Research progress of alginate in biomedicine

Zongmei Wu¹, Weixi Fan, Xiaoming Cai, Chunli Zhu*

School of Chemistry and Biological Engineering, Qilu Institute of Technology, Jinan, 250200, P. R. China.

*Corresponding author: Chunli Zhu; e-mail: chunli0125@163.com

Abstract. Sodium alginate was widely used in biomedicine because of its biocompatibility, biodegradability, safety, non-toxicity and easy processing. The development of the application of micelles, microspheres, nanoparticles and hydrogels prepared by sodium alginate polymers in drug release is described in this paper.

1. Introduction
Sodium alginate is a water-soluble natural ionic polysaccharide with excellent properties such as biocompatibility, biodegradability and safety. It is widely used in biomedical applications because of its stability, solubility, viscosity and other properties required for pharmaceutical preparations.

In recent years, natural biodegradable polymers have attracted widespread attention in controlling drug release. The traditional drug release has the disadvantages of too fast release rate, short duration of drug action, unstable drug concentration in the drug receiving system, and short drug half-life, which reduces the therapeutic effect of the drug. The biodegradable sodium alginate polymer has physical and chemical properties stability and easy processing, and can be used as a carrier for a drug release system, also which can be classified into a system of micelles, microspheres, nanoparticles and hydrogels.

2. Alginate micellar
Macromolecules containing both hydrophilic and hydrophobic groups are often referred to as polymeric surfactants and are also described in the relevant literature as amphiphilic polymers, hydrophobically modified water-soluble polymers, micellar polymers, and associated polymers and other related terms. Due to the presence of hydrophilic groups and hydrophobic groups, polymeric surfactants exhibit different association behaviors in different solvents, eventually forming spherical, rod-like, layered association-micelles. Polymer micelles having a core-shell structure can be used as a pharmaceutical carrier to increase the solubility of poorly soluble drugs in aqueous/oil solutions. The drug is then delivered to the lesion site and slowly released for targeted therapy. As a good drug-loading system, polymer micelles can reduce the body’s adverse reactions to drugs and improve the bioavailability of drugs.

Sodium alginate is a strongly hydrophilic natural ionic polysaccharide whose macromolecular chain has a coiled conformation in an aqueous solution. In order to expand the application of sodium alginate in biomedicine, in the previous work, the sodium alginate was hydrophobically modified to obtain an amphiphilic sodium alginate derivative-hydrophobically modified sodium alginate (HM-alginate) [1-2]. As shown in Figure 1, the micelle image of hydrophobically modified sodium alginate was confirmed by confocal laser scanning microscope (CLSM). By using fat-soluble Sudan IV as a mimetic drug, it was found that the amphiphilic sodium alginate derivative formed a core-shell
micelle in an aqueous solution, and the Sudan IV was encapsulated in its hydrophobic core, thereby increasing the solubility of the fat-soluble drug in an aqueous solution (As shown in Figure 2). Meng[3] studied the release properties of hydrophobically modified sodium alginate, and the results showed that the amphiphilic sodium alginate derivative (0.8 mg/mL) had a slower release rate to clofazimine: after 17 hours of release, it basically reached the release balance, and the cumulative release amount was about 72%. Sodium alginate derivatives make it possible to release the drug due to its unique configuration and adhesion. The application of polymer micelles in drug development has been extensively studied and plays a potential carrier role in the research of drug carriers.

Figure 1. CLSM images of the HM-alginate

Figure 2. Schematic of the HM-alginate micelle. (A) Synthesis of HM-alginate (B) HM-alginate formed spherical micelles in aqueous solution (C) Sudan IV was loaded in HM-alginate micelles

3. Alginate microspheres

Microsphere is a microparticle polymer framework with a size of about 1-1000 μm, which refers to the microsphere formed by drug dispersion or adsorption in the polymer matrix. The matrix materials for microspheres are usually natural or synthetic polymers, while polysaccharides have the possibility of preparing microspheres to encapsulate biological and drug molecules due to their biodegradability and non-toxic side effects[4]. For example, sodium alginate[5], chitosan[6,7], cellulose[8], okra mucus[9] and other biodegradable polymers are widely used in the design and development of different drug delivery systems.

When sodium alginate is used as carrier to wrap or absorb polymer or target drug, spherical or quasi spherical particles are called sodium alginate microsphere system. The preparation of microspheres is the key to the selection of drug delivery routes and the control of drug release. Sodium alginate microspheres[10] can be prepared by emulsion ion crosslinking, microemulsion and complex
coacervation, which can be divided into drug loaded microspheres and material microspheres.

3.1 Drug loaded microspheres
Ghumman[9] used sodium alginate as the dispersion medium and added okra gum to prepare the mixed microspheres under the condition of agitation. After that, oxcarbazepine, a neurogenic drug, was added to prepare alginate/okra pod gum microspheres loaded with oxcarbazepine by Ion Gel Technology. The encapsulation efficiency of the microspheres was 76%-90%, and the average particle size was 496-692 μm. The release rate of the drug was 84.47% at 24 hours.

3.2 Material microspheres
Shi[11] reported the preparation of polymeric microspheres by combining magnetic Fe₃O₄ nanoparticles with sodium alginate: glucose oxidase was immobilized using glutaraldehyde as a crosslinking agent, and the immobilization conditions of the material for glucose oxidase and the enzymatic properties of the magnetic immobilized enzyme were investigated.

Fan[8] reported the preparation of a polyethylenimine-functionalized sodium alginate/cellulose nanocrystal/polyvinyl alcohol core-shell microsphere (pva/sa/cnc@pei) using sodium alginate as a matrix. Fan uses the non-steroidal anti-inflammatory drug diclofenac sodium as a typical drug. Due to the high specific surface area and affinity of pva/sa/cnc@pei, the maximum adsorption capacity of diclofenac sodium is much higher than that of other adsorbent materials. It demonstrates the applicability and potential of pva/sa/cnc@pei microspheres for drug adsorption.

4. Alginate nanocarrier
Targeted drugs refer to drugs with targeting ability, which is a research hotspot of current researchers. The targeted drug can be enriched in the lesion, so that the drug forms a relatively high concentration in the target, and the targeted drug has high selectivity, and the toxic side effect is suppressed while improving the drug effect. Nano carriers are all kinds of nanoparticles with sizes between 1-1000 nm that can dissolve or disperse drugs.

Wan[12] designed and constructed amphiphilic 6-thioguanine sodium alginate prodrug with 6-thioguanine as hydrophobic drug and biodegradable dialdehyde sodium alginate as drug carrier. The prodrug nanoparticles with pH response were prepared by ultrasonic dispersion. The core-shell particle size of 6-thioguanine sodium alginate is about 98 nm, which can significantly inhibit the cytotoxicity of 6-thioguanine and protect L-O2 cells. It can respond to the weak acid pH stimulation decomposition in cancer cells, release the bound drug molecule 6-thioguanine, so as to achieve targeted treatment.

5. Alginate gel
Hydrogel is a kind of polymer with high hydrophilicity and three-dimensional network structure. It has high water locking property and has good permeability to nutrient inflow and excretion of metabolites. When the gel is used as a carrier to coat the drug, the absorbent will expand and form gel diffusion layer in the medium because of the high water absorption of the gel, which will delay the release of the drug.

Huang reported a method of preparing soluble self-healing alginate polymethacrylic acid (SAMA) hydrogel based on natural polysaccharide alginate and functional monomer of sodium methacrylate, and explored the sustained release property of SAMA hydrogel by using 6 g Luo Danming as a drug template. The results showed that the SAMA hydrogel without crosslinking agent could completely release the loaded drug molecules and ensure the full utilization of the drug. The release time of Luo Danming’s release from hydrogel containing 0.6 wt% crosslinking agent epichlorohydrin was extended from 5 h to 24 h, and the complete release of the drug was ensured. The good biodegradability, mechanical strength and multiple biological functions of the hydrogel can effectively prevent the immune response and severe inflammation during drug delivery and tissue engineering. Therefore, hydrogels have potential application properties in the biomedical field.
6. Conclusion and Outlook
Sodium alginate is a natural polymer with adjuvant properties. It has excellent properties such as stability, biodegradability, bioadhesiveness and non-toxicity required for pharmaceutical preparations. It can improve the convenience and compliance of patients in biomedicine. As a pharmaceutical preparation, the sodium alginate has a high added value and a broad market prospect. As the research progresses further and the applied clinical practice will bring huge economic benefits.

Acknowledgments
The authors are thankful to Research Project Foundation of Qilu Institute of Technology (No. QL19K055) for financial support of this work.

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