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Review article

Strategies to improve chitosan hemocompatibility: A review

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ABSTRACT

Due to its remarkable physicochemical and biological properties, chitosan is one of the most promising polymers for biomedical applications. The cationic nature of chitosan may induce thrombosis making it unsuitable as blood – contacting material. Nevertheless, in the last decade many researchers are attempting to modulate the biopolymer-blood interactions and to develop hemocompatible chitosan derivatives, which will broaden the biopolymer applications. This paper provides an overview of the strategies used to enhance chitosan hemocompatibility, focusing on two specific topics: (i) strategies based on chemical modifications of chitosan and (ii) strategies based on association of this biopolymer with compounds that exhibit complementary properties. It also highlights the current progress in the design of hemocompatible functionalized chitosan-based systems for biomedical applications such as: drug delivery, central nervous system disease treatment, theragnosis and cardiovascular applications.

Contents

Abbreviations: APTT, activated partial thromboplastin time; Bb, fragment of complement of factor B; BBB, blood brain barriers; BCI, blood coagulation index; C3a, C4a and C5a, peptide anaphylatoxins; C4d, cleavage product of complement component C4; CH-50, hemolityc complement; DD, degree of N-deacetylation; Fb, fibrinogen; FDP, fibrin degradation products; FPA, fibrinopeptide A; FXII, Hageman factor; HMWK, high molecular weight kininogen; iC3b, proteolytic fragment; LSCs, lauroyl sulphated chitosan; MW, molecular weight; N-CMCs, N-carboxymethyl chitosan; N,O-SCs, N,O-succinyl-chitosan; N,O-CMCs, N,O-carboxymethyl chitosan; N-PCCs, N-phosphorylcholine-chitosan derivative; N-SCs, N-succinyl chitosan; O-CMCs, O-carboxymethyl chitosan; O-SCs, O-succinyl-chitosan; PC, phosphorylcholine; PEG, poly (ethylene glycol); PT, prothrombin time; PTT, partial thromboplastin time; RES, reticuloendothelial system; SC5b-9, terminal complement complex; TAT, trombin-antitrombin III complex; TEG, thromboelastography; TCC, terminal complement complex; TT, thrombin time.

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1. Introduction

In recent years, various natural and synthetic polymers (cellulose, chitosan, poly (tetrafluoroethylene), poly (vinyl chloride), polyethylene, polysulfone) have been used in biomedical applications that imply a contact with bloodstream including artificial organs, biodegradable medical devices and disposable clinical apparatus such as vascular prostheses, heart valves, blood pumps, peacemaker, dialysers and plasma separators [26,68,166,138]. Despite the initial promising results achieved using synthetic polymers [75,206], one of the main drawbacks related with the development of blood-contact medical devices remains the lack of surface hemocompatibility [206]. Hemocompatibility is a complex issue that concerns materials or devices used in contact with blood. This property is governed by coagulation biochemistry and blood materials interactions, but also, by the design and function of the device into the bloodstream [145]. In this matter, blood-compatible materials development remains one of the most challenging problems in the field of biomaterials [147].

Neverless, chitosan is a biocompatible polymer with exciting properties that recommend it for a great variety of biomedical applications. As chitosan use is growing in the medical field, it is imperative to describe its interactions with blood as well. In the last years, hemostatic potential of chitosan has been extensively exploited for wound healing. Several characteristics such as: chemoattraction and activation of macrophages and neutrophils, promotion of granulation tissue and re-epithelialization, limitation of scar formation and retraction; analgesic, hemostatic and intrinsic antimicrobial activity [20] sustain chitosan use as a suitable material for efficient wound dressings. Various forms of chitosan-based hemostatic bandages approved by FDA and certified by CE and NATO are currently used in emergency and battlefields [37,140,197,198]. However, the hemostatic prospective of chitosan is not the aim of this paper and therefore it will not be further discussed in detail. For more information concerning this subject, readers are asked to study some relevant and comprehensive papers already published in this field [20,73,121,126,88].

At the same time, due to its beneficial physicochemical properties, functionality and processability, chitosan has been considered for a series of biomedical applications such as: cardiovascular surgery, drug delivery, gene therapy or theragnosis. For systemic therapy or disease diagnosis, the mostly used route is represented by intravenous administration; for a succesfully usage in these applications, chitosan and its derivates should be hemocompatibile. Even by other administration routes, the biopolymer or their degradation products would more or less enter into the systemic circulation. This is also applicable to biodegradable polymeric materials for tissue-engineering scaffolds, because the degraded polymer fragments would finally rich the blood circulation [99]. For this reason an increasing consideration has been dedicated to the blood compatibility of chitosan and its derivates [95,101,161,205].

Countless data are found in the literature concerning chitosan hemocompatibility. Most of the studies suggested that the interactions of free amino groups of chitosan with plasma proteins or/and blood cells could induce a thrombogenic or/and a hemolytic response. Some of them reported that chitosan is highly thrombogenic [57] since it has the capacity to activate both complement [174] and blood coagulation systems [19]. Mechanism of blood–chitosan interaction has been explained by an initial adsorption of plasma proteins on chitosan-based systems, followed by adhesion and activation of platelets that lead to the formation of thrombus [31,215]. According to Furie and Furie [49], the blood coagulation mechanism triggered by positive surfaces is mainly related to extrinsic pathway. The positive charge can induce fibrinogen adsorption, followed by its conformational modification and adhesion of platelets and leukocytes (monocytes). Adherent cells are activated; they release numerous molecules that will cleave the fibrinogen and a fibrin network (clot) will be formed [21]. Indeed, it has been reported that deacetylated, but not acetylated forms of chitosan bind preferentially to fibrinogen [15]. Meanwhile, it has been found that chitosan promotes coagulation in vitro with whole blood clotting time reduced by 40% compared to whole blood alone [144]; these events seems to be independent of the classical coagulation pathway, suggesting that the biopolymer can induce hemagglutination due to the interactions of free amino groups of chitosan with acidic groups of blood cells and forming of polyelectrolyte complexes