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Ibuprofen-loaded chitosan and chemically modified chitosans—Release features from tablet and film forms

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ABSTRACT

The biopolymer chitosan was chemically modified in two sequences of reactions: (i) immobilization of methyl acrylate followed by cysteamine and (ii) the sequence of immobilization reactions involving ethylene sulfide, methyl acrylate and finally cysteamine. In both cases the pendant chains have attached nitrogen, oxygen and sulfur basic centers. The corresponding structures were characterized through elemental analysis, infrared spectroscopy, nuclear magnetic resonance in the solid state for carbon, thermogravimetry and scanning electron microscopy. The newly synthesized biopolymers have abilities to immobilize and controllably release the non-steroidal drug ibuprofen. The ibuprofen-loaded biomaterials as tablets or as films crosslinked with glutaraldehyde revealed that drug release is pH sensitive. The chemically modified chitosan may allow reduction of drug release in stomach fluids, since the functional groups cause a decrease in swelling rate at pH 1.2, opposite to the behavior that occurs at pH 7.4, that of nutritional fluid, where an increase of the rate of swelling occurs. In such conditions the negatively charge ibuprofen is electrostatically repelled by negative chitosan derivative surfaces.

1. Introduction

Convenient pristine inorganic or organic polymers may change the ability of surfaces to react in a subsequent step and the products have their chemical properties modified. Based on this principle, low cost polymeric organic materials, abundant in nature, have been widely used in these types of investigations. Among these chitosan stands out as it is favorably extracted from natural sources and used as a valuable biopolymer applied in several academic and technological applications [1–4].

Its extensive utility is associated with immobilization of organic pendant chains, active moieties that can interact with drugs so that their controlled release is highlighted. This behavior is favorable due to the fact that chitosan is a linear biopolymer containing D-glucosamine and N-acetyl glucosamine, units which give to the biopolymer great advantages in properties such as biodegradability, biocompatibility, and non-toxicity [5,6]. However, its application as a matrix to release drugs is limited due to its low solubility in water under physiological conditions and lack of amphipathicity. Meanwhile, several chitosan derivatives obtained from exploitation of a series of reactions resulted in improvement in these biopolymers and their applicabilities [7–9]. For example, the effective control of swelling behavior that is susceptible to the pH of the environment depends on acid-sensitive drug incorporation into such arrays, which would be protected in gastric juice [8].

Based on biopolymer applicability, the main purpose in this field is the search for the best conditions to retain the desired drug for later use in a next step. So, drug-loaded chitosan or one of its chemical derivatives might provide these advantages for nonsteroidal anti-inflammatory drugs such as ibuprofen that has an amphiphilic character and leads to gastric irritation [10–14]. An encapsulation procedure would avoid various musculoskeletal disorder effects and lead more directly to reduce painful conditions [15]. The importance of this drug is reflected in its wide use for the symptomatic relief of headache (migraine), muscle pain, rheumatoid arthritis, osteoarthritis, primary dysmenorrhea, dislocations and fractures, and fever and pain relief associated with acute or chronic inflammatory reaction [16].

It is worth mentioning that there is an inconvenience in the use of non-steroidal anti-inflammatory drugs, often associated with gastrointestinal complications. This behavior is clearly justified by the fact that 15–30% of patients who utilize these kinds of drugs for a long time have gastrointestinal ulcers and bleeding or renal dysfunction [17]. Thus, the need arises to minimize these adverse effects and to extend its inflammatory action, where the targeted delivery of drug through the use of a matrix, such as chitosan or chitosan derivatives, can help to reduce a series of undesirable side effects [12,15,18].

The present investigation deals with derivative biopolymers from chitosan for controlled release of non-steroidal drugs. For this application, the drug loading matrix was prepared in crosslinked

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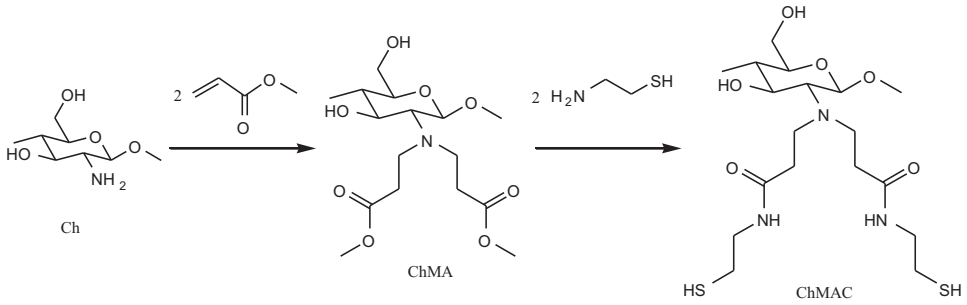


Scheme 1. Reaction of chitosan (Ch) with methyl acrylate (MA), followed by cysteamine (C) to yield ChMA and ChMAC, respectively.

film and tablet forms, to accommodate the selected drug ibuprofen inside the polymeric material.

2. Experimental

2.1. Materials

Powdered chitosan, with a degree of deacetylation of 84.8%, determined from infrared spectroscopy, was obtained by extraction from crab shells and supplied by Primex Ingredients A.S. (Norway). Methyl acrylate (Acros), cysteamine (Aldrich), ethylene sulfide (Aldrich), ibuprofen (Galena), glutaraldehyde (Dinâmica), triethylamine (Aldrich), acetone (Synth) and ethanol (Synth) were all reagent grades and were used without prior purification.

2.2. Syntheses of chitosan biopolymer derivatives

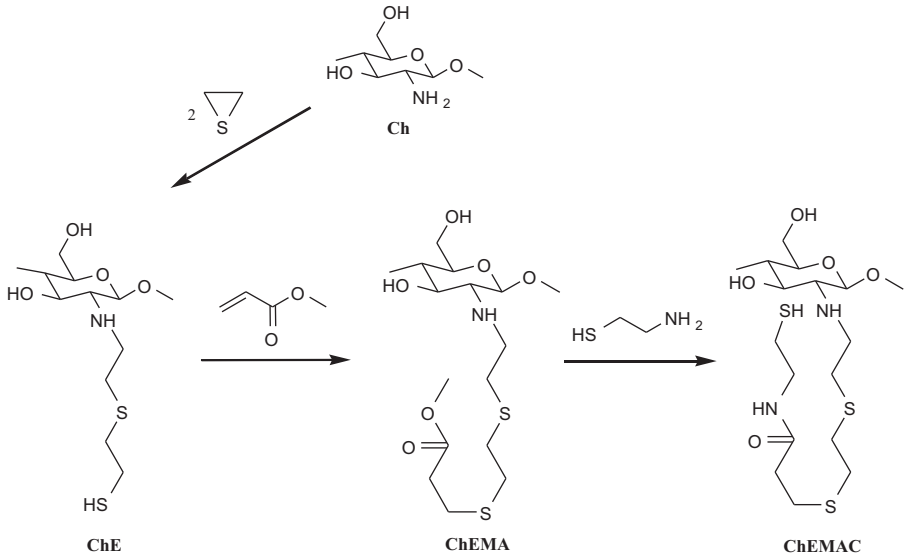
Two sequences of chitosan derivation were performed in two and three independent steps, to incorporate pendant chains on the available basic amino groups, as follows:

I. (a) The first stage consisted of adding methyl acrylate (MA) to a sample of 15.0 g of chitosan (Ch), maintaining a 1:2 chitosan/methyl acrylate molar ratio, followed by addition of 2.0 cm^3 triethylamine in a reaction flask immersed in a sand bath at 318 K. The chemical mixture was heated under magnetic stirring for 24 h. Then, the biopolymer (ChMA) obtained from this reaction was washed with acetone and dried in vacuum at 323 K. (b) In the second step, a sample of 5.0 g ChMA was suspended in 80 cm^3 of ethanol, followed by the addition of cysteamine (C) in a 1:2 molar ratio and 2.0 cm^3 of triethylamine. The reaction was carried out as in the preceding stage and the new biopolymer (ChMAC) was similarly washed and dried. This series of reactions is illustrated in Scheme 1.

II. (a) To a sample of 15.0 g chitosan (Ch) was added ethylene sulfide (E) in a 1:2 molar ratio in the absence of solvent at 328 K, under magnetic stirring, and then heated for 3 h, according to a previously described procedure [19]. The biopolymer (ChE) obtained from this reaction was then washed with acetone and dried at 323 K. (b) To a sample of 10.0 g ChE was added methyl acrylate (MA) in 1:1 molar ratio and 3.0 cm^3 of triethylamine in a reaction flash immersed in a sand bath at 318 K, and kept under reflux with mechanical stirring for 24 h. The resulted biopolymer (ChEMA) from this reaction was washed with acetone and dried at 323 K. (c) Finally, 5.0 g of ChEMA was suspended in 80 cm^3 of ethanol, followed by the addition of cysteamine (C) in a 1:1 molar ratio and 3.0 cm^3 of triethylamine in a reaction flash immersed in a sand bath at 318 K, and refluxed under mechanical stirring for 24 h. The biopolymer (ChEMAC) formed from this reaction was washed with acetone and dried at 323 K. The set of reactions for this sequence is shown in Scheme 2.

2.3. Characterization

Carbon, hydrogen, nitrogen and sulfur elemental analyses were performed on a Perkin Elmer model PE 2400 elemental



Scheme 2. Reaction of chitosan (Ch) with ethylene sulfide to produce the ChE biopolymer, which is then reacted with methyl acrylate, followed by cysteamine, to yield ChEMA and ChEMAC, respectively.