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Review

Combination of Alginate and Chitosan Polymers in the Preparation of Nanoparticles-A Mini Review

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ABSTRACT:
Natural polymers, commonly include polysaccharides (chitin/chitosan, hyaluronic acid derivatives, alginate, etc.) and proteins (albumin, collagen, etc.), are non-toxic and biocompatible biomaterials widely used in various biomedical applications (such as drug and/or imaging agent delivery system, tissue regeneration scaffolds, as excipients in pharmaceutical formulations). Especially, alginate and chitosan are widely used for the preparation of drug delivery systems. Unfortunately, the primary drawback of both alginate and chitosan is the lack of strong mechanical properties. However, using the combination of these polymers can enhance their mechanical properties. Besides, the alginate-chitosan nanoparticles had higher drug encapsulation and a slower drug release due to the polyelectrolyte complex structure formed by the interaction between chitosan and alginate.

Keywords: Alginate, chitosan, nanoparticles, polyelectrolyte complex

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1. INTRODUCTION

Polymers can be classified according to their origin (natural or synthetic), function, source (from plants, animals, and microbial sources), polymerization mechanism, polymer structure, preparation techniques, or thermal behavior [1,2]. Natural polymers, commonly include polysaccharides (chitin/chitosan, hyaluronic acid derivatives, alginate, etc.) and proteins (albumin, collagen, etc.), are non-toxic and biocompatible biomaterials widely used in various biomedical applications (such as drug and/or imaging agent delivery system, tissue regeneration scaffolds, as excipients in pharmaceutical formulations) [3,4]. Chitosan is a cationic polysaccharide polymer while alginate is an anionic polysaccharide polymer. Chitosan is obtained by the alkaline deacetylation of chitin that is found in the cells walls of fungi, the exoskeletons of crustacean and insects [5-8].

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Alginates are the cell-wall constituents of marine brown seaweed or algae, and extracellularly in several bacteria. Alginates are produced mainly from *Macrocystis pyrifera, Laminaria hyperborea, Laminaria digitata, Ascophyllum nodosum* spp. etc. [6-9]. Alginate is a copolymer composed of mannuronic acid and guluronic acid, and it forms gel in the presence of divalent cations (such as Mg2+, Ca2+) by cross-linking the carboxylate groups of the guluronate groups at room temperature [8, 10,11]. The molecular weight of alginates ranges from 20 to 600 kDa. Alginate, which is non-toxic and biocompatible, is also widely used in the preparation of different drug delivery systems (nanoparticles, beads, microparticles, etc.) for various drug administration routes [6, 8, 12]. Sodium alginate, which is the salt of alginic acid, is the major form now widely used [7]. Due to the lack of an enzyme (alginase), alginate is not degraded inherently in mammals. Therefore, partial oxidation of alginate chains is seen as an attractive approach to render alginate degradable under physiological conditions. Slightly oxidized alginate can be degradable in aqueous media and the alginates have potential for the preparation of drug delivery systems. Also, partial oxidation of the alginate does not significantly affect its gel-forming ability in the presence of divalent cations. The rate of degradation of the gels depends extremely on the degree of oxidation as well as the temperature and pH of the medium [13].

Chitosan is composed of N-acetyl glucosamine and D-glucosamine (deacetylated units) linked by beta-(1,4) glycosidic bonds [14]. The degree of deacetylation and molecular weight of chitosan, which are very important in terms of its properties, depend on its source and production process [6]. Chitosan has a large molecular weight range and thus, it shows different properties (blood thinning, cholesterol-lowering, anti-oxidant, and antibacterial properties, drug delivery efficiency, permeation resistance, pollutant removal properties etc.) [15,16]. The biodegradability of chitin and chitosan is attributed to their sensitivity to enzymatic hydrolysis by colonic bacterial enzyme and lysozyme in human body. Lysozyme found in human tissues break the linkage between acetylated units and reduce chitosan/chitin to oligosaccharides [17-19]. Due to its biodegradable, non-immunogenic and non-toxic properties, chitosan and its derivatives have been widely used for the preparation of the different drug delivery systems (microparticles, nanoparticles, oral prolonged-release drugs, beads etc.) for the different application routes such as oral, nasal, parenteral, ocular, transdermal [14,19].

The primary drawback of both alginate and chitosan is the lack of strong mechanical properties. However, using the combination of these polymers can enhance their mechanical properties. Also, the alginate can be combined with chitosan to improve cargo protection and absorption in oral drug delivery [6,8].

Nanotechnology is an encouraging approach in the development of drug delivery systems that contain drugs with poor solubility, low absorption/permeability, low

bioavailability and other poor biopharmaceutical properties. Drug design at nanoscale has been studied extensively and nanoparticle applications are the most advanced technology in this field. In the diagnosis and/or treatment of various diseases, nanoparticulate delivery systems provide many benefits such as improving the solubility and bioavailability of drug that is poor-soluble in water, providing controlled/sustained drug release, fewer side effects, lower toxicity, site-specific delivery (targeting) of drug and/or imaging agents. Polymeric nanoparticles made from synthetic (biodegradable and non-biodegradable) and natural polymers [20-22]. Chitosan is used in the encapsulation of drug or coating of different types of nanoparticles. It has mucoadhesive properties and also is thought to disrupt intercellular tight junctions. Besides, alginate, which has carboxyl groups, is also classified as an anionic mucoadhesive polymer used for the preparation of nanoparticles [21]. The ability of alginate to form hydrogel by chelating with divalent cations enables the alginate to be widely used in the pharmaceutical field. Easy-gelling property is very useful to prepare polyelectrolyte complexes. The polyelectrolyte complex of alginate and chitosan is formed by the ionic interactions through ionic gelation between the carboxylic group of alginate and the amine group of chitosan. The interactions between these two polymers reduce the porosity of the complex. Thus, the resulting complex preserves the encapsulated drug, prevents the premature leakage/release of the drug, and effectively slows the drug release compared to drug release observed when using alginate or chitosan. The alginate network is stabilized at high pH by chitosan (it is less soluble at high pH), while the high solubility of chitosan at acidic pH is reduced by the poor solubility of the alginate network at acidic pH [23].

1.1. The alginate-chitosan nanoparticles/polyelectrolyte complex in literature

Alginate nanoparticles are usually prepared by ionotropic gelation using cationic polymers (such as chitosan) or divalent cations. Mujtaba et al. [24] prepared rosuvastatin calcium (antilipidemic drug)-containing alginate-chitosan nanoparticles to improve the solubility, dissolution, and therapeutic efficacy of the drug. Because rosuvastatin calcium has low solubility in water and poor oral bioavailability. For the preparation of nanoparticles, ionotropic pre-gelation of alginate with calcium chloride as a cross-linking agent and then polyelectrolyte complexation with chitosan was performed. The mean particle size of rosuvastatin calcium-containing alginate-chitosan nanoparticles was 349.3 nm, and the nanoparticles had positive zeta potential of 29.1 mV, and high drug encapsulation efficiency (83.65%). While a rapid drug release was obtained from the nanoparticles within the first 2 hours, a more gradual and continuous drug release was observed for the following 24 hours in phosphate buffered saline solution (PBS)-pH 7.4. Furthermore, they performed an FT-IR analysis to investigate potential interactions and reported that the carboxylic groups of the alginate interacted with the amine groups of chitosan via electrostatic interactions to form

the polyelectrolyte complex. It has been stated that the addition of chitosan for structural support to the dispersion containing calcium chloride, alginate, and drug may be beneficial in terms of achieving high encapsulation efficiency and sustained drug release [24].

In another study, doxorubicin (anti-cancer drug)-containing chitosan-alginate nanoparticles were prepared using modified ionic gelation method [23]. In this method, alginate as a crosslinker and Tween 80 as a surfactant were used. During the preparation of doxorubicin loaded-chitosan-alginate nanoparticles, firstly, chitosan particle formation was achieved by mixing the solution of chitosan in acetic acid with Tween 80 and later, this solution was added to the dispersion of alginate-doxorubisin complex by dropping and mixed to form nanoparticles. The formation of polyelectrolyte complex was achieved by ionic cross-linking (between the amine groups of chitosan and the carboxylic groups of alginate). Doxorubicin-loaded chitosan-alginate nanoparticles had positive zeta potential (about +35 mV), a mean particle size of 100 nm, and very high encapsulation efficiency (95%). It was observed that after an initial burst doxorubicin release (up to 24 hours), chitosan-alginate nanoparticles presented a more gradual and sustained doxorubicin release for the following 72 hours in PBS-pH-7.4 [23].

Also, paclitaxel (anti-cancer drug)-containing alginate or alginate-chitosan or folate-chitosan–alginate (for targeting) nanoparticles were developed in another study [25]. They used the double emulsion cross-linking method for the preparation of the nanoparticles. In this method, CS was used for the electrostatic interaction with alginate and it was also regarded as a cross-linking agent [25]. Briefly, both alginate aqueous solution with Tween 80 and the solution of paclitaxel in dichloromethane were added into soybean oil for the formation of O/W/O emulsion by ultrasonic emulsification. On the other hand, calcium chloride and chitosan aqueous solution was added into soybean oil for the formation of W/O emulsion by ultrasonic emulsification. Later, the W/O emulsion was dropped into O/W/O emulsion and mixed for cross-linking (at 35 °C) for 4 h. The authors reported that paclitaxel-loaded-chitosan-alginate nanoparticles had a positive zeta potential value (31.1 mV), higher encapsulation efficiency (26.13%), and drug loading capacity (10.19%) compared to paclitaxel-loaded alginate nanoparticles [zeta potential: (-)26.5 mV; encapsulation efficiency: 19.66%; drug loading capacity: 8.92%]. With the addition of chitosan to the formulation, the average particle size of the nanoparticles increased from about 201 nm to about 307 nm. They also stated that the release of paclitaxel from all nanoparticle formulations took place in two stages (initial burst release followed by sustained release), however, the release of paclitaxel from chitosan-alginate nanoparticles was slightly slower than the drug release from alginate nanoparticles [25].

In another study, paclitaxel and doxorubicin-loaded alginate coated chitosan hollow nanospheres were prepared by a hard template method [26]. In this

method, the authors added the solution of chitosan in acetic acid to the suspension of sulfonated polystyrene (SPS) nanospheres used as a template. After mixing and centrifugation, the obtained product was suspended in the solution of sodium alginate and centrifuged. The final product was suspended slowly in glutaraldehyde solution and the cross-linking process was carried out for 2 h. Then, the SPS template was removed by adding of tetrahydrofuran and alginate coated chitosan hollow nanospheres were obtained. Paclitaxel and positively charged doxorubicin were loaded to nanospheres by an adsorption method and by electrostatic interaction, respectively. It was found that the drug content in the nanospheres was about 18% for paclitaxel and about 74% for doxorubicin. The authors explained that the high doxorubicin content was due to the electrostatic interaction between positively charged doxorubicin and negatively charged alginate. Also, a sustained drug release from the nanospheres was observed for both drugs [26].

On the other hand, chitosan-alginate nanoparticles loaded with nifedipine used to treat increased blood pressure were prepared by Li et al. [27]. The nanoparticles were obtained by ionotropic pre-gelation of an alginate core with calcium chloride followed by the addition of chitosan solution to form a polyelectrolyte complex. In this method, guluronic acid units on alginate react with Ca^{+2} to form "egg-box" structure (Ca^{+2}-alginate complex in pre-gel state). It has been stated that the pre-gel state is essential to allow the ionic interactions between alginate-Ca^{+2} complex and chitosan for the formation of nanoparticles. The particle sizes of the prepared nanoparticles were in the range of 20-50 nm. In various release media (phosphate buffer solution-pH 7.4, simulated intestinal fluid-pH 6.8, and simulated gastric fluid-pH 1.5), the release profile of nifedipine from nanoparticles was characterized by an initial burst release for the first two hours followed by a sustained drug release for 22 hours [27].

Thai et al. [28] prepared lovastatin (a cholesterol-lowering agent)-loaded alginate-chitosan nanoparticles by the ionic gelation method. They added calcium chloride to alginate aqueous solution and later, the obtained mixture was dropwise to chitosan solution in acetic acid, and finally, lovastatin solution in ethanol was added to the mixture and ultrasonicated to obtain lovastatin-loaded alginate-chitosan nanoparticles. They obtained the nanoparticles with the particle size in the range of 50–100 nm and observed that lovastatin release from the nanoparticles took place in two stages (initial burst release followed by slow release) [28].

In a study, the biodegradation of chitosan–alginate polyelectrolyte complexes was investigated by incubation in the solution of lysozyme, which was used for enzymatic degradation. It was reported that the polyelectrolyte complexes showed a low degradation rate due to the steric hindrance that was a result of the strong interaction between alginate and chitosan, and also that the complexes partially degraded by hydrolysis [29].

2. CONCLUSION

As a result, it has been shown in the mentioned above articles that the alginate-chitosan nanoparticles had higher drug encapsulation and a slower drug release due to the polyelectrolyte complex structure (providing strong mechanical properties) formed by the interaction between chitosan and alginate. The alginate-chitosan nanoparticles not only protect drugs but also facilitate to obtain the sustained drug release. Chitosan and alginate are natural, non-toxic, biocompatible, and oppositely charged polyelectrolyte polymers. In addition to these advantages, these polymers in single/combination are very promising biopolymers used widely in the preparation of drug delivery systems due to their low processing costs and abundance in nature.

Conflict of Interest

Author has no personal financial or non-financial interests.

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