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Review

Biomedical applications of carboxymethyl chitosans

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ABSTRACT

This review outlines the recent developments on carboxymethyl chitosan-based bio-medical applications. Carboxymethyl chitosan, a water soluble derivative of chitosan, with enhanced biological and physicochemical properties compared to chitosan, has emerged as a promising candidate for different biomedical applications. Introducing small chemical groups like carboxymethyl to the chitosan structure can drastically increase the solubility of chitosan at neutral and alkaline pH values without affecting their characteristic properties. Due to improved biocompatibility, high moisture retention ability more viscosity and enhanced antimicrobial property of carboxymethyl chitosan than chitosan makes it promising candidate for hydrogels and wound healing applications. The biodegradability and biocompatibility of carboxymethyl chitosan has significant interest with application as biomaterial for tissue engineering. Apart from this, the easy of carboxymethyl chitosan can be easily processed into nanoparticles so it has shown promise for drug delivery, bioimaging, biosensors and gene therapy applications. The contribution of carboxymethyl chitosan to green chemistry in the recent years has also been given in detail. This review will focus on preparative methods and physicochemical and biological properties of carboxymethyl chitosan with particular emphasis on biomedical and pharmaceutical applications of this derivative of chitosan.

Contents

Abbreviations: CM-chitin, carboxymethyl chitin; CM-chitosan, carboxymethyl chitosan; CE-chitosan, carboxyethyl chitosan; OCM-chitosan, O-carboxymethyl chitosan; NCM-chitosan, N-carboxymethyl chitosan; NOCM-chitosan, N,O-carboxymethyl chitosan; NCB-chitosan, N-carboxybutyl chitosan; NNDCM-chitosan, N,N-dicarboxymethyl chitosan; NCE-chitosan, N-carboxyethyl chitosan; NCM-chitin, N-carboxymethyl chitin; MW, molecular weight; BMP-2, bone morphogenetic protein-2; DA, degree of acetylation; DD, degree of deacetylation; DS, degree of substitution; HRP, horseradish peroxidase; ROS, reactive oxygen species; IPN, interpenetrating networks; semi-IPN, semi-interpenetrating networks; XPS, X-ray photoelectron spectroscopy; MRI, magnetic resonance imaging; CAC, critical aggregation concentration; CM chitosan-SPIONS, carboxymethyl chitosan modified superparamagnetic iron oxide; FA, folic acid; BSA, bovine serum albumin; GFLX, gatifloxacin; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; HEMA, 2-hydroxyethylmethacrylate.

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1. Introduction

A most recent article by Muzzarelli et al. (2012) celebrated the bicentennial of the discovery of chitin, and in the light of our current knowledge, reviewed the major research topics explored by Henry Braconnot, who described for the first time a polysaccharide containing a substantial percent of nitrogen, later to be called chitin. Its importance has been assessed with details on acids isolated from plants, that were later used for the preparation of soluble chitosan derivatives that paved the way for a number of applications. The biocompatibility, biodegradability, antimicrobial activity, absence of toxicity and hydrating properties of chitin and chitosan are today well established. Due to these desirable properties, chitin and chitosan can be easily processed into scaffolds (Duarte, Mano, & Reis, 2010), nanoparticles (Csaba, Hoggard, & Alonso, 2009), microparticles (Lameiro, Lopes, Martins, Alves, & Melo, 2006), beads (Gandhi, Kousalya, Viswanathan, & Meenakshi, 2011), membranes (Beppu, Vieira, Aimoli, & Santana, 2007) and nanofibers (Homayoni, Ravandi, & Valizadeh, 2009) forms. In the recent decades, CM-chitosans have received much attention to their better solubility in water, enhanced antibacterial property (Liu, Guan, Yang, Li, & Yao, 2001), improved biocompatibility (Chen, Wang, Liu, & Park, 2002; Zhu, Chan-Park, Dai, & Li, 2005) and safety for humans (Fu et al., 2011). CM-chitosan is also known to exhibit low toxicity (Tokura, Nishimura, Sakairi, & Nishi, 1996). The carboxymethylation procedure of both chitin and chitosan has been earlier reported (Muzzarelli, 1988). The inspiration behind the development of NCM-chitosan was the functionalization of chitosan in such a way as to have an amino acid moiety in it, actually glycine. The active hydroxyl and amino groups in the polymer chains of CM-chitosan are known to take part in free radical scavenging and hence contribute to its increased antioxidant activity. The enhanced antioxidant property and bile acid binding property of this derivative of chitosan have been well established (Zhao, Huang, Hu, Mao, & Mei, 2011). The influence of MW and the presence of hydroxyl, amino and amido groups in the polymer chain of CM-chitosan on its antioxidant activity have also been described by various researchers (Feng, Du, Li, Hu, & Kennedy, 2008; Sun, Zhou, Xie, & Mao, 2007). Therefore, carboxymethylation of chitosan makes it a promising candidate in a number of biomedical, pharmaceutical, and environmental fields (Chen et al., 2007; Mishra et al., 2011; Wang, Yang, & Niu, 2010; Xu, Mao, Liu, Zhu, & Shen, 2006; Yin, Fei, Cui, Tang, & Yin, 2007). Here we have reviewed the considerable research performed to date on the water-soluble CM-chitosans, particularly with respect to their biomedical applications, but potential applications of this derivative in the other fields will also be discussed.

2. Carboxymethyl chitosan: structural and functional features

2.1. Preparation and characterization of various carboxymethyl chitosans

2.1.1. Preparation of O-carboxmethyl chitosan

OCM-chitosan is an amphiprotic ether derivative which contains —COOH groups and $-NH_2$ groups. The preparation of OCM-chitosan involves suspension of chitosan in the isopropanol + NaOH; then, monochloroacetic acid dissolved in isopropanol is added drop wise within 30 min and reacted for 4 h at 55 °C. The solid is filtered and washed with ethyl alcohol and dried in vacuum. Thus the reaction medium used for OCM-chitosan synthesis is strongly alkaline. The water solubility of OCM-chitosan is governed by the preparation conditions as well as degree of carboxymethylation. While OCM-chitosan prepared between 0 and 10 °C was found to be water soluble, the other prepared between 20 and 60 °C was found to be water insoluble at neutral pH (Chen, Du, & Zeng, 2003). OCM-chitosan has been employed for immobilization of enzymes of clinical significance (Xu, Mao, Liu, Zhu, & Shen, 2006), as well as grafting of polyacrylamide induced by cericammonium onto OCM-chitosan (Joshi & Sinha, 2007). The schematic representation of preparation methods for various carboxymethyl derivatives of chitosan is shown in Fig. 1.

2.1.2. Preparation of N-carboxmethyl chitosan

The preparation of NCM-chitosan involves reacting free amino group of chitosan with glyoxylic acid to give soluble aldimine and then reduction of the latter with sodium borohydride. The choice of chitosan (in terms of DA and MW) and the amount of glyoxylic