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Review

Recent development of chitosan-based polyelectrolyte complexes with natural polysaccharides for drug delivery

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ABSTRACT

Chitosan, as a unique positively charged polysaccharide, has been one of the most popular biopolymers for development of drug delivery systems for various applications, due to its promising properties, including high biocompatibility, excellent biodegradability, low toxicity, as well as abundant availability and low production cost. Since last decade, increasing attention has been attracted by delivery systems fabricated from natural biopolymer-based polyelectrolyte complexes (PEC), formed by electrostatic interactions between two oppositely charged biopolymers. In order to tailor specific applications of chitosan-based PEC drug delivery systems, various forms have been developed in recent years, including nanoparticles, microparticles, beads, tablets, gels, as well as films and membranes. The present review focuses on the recent advances in drug delivery applications of chitosan-based PEC with other natural polysaccharides, including alginate, hyaluronic acid, pectin, carrageenan, xanthan gum, gellan gum, gum arabic, and carboxymethyl cellulose, etc. The fabrication techniques, characterizations, as well as *in vitro* and *in vivo* evaluations of each PEC delivery system are discussed in detail.

Contents

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1. Introduction

1.1. Chitosan

Chitosan, the *N*-deacetylation product of chitin, a natural and ubiquitous polysaccharide, is mostly found in the exoskeleton of crustaceans, insects, and fungi. Chitosan is a linear polysaccharide, composed of glucosamine and *N*-acteyl glucosamine units via β-(1 → 4) linkages, randomly or block distributed throughout the biopolymer chain, depending on the preparation method to derive chitosan from chitin. The deacetylation degree is defined as the molar ratio of glucosamine to *N*-acetyl glucosamine, which is an important parameter determining its properties and applications. After deacetylation process, chitosan is able to dissolve in acidic medium and becomes the only polysaccharide that possesses high density of positive charges, due to the protonation of amino groups on its backbone. Besides this unique characteristic, chitosan has been proved to have many other intrinsic properties, such as non-toxicity, biocompatibility and biodegradability [1]. Chitosan and its derivatives have been receiving significant scientific interests and become one of the hottest topics in recent decades, especially for its food, medical and pharmaceutical applications, including nutrient [2–5] and drug delivery [6–9], and tissue engineering [10,11].

1.2. Polyelectrolyte complexes (PEC)

Polyelectrolytes are macromolecules carrying a relatively large number of functional groups that either are charged, or under suitable conditions can become charged [12]. Polyelectrolyte complexes (PEC) are formed simultaneously by mixing oppositely charged polyelectrolytes in solution without any chemical covalent cross-linker. The major interactions between two polyelectrolyte polymers include the strong but reversible electrostatic and dipole–dipole association, as well as hydrogen and hydrophobic bonds [13]. In contrast to chemically cross-linked complexes, PEC is generally non-toxic, well-tolerated and biocompatible. Because chemical cross-linkers may induce toxicity if un-reacted residuals found in free traces before administration, further purification and verification steps are needed for covalently cross-linked complexes [14,15]. For instance, compared with synthetic polymers, PEC plays an important role in designing drug delivery systems for protein or peptide drugs through oral route, which is the most preferred route. Most of the synthetic polymers are immunogenic and encapsulation of proteins into these delivery systems involves harsh processing conditions which might cause denaturation and inactivation of the encapsulated proteins. The stability of PEC could be affected by many factors, including density of charges, degree of ionization, pH of reaction medium, concentration of polyelectrolytes, distribution of ionic groups, molecular weight, mixing ratio, order of reacting polyelectrolytes, and drying process, etc. Recently, PEC of polysaccharides and proteins has been extensively investigated and widely used for biomedical applications, such as drug encapsulation and delivery, DNA-binding, enzyme immobilization, tissue engineering, biosensor, etc. [16–19].

1.3. Chitosan-based PEC

Due to the protonation of amino groups on the backbone, chitosan becomes a cationic polyelectrolyte in acidic medium, which could form PEC with negatively charged polyelectrolytes, resulting in various applications. The different types of chitosan-based PEC with various polyelectrolytes and their biomedical applications are briefly summarized in Table 1. Many polyanions from different categories have been well investigated to form PEC with chitosan, including natural polymers (alginate, pectin, xanthan gum, carrageenan, cellulose, collagen, etc.) [13,20], synthetic polymers [14], metal anions [21], tripolyphosphate (TPP) [22,23], and so on. Based on different preparation methods as summarized in Fig. 1, the chitosan-based PEC can be developed to different forms, including fibrous membranes/films [24], hydrogels/beads [7,14,15], micro/nanoparticles [25,26]. Chitosan-based PEC has been proved to possess various applications in biomedical and pharmaceutical areas, such as drug delivery for nutrients with delayed digestibility and controlled release [27,28], nonviral vector for gene delivery system [29], three-dimensional scaffold to mimic tumor microenvironment [30] and for bone tissue engineering [31]. Since the biocompatibility of chitosan is maintained after PEC formation, the applications of chitosan-based PEC in different forms are somewhat dependent on the polyanionic materials used [14]. This review specifically focuses on the development in recent ten years (2003–2013) of PEC formed between chitosan and other natural polysaccharides, focusing on their different geometries, fabrication techniques, characterizations, as well as drug delivery applications.