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Review

Chitosan-based hydrogels: From preparation to biomedical applications

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ABSTRACT

The advances in the field of biomaterials have led to several studies on alternative biocompatible devices and to their development focusing on their properties, benefits, limitations, and utilization of alternative resources. Due to their advantages like biocompatibility, biodegradability, and low cost, polysaccharides have been widely used in the development of hydrogels. Among the polysaccharides studied on hydrogels preparation, chitosan (pure or combined with natural/synthetic polymers) have been widely investigated for use in biomedical field. In view of potential applications of chitosan-based hydrogels, this review focuses on the most recent progress made with respect to preparation, properties, and their salient accomplishments for drug delivery and tissue engineering.

1. Introduction

In the past few years, the advances in the field of biomaterials has led to several studies on alternative biocompatible materials and to the development of these materials focusing on properties, benefits, limitations, and the use of alternative resources (such as polysaccharides and proteins) for its preparations. Among the most studied biomaterials, hydrogels (HGs) have been standing out owing to their advantages, like biocompatibility, biodegradability, mechanical properties, and responsiveness.

HGs are soft materials composed of three-dimensional networks of hydrophilic polymers, which are able to swell either in water or in biological fluids (Grainger, 2013; Kakkar & Madhan, 2016; Lima-Tenório, Pineda, Ahmad, Fessi, & Elaissari, 2015; Soares et al., 2014; Ullah, Othman, Javed, Ahmad, & Akil, 2015). Depending on the preparation method, hydrogels can be classified into 'physical' gels or 'chemical' gels. In physical ones the polymeric chains are held together by molecular entanglements and/or secondary interactions including ionic crosslinks, hydrogen bonds and hydrophobic interactions. In contrast, in chemical gels the polymeric chains are hold together by irreversible covalent bonds.

The swelling ability of hydrogels in biological conditions, allows the diffusion of nutrients, making them very similar to natural tissues, allowing its biomedical applications. If the HGs have stimuli-responsive properties, they are also called as smart material, and the release of the drug may be controlled by an external stimulus, such as pH, light, magnetic field, temperature, and so forth. In addition, those materials have a wide range of applications, including controlled drug release, contact lenses, scaffolds, cell growth, agriculture, and regenerative medicine.

The interest in the development of polysaccharide-based hydrogels, as smart biomaterials, has strongly grown in the last decade. The polysaccharides possess intriguing properties for development of biomaterials, such as biocompatibility, biodegradability, non-toxicity, and low-cost (Lima-Tenório and Tenório-Neto et al., 2015). Starch, carboxymethylcellulose, alginate, carrageenan, and chitosan are some examples of polysaccharides commonly utilized to prepare hydrogels for biomaterial-related applications (Lima-Tenório and Tenório-Neto et al., 2015). Among them, chitosan, which is a natural cationic and hydrophilic polymer, has been the object of several studies by researchers in the areas of biotechnology (Arteche Pujana, Pérez-Álvarez, Cesteros Iturbe, & Katime, 2013; Soares et al., 2014; Xu et al., 2012).

Chitosan, (1–4)-2-amino-2-deoxy-β-D-glucan (Arteche Pujana et al., 2013), is a polysaccharide obtained from alkaline hydrolysis of chitin, one of the most abundant natural amino polysaccharide extracted from the exoskeleton of crustaceans and insect, from fungal cell walls, etc. (Soares et al., 2014; Xu et al., 2012). There are plentiful of amine groups (-NH_2) and hydroxyl groups (-OH) along the chitosan chain, which can be used as cross-linkable functional groups to react with cross-linking agents for in-situ chemical cross-linking (Arteche Pujana et al., 2013; Xiao, You, Fan, & Zhang, 2016). Moreover, the amine groups can be easily converted to ammonium groups, below pH 6.3,

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making chitosan an ideal candidate for use in the preparation of pH-responsive HGs. Besides non-toxicity and biocompatibility, chitosan can be degraded in vivo by several enzymes, mainly by lysozyme (a non-specific protease present in all mammalian tissues) (Ren, Yi, Wang, & Ma, 2005; Szymańska & Winnicka, 2015). Furthermore, the products from degradation are non-toxic oligosaccharides which can be then excreted or incorporated to glycosoaminoglycans and glycoproteins. These properties make chitosan suitable for clinical use. In addition, chitosan may enhance drug penetration by opening the tight junctions between epithelial cells (Jin, Zhang, Li, Liang, & Jia, 2016; Mohammed, Syeda, Wasan, & Wasan, 2017). These properties make chitosan an ideal candidate for use in the preparation of new materials for biomedical applications.

Present review aims to report and to update the state of the art regarding chitosan-based hydrogels in biomedical field. In this direction, special attention is dedicated to their preparation, properties, and application in both drug delivery and tissue engineering.

2. Formation and properties of chitosan-based hydrogels

Chitosan-based HGs can be prepared either directly from native chitosan (combined by itself or with anionic small molecules) or combined with other polymers. It is well reported that chitosan is soluble in acid medium owing to the presence of amine groups (N-free) from D-glucosamine units. At this pH, N-free units are positively charged limiting the interchain interactions (Sereni et al., 2017). Moreover, the ability to change the apparent charge density under certain experimental conditions (e.g. pH, Ionic strength, temperature) has been exploited to produce hydrogels.

Chitosan (CS) can be self-crosslinked either by increasing the pH or by dissolving in a nonsolvent (Peppas, Hilt, Khademhosseini, & Langer, 2006). This kind of material has biocompatibility (intrinsic of chitosan) and can be considered safe for clinical applications, since, no organic solvent or toxic crosslinker is needed (Kiene, Porta, Topacogullari, Detampel, & Huwyler, 2018). For example, as demonstrated by Montenbault et al. physically-crosslinked chitosan hydrogels were obtained after solvent evaporation of a mixture water/1,2-propanediol (Montembault, Viton, & Domard, 2005). More recently, Xu, Y. and co-authors prepared chitosan hydrogels by adjusting the pH and by freezing the solution. Their hydrogels showed a high cytocompatibility for L929 fibroblasts cells and pH-responsive properties (Xu, Han, & Lin, 2017).

Despite the aforementioned advantages, CS-based hydrogels crosslinked by itself possess a dense scale-mesh like network which only allow for passive diffusion nutrients and metabolic wastes being not suitable for biomedical applications (Chen et al., 2017). Furthermore, it has a weak mechanical properties and uncontrolled dissolution (Kiene et al., 2018). On the other hand, this drawback can be avoided by combining chitosan with either natural or synthetic polymers for tuning the HG properties.

Several approaches have been reported to combine chitosan with synthetic/natural polymers. Each one is chosen in order to obtain desired properties. In general, they include: i) chemical reaction of chitosan with a crosslinker, ii) chemical modification of CS chains to obtain a macromonomer (crosslinker agent), iii) hydrophobic association, iv) electrostatic interactions, and v) hydrogen bonding (Sacco et al., 2014, 2016; Yoo, Seong, & Park, 2016). Furthermore, the amine groups can interact between the polymer chains (by hydrogen bonding) to produce chitosan hydrogels (Baghaie, Khorasani, Zarrabi, & Moshtaghian, 2017; Mahdavinia, Soleymani, Etemadi, Sabzi, & Atlasi, 2018). The advantage of combining CS with other polymers is to obtain a hybrid material with new properties. For example, due to their non-covalent nature of the chitosan-based HGs physically crosslinked, these systems are inherently responsive to external stimulus, such as, pH and temperature. Furthermore, the gel formation may be obtained in mild conditions without a crosslinker allowing, for example, the entrapment of proteins during the synthesis (Yuan et al., 2018). Moreover, the physical interactions are reversible providing to the HGs self-healing properties. Thus, in the last years, several combinations of physically crosslinked chitosan-based hydrogels have been investigated, especially, in biomedical field.

On the other hand, the HG formed by chemical crosslinking are stable with time, preserving the gel properties (Lima-Tenório and Tenório-Neto et al., 2015). In this sense, Tsuda and coworkers reported the synthesis of flexible HGs based on modified chitosan using the UV-light approach. This material decreased bone formation ratio in mice skulls and fibula defects (Tsuda et al., 2009). Mirzaei and coworkers studied the effect of different amounts of glutaraldehyde as crosslinker agent on the preparing chitosan hydrogels. They analyzed the interactions polymer-polymer and polymer-drugs and observed that an increase in the crosslinking agent concentration resulted in a considerable decrease of swelling. Furthermore, the crosslinker concentration have changed the enzymatic activity under gastric conditions (Mirzaei, Ramazani, Shafiee, & Danaei, 2013).

More recently, Zhang and co-authors reported a series of chitosan-based self-healing hydrogels, using a benzaldehyde terminated poly (ethylene glycol), to crosslink chitosan or chitosan derivatives by Schiff base (Li, Wang, Wei, & Tao, 2017; Zhang, Tao, Li, & Wei, 2011). Focusing on the tissue engineering, the advantage of using Schiff-base system is complete avoidance of extraneous toxic crosslinking agents and other triggers that can cause an unwanted tissue response besides being easy prepare due to their simple methodology. However, the Schiff-base (imine) linkages may be hydrolyzed under acidic conditions which is not suitable for oral drug delivery (Li et al., 2017).

Hydrogels formed by two (or more) different monomeric units, with at least one of them hydrophilic have also been reported (Ullah et al., 2015). The polymeric network may be arranged in blocks, alternating or random configuration. Moreover, by adjusting the monomer composition, the properties of copolymers can be tuned, and thus, copolymers present advantages not usually seen in homopolymers. For example, Yang and co-workers have reported the synthesis of a pH-responsive HG film based on a chitosan/poly (acrylic acid) (CS/PAAc) copolymer. The hydrogel swollen in both acidic and basic conditions depending on the composition (Yang et al., 2005). Another example can be found in a work reported by Cao and co-workers. They reported a double-network HG based on oligo(trimethylene carbonate) (TPT)-b-poly(ethylene glycol)-b-oligo(trimethylene carbonate) diacrylate and methacrylate chitosan (CS-MA) where the concentration of CS-MA influenced the swelling behavior and the mechanical properties of the HG (Cao, Yang, Fan, Liu, & Liao, 2015).

Inorganic particles have also been used to confer dual-responsiveness properties to CS-hydrogels. Magnetic- and pH-responsive beads based on chitosan and laponite were reported by Mahdavinia et al. (2018). The beads have shown to be pH-sensitive owing to the $-NH_2$ groups from CS. They investigated adsorption capacity of BSA as function of pH and Ionic strength. The maximum adsorption capacity of hydrogels beads was obtained between isoelectric point of BSA and points zero charge of hydrogel beads. Other examples of chitosan combined to other compounds to form hydrogels with specific properties are summarized in Table 1.

3. Preparation of chitosan-based hydrogels

It is well known that many properties, such as, self-healing, biodegradability, swelling degree, mechanical resistance, and so forth of hydrogels are intrinsically related to the crosslinking methods. Thus, for biomedical applications, the choice of the preparation methods of CS-HG has an important role. For example, to produce biodegradable HGs, it is highly recommended the introduction of labile/unstable bonds which may be cleaved in physiological conditions (Gulrez, Al-Assaf, & Phillips, 2011).

Several crosslinking methods have been developed to form the