Progress in the application of thiol chitosan

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Abstract: Chitosan is a natural cationic polymer composed of glucosamine and N-acetylglucosamine. It has good biocompatibility, biodegradability and non-toxicity. It is an excellent bio-carrier material. Chitosan reacts with its sulfhydryl reagent to obtain a novel polymer material of thiol chitosan, and its properties are improved. This paper summarizes the recent progress in the application of thiolated chitosan in the biomedical field.

1. Introduction

Chitosan is a natural adhesion material and is a chitin deacetylation product. Chitosan contains glucosamine and N-acetylglucosamine, and its primary amino group is easily reacted with an acid to form a salt for chemical modification. Under acidic conditions, the amino group is protonated and chitosan is soluble; under alkaline or neutral conditions, chitosan cannot be dissolved [1]. Due to its biocompatibility, enzymatic degradation, non-toxic and other excellent properties [2], chitosan has attracted much attention in new drug delivery excipients and was included in the European Pharmacopoeia in 2002. At present, chitosan has been widely used in various fields of pharmaceutical technology, including controlled release preparations such as tablets, gels and microspheres [3,4]as an adhesive or penetration enhancer for oral cavity, nasal cavity and eye. Department and buccal mucosal drug delivery system, non-viral gene delivery system [5,6] and so on.

Studies have shown that thiol-containing adhesives have a stronger adhesion than ordinary adhesives because the sulfhydryl polymer reacts with the cysteine in the mucus layer to form a covalent bond. In order to further enhance the solubility of chitosan and improve its bioadhesion and/or osmotic action, many different derivatives such as cyclopropyl chitosan, mono N-carboxymethyl chitosan, N-thiochitosan and chitosan-EDTA. To further optimize the properties of chitosan, chitosan-TGA, chitosan-Cys and chitosan-TBA were synthesized. . These thiolated chitosan have many advantages over unmodified chitosan, such as bioadhesiveness and penetration promotion are significantly improved [7-10]. The high adhesion of thiol chitosan makes it an excellent controlled release formulation excipient. In addition, thiolated chitosan exhibits the properties of in situ gels at physiological pH [1]. This paper summarizes the recent progress in the application of thiolated chitosan in the biomedical field.

2. Oral administration

In vivo studies have shown that thiolated chitosan has broad prospects for oral hydrophilic macromolecular drugs [12,13], such as the model drug sputum calcitonin, a cationic peptide drug with a molecular weight of 3.2 kDa. Calcitonin is a drug for the treatment of chronic bone disease. The current route of administration is mainly nasal spray and injection, but the two methods are less compliant. The most acceptable method for patients is oral administration, but after oral administration, the bioavailability of the drug is greatly reduced, so that the therapeutic effect can not be achieved [14]. Therefore, the use of salmon calcitonin as a model drug is a challenge for thiolated chitosan.

Experimental studies in rats showed that blood calcium levels were not significantly decreased after oral administration of salmon calcitonin solution ($P<0.05$). In addition, although it is reported

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that natural chitosan has bioadhesiveness and enhances the permeability of hydrophilic macromolecular drugs, experiments have shown that after oral administration of unmodified chitosan as a carrier of calcitonin tablets There is no obvious pharmacological effect [15].

3. Stomach adhesive film

The currently synthesized drug carrier substrates include chitosan-TBA, thiol chitosan containing a osmotic adjusting agent-reduced GSH, and the like. In order to avoid enzymatic degradation of peptide drugs in the gastrointestinal tract, chitosan containing an enzyme inhibitor was invented. These composite excipients do not require treatment and can be directly compressed. In order to target the enteric coated tablets to the small intestine, a chitosan-BBI (Bowman-Birk inhibitor) complex and a chitosan-elastatinal (elastase inhibitor) complex were invented. In addition, the chitosan-pepstatin A (painstatin A) complex of gastric targeted drug delivery was also invented, and the calcitonin gastric adhesion sheet prepared by using chitosan-pepstatin as a carrier can also avoid the calcitonin-enzyme digestion. In order to prevent these tablets from sticking to the mouth or esophagus, the tablets are coated with triglycerides.

Chitosan-TBA is a key factor in promoting calcitonin absorption. Tablets based on thioglycol chitosan reduce blood calcium levels by more than 5% and can be maintained for several hours. This is mainly because of the high stability and cohesiveness of thiol chitosan, which enables sustained release of peptide drugs, while its bioadhesiveness prolongs the residence time of the drug at the absorption site. In addition, thiol chitosan containing osmotic regulator reduced GSH also has an effect on the biological effects of oral calcitonin. The GSH-containing thiol chitosan tablets have much higher pharmacological effects than the equivalent GSH-free thiol chitosan tablets, indicating that GSH promotes drug absorption.

Among all the thiol chitosan derivatives, the gastric-targeted adhesive sheets with chitosan-TBA combined with GSH and chitosan-pepstatin A were the best pharmacological effects. These two substrates allow peptide drugs to reach the body by oral administration, reducing blood calcium levels by 10% and reducing blood calcium for more than 12 hours. [3]In addition, through this new mode of administration, the drug effect is faster and the reproducibility is better, which is a hot topic of current research.

4. Non-invasive delivery of peptide drugs

The positively charged peptide drug interacts with the anionic polymer, which on the one hand reduces the adhesion of the polymer and, on the other hand, prevents the release of the drug from the polymer network. Therefore, peptide drugs such as calcitonin or desmopressin should use cationic or non-ionic adhesive materials to achieve good absorption. However, the bioadhesive properties of nonionic polymers tend to be poor. [5]Mercapto chitosan has the highest adhesion among all cationic materials and is therefore an ideal carrier for oral administration of cationic peptide drugs. In addition to oral administration, thiolated chitosan is also useful for other non-invasive routes of administration of peptide drugs, such as nasal, vaginal, buccal mucosa, and ocular mucosa.

5. Microspheres, nanospheres

Chitosan itself has no good cohesive force, is unstable after being made into microspheres, and is easily disintegrated. By combining it with a negatively charged sulfate or alginate, the microspheres can be stabilized by ion crosslinking, but the bioadhesive property of chitosan is significantly lowered due to the addition of the polyanionic compound. [7]In contrast, the thiol-based chitosan microspheres enhance the stability of the microspheres due to the disulfide bonds formed in the polymer network structure, and are not easily disintegrated, and the ruthenium-based shells are aggregated compared with the addition of the polyanionic compounds. The sugar microspheres are more adherent.

6. Tissue Engineering

Mercapto chitosan can also be used in tissue engineering. The rapid development of tissue engineering has intensified the development of polymer materials. The scaffold materials required must be biocompatible, degradable, and have similar rigidity to the target tissue. Degradability and biocompatibility are two prerequisites for scaffold materials, and no inflammatory or toxic degradation occurs when new tissue is formed. Recently, Kast et al. confirmed the biodegradability of thiol chitosan and laid the foundation for its new scaffolding material [16]. In a further study, the culture of L-929 rat fibroblasts was carried out using chitosan-TGA as a medium. The results showed that thiol chitosan could provide a porous porous scaffold structure to facilitate cell anchorage, proliferation and tissue formation.]. In addition, due to the in situ gel properties of thiol chitosan, its cell suspension can be poured into a mold to form a stent of a specific shape; its cell suspension can also be injected into the tissue injury site to form a semi-solid at the tissue damage site. support. Furthermore, the low concentration of the thiol chitosan aqueous solution is in a solution state under the storage condition in an inert state, and is rapidly gelled under the condition of introducing oxygen, and this property also has a good application prospect.

7. Coating bracket

Another promising application of thiol chitosan is as a scaffold coating material. Polymer-coated stents are a highly promising technology that enables drugs to reach high local concentrations in time for precise vascular injury. Studies have shown that the scaffold material is immersed in a thiol-based chitosan solution and then dried in air. Due to the oxidation of air, a disulfide bond is formed, and chitosan forms a cross-linked network structure and is fixed on the stent. The chitosan coating should be capable of sustained release of the drug, such as anti-inflammatory drugs or drugs that avoid cell proliferation. Recent studies have shown that the use of sulfhydryl-based polyacrylic acid-coated stents allows sustained release of peptide drugs from the coating. Chitosan-based chitosan should also produce similar results, but research is needed.

8. Conclusion

The chitosan modified by the thiol reagent has significantly improved bioadhesion and stability and enhanced permeability. If the osmotic regulator glutathione is attached to the thiol chitosan, the penetration enhancer will be further improved. In addition, thiol chitosan also has in situ gel properties and controlled release properties. Based on these excellent properties, thiolated chitosan has been successfully applied to oral drug delivery systems for peptide drugs. Sulfhydryl chitosan is a new generation of polymer adhesion excipients, especially suitable for non-invasive drug delivery systems of hydrophilic macromolecular drugs, which has great application prospects.

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