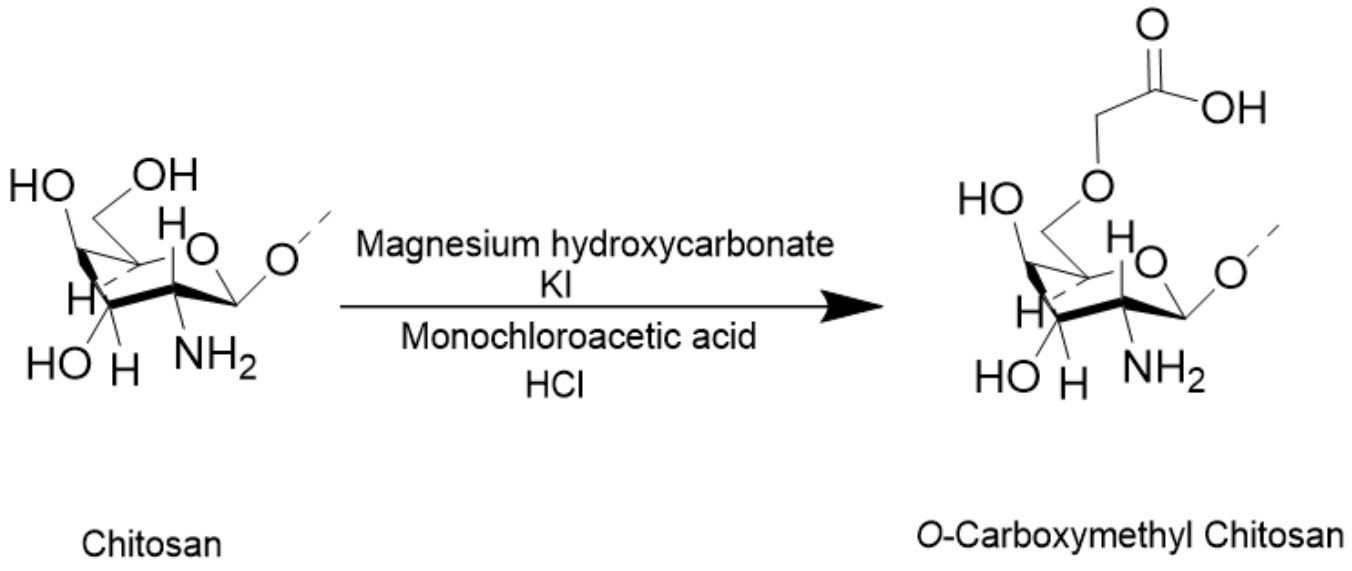

Figure 1. *Cont.*

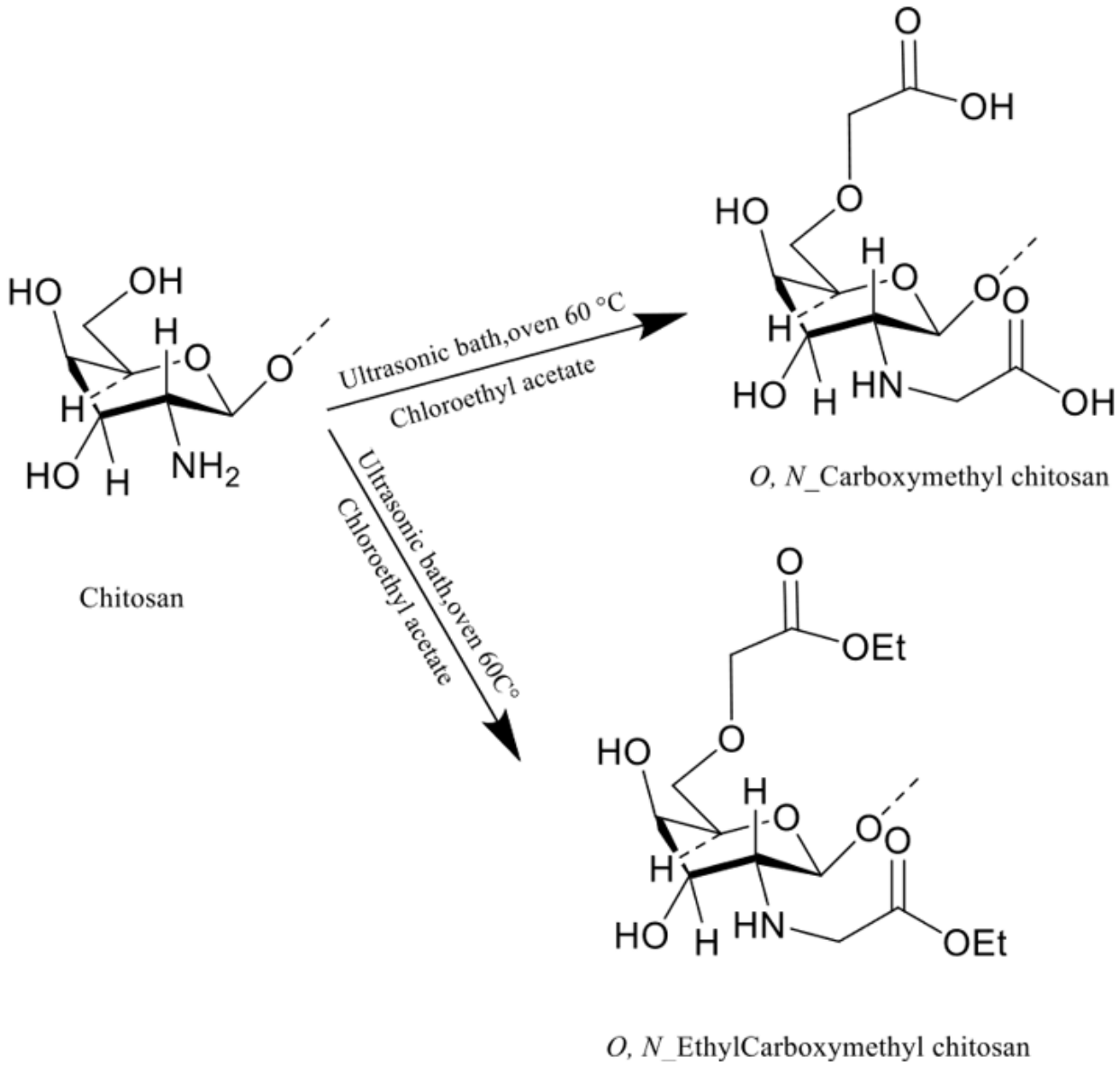

Figure 1. The chemical structures of chitosan (CS) and carboxymethyl chitosan (CMC) derivatives.

3. Results

3.1. Characterization

3.1.1. FTIR Analysis

The chitosan IR spectrum is illustrated in Figure 2, which is interpreted below: the O-H stretching band at (3427 cm^{-1}), the aliphatic C-H band at (2865 cm^{-1}), N–H bend at (1595 cm^{-1}), and bridge-O stretch and C-O stretching band at (1154 cm^{-1}) and (1089 cm^{-1}), respectively. All CMC products, which were prepared under different modifying conditions, had a similar IR spectrum (Figure 3). All samples had a broad –COOH group and $–NH3^{+}$ group bands at (1743 cm^{-1}) and (1508 cm^{-1}). The IR spectrum of Et-CMC is illustrated in orange line in (Figure 3).

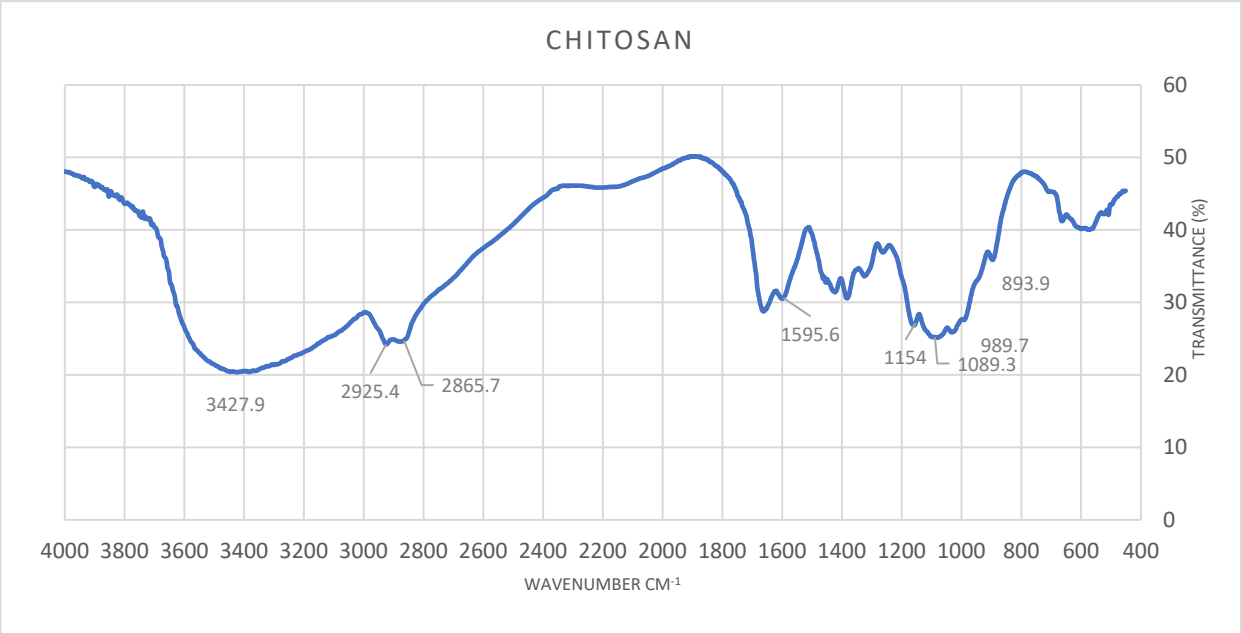

Figure 2. The IR spectrum of chitosan.

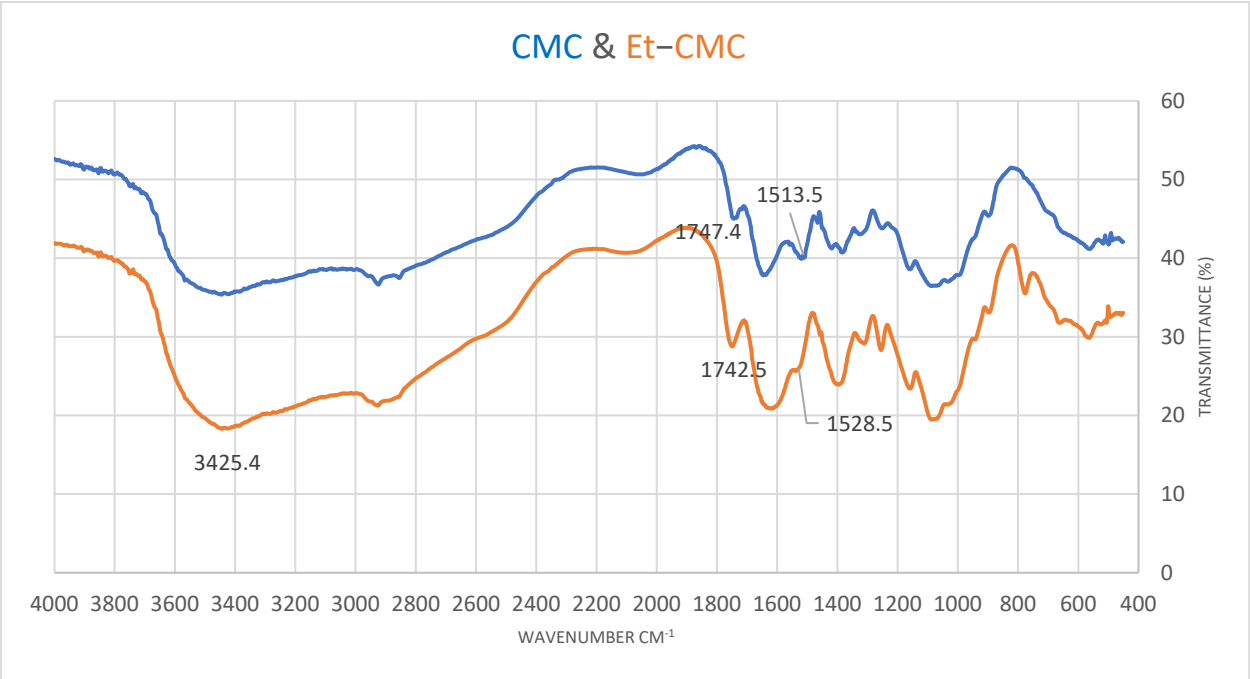

Figure 3. The IR spectrum of CMC (blue line) and Et−CMC (orange line).

3.1.2. The Water Solubility

The water solubility of the samples was estimated as follows. An amount of 0.01 g of samples was added to 1 mL distilled water and mixed at room temperature for 1 h to obtain the clear solution or transparent jelly form.

4. Biomedical and Pharmaceutical Applications of Carboxymethyl Chitosan

4.1. Anticancer

One of the most important applications of theses substrates is in drug delivery for anticancer pharmaceuticals. Nanoparticulate drug delivery systems are suitable for the treatment of various types of cancers. For instance, doxorubicin·HCl, a water-soluble anticancer drug was loaded on calcium carbonate/CM−chitosan ($CaCO_3$/CM-chitosan) hybrid microspheres and nanospheres. The hybrid microspheres and nanospheres with high encapsulation efficiency and effective sustained in vitro drug release was investigated as well [20]. Moreover, methoxy poly(ethylene glycol)-grafted CM-chitosan has been synthesized to make nanoparticles with incorporated doxorubicin and tested with doxorubicin-resistant C_6 glioma cells. The result showed that the penetration rate of doxorubicin-incorporated nanoparticles into tumor cells was faster than doxorubicin alone; therefore, the doxorubicin-incorporated nanoparticles of CM-chitosan-poly(ethylene glycol) are more aproporiate for antitumor drug delivery [21].

4.2. Application in Drug/Enzyme Delivery

CMC hydrogels showed excellent pH sensitivity. The superior swelling/release characteristics in pH-dependent drugs, at pH values 6.8 and 7.4, has demostrated that these hydrogels were suitable carriers of ornidazole as a colonic drug [22]. Other examples in this field were the CMC−functionalized Fe_3O_4 nanoparticles [23], and chitosan/CMC stabilized superparamagnetic Fe_3O_4 nanoparticles [24], which properly applied in targeted drug delivery.

4.3. Antioxidant Properties

It has been reported that CMC could display appropriate antioxidant activity, mainly due to the existence of hydroxyl and amino groups in the polymeric chains [25]. It was also found that by decreasing the CMC molecular weight, its antioxidant activity increases, which can be attributed to the decreased number of intra-/inter-molecular hydrogen bonds. The superoxide anion scavenging activities of low molecular weight CMCs obtained by oxidative degradation were evaluated and it was shown that lower molecular weight CMC had a higher activity [26,27]. In contrast, the CMC Schiff bases did not illustrate improved antioxidant potency which was related to the breaking of some hydrogen bonds, the formation of some new hydrogen bonds, and converting the NH_2 groups to C−N bonds [27,28].

Author Contributions: M.R. worked on the topic, as her thesis, and prepared the initial draft of the manuscript. M.G.D. is the supervisor of M.R. and M.D. as his students. In addition, he edited and revised the manuscript completely. M.D. has worked closely with M.R. for doing experiments and interpreting of the characterization data. M.D. also worked closely with M.R. for doing some experiments and drawing of graphs. M.D. has revised the manuscript before final submission. All authors have read and agreed to the published version of the manuscript.

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