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A pH-responsive composite hydrogel beads based on agar and alginate for oral drug delivery

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ABSTRACT

To improve the mechanical strength of calcium alginate hydrogel and obtain sustained drug delivery, the pH-sensitive composite gel beads composed of agar and alginate were prepared in the presence of agar as a modifying agent. All the obtained gel beads were characterized by Fourier transform infrared (FTIR) spectroscopy and scanning electron microscopy (SEM). The influence of the content of agar on the properties of the hydrogel including mechanical strength, swelling and drug release behavior was evaluated in simulated intestinal fluid (pH 7.4) and gastric fluid (pH 2.1) at 37 °C. Results illustrated that mechanical strength of agar/alginate beads (AALB) was significantly improved compared with the native alginate beads (NALB) without agar. The swelling and drug release behavior of AALB was markedly dependent on the content of agar. The gel beads with higher content of agar exhibited a lower rate of swelling and drug release within 720 min. Drug release behavior of AALB was further studied in simulated intestinal fluid and gastric fluid, and results showed that AALB could serve as a potential candidate for controlled drug delivery.

1. Introduction

Hydrogel is a significant class of polymeric materials due to their desirable properties for potential application in various fields such as biomedical, pharmaceutical and environmental protection [1]. Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water. They resemble natural living tissue more than any other class of synthetic [2,3]. The amount of water existing in various hydrogels may vary from 10% to thousands of times of the weight of the xerogel [4]. Through certain chemical or physical crosslinking, water soluble or hydrophilic polymers can form a hydrogel. The intelligent hydrogel is research focus in the hydrogel.

The intelligent hydrogel can sensitively respond to external environment changes such as pH, temperature, ion, light, etc. The intelligent hydrogel is a kind of complex system that can change its own chemical or physical properties with a variation in its immediate external conditions. The volume or phase transition is the most important characteristics of the system. pH-responsive hydrogels are high molecular polymers that undergo volume or phase transition when the pH value of the external environment changes. It can be divided into anionic (acidic) and cationic (alkaline) hydrogels. On the molecular chain of anionic hydrogels, there are groups which can dissociate in alkaline medium. Such as -COOH, it protonated at low pH and deprotonated at high pH. It is easy to combine with water molecules and exhibits swelling properties. On the molecular chain of cationic hydrogels, there are alkaline groups (such as -NH_2), the swelling property is opposite to anionic hydrogels.

Alginate has been widely used in intelligent gels because of its unique properties including nontoxicity, biocompatibility and biodegradability [5]. Alginate is a natural polysaccharide, and polysaccharides are natural polymers which have received increased attention in various industrial fields including food, pharmaceuticals and waste water treatment [6]. Sodium alginate is a purified carbohydrate product extracted from brown seaweeds by using dilute alkali. As can be seen from Fig. 1, alginate is a polyanionic linear natural polymer of 1,4-α-*l*-guluronic acid and β-*d*-mannuronic acid residues [7,8]. Polysaccharide hydrogels have attracted biomedical researchers due to their good biocompatibility and natural characteristics. This has promoted the application of alginate in a wide range of fields including medical, pharmaceutical, chemical, agricultural and environmental.

Agar is colloidal substance extracted from Gelidium

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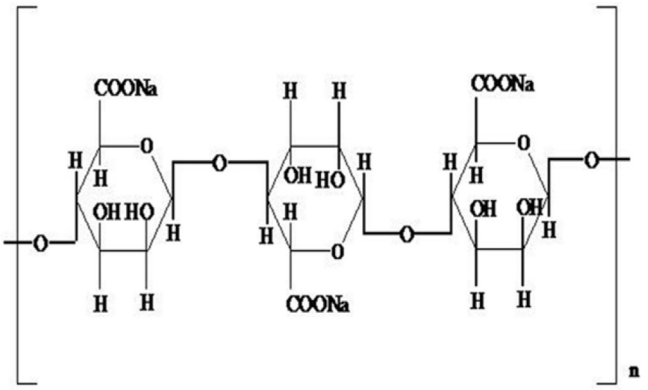

Fig. 1. The structure of alginate.

cartilagineum (Gelidiaceae), Gracilaria confervoides (Sphaerococcaceae) or related red algae (Class Rhodophyceae) [9]. It is a kind of unbranched hydrophilic polysaccharide, which has an alternating copolymer of 3-linked β-D galactopyranose and 4-linked 3-6-anhydro-a-L-galactopyranose [10]. The molecular weight of agar was about 120000 and the structure of agar is shown in Fig. 2. It is widely used as gel-forming agents, thickeners, water-holding agents and stabilizers in fields of biomedicine, chemicals and food industry. This due to its properties of the inexpensive, thermoreversible and high-strength material, it has found an increasing wide utilization in all fields. Based on the above characteristics of agar, the preparation of agar beads was considered to be able to control drug delivery system [11]. One of the most important properties of agar is its ability to form reversible gels even at low concentration [12]. There are some researches on agar or alginate, however, research on blending of agar and natural or synthetic polymers to modify its properties is very little. The application of the agar in different products depends on its chemical composition (sulphate, methoxyl, sugar contents), which can be significantly affected by the variables used in the extraction process. Its enormous gelling power and the simplicity of the extraction process, agar has been picked out as a promising candidate for environmental-friendly materials as results of its renewability and biodegradability features.

Recent studies have been directed towards either the use agar alone or alginate only for the delivery of oral drugs. However, the research on blending both the agar and natural or synthetic polymers to modify its properties is very minimal. This research reports

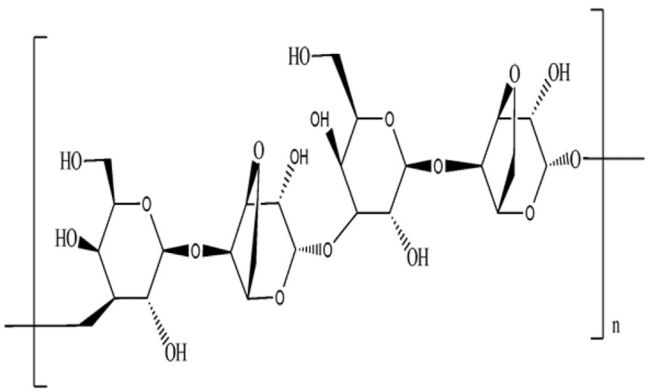

Fig. 2. The structure of Agar.

on the preparation of agar-alginate composite hydrogel beads made in different proportions, which was crosslinked by Ca^{2+}. FTIR spectral analysis was used to study the variation in the chemical composition of the agar-alginate blends and the formation of crosslinked structure. Scanning electron microscope (SEM) was used for observing the structure characteristics of the sample surface. The obtained composite agar-alginate gel samples were investigated to evaluate their pH-responsive swelling and controlled drug release behaviors.

2. Experimental

2.1. Materials

Na-alginate (viscosity of 1% solution at 20 °C equal 20 cps) and agar (gelling temperature 35–37 °C, dissolution in water at 90 °C) were purchased from Shanghai Chemical Reagent Co. Ltd. (China). The weight average molecular weight of Na-alginate was 2.1×10^5Da. The weight average molecular weight of agar was 1.2×10^5Da. Indomethacin (IDMC) was obtained from Shanghai Hou-cheng Fine Chemical Co. Ltd. (China). All Other chemicals were commercial products with high analytic purity.

2.2. Preparation of native alginate beads (NALB) and agar/alginate beads (AALB)

In the preparation of AALB, agar was dissolved in distilled water at about 90 °C and the resulting solution was cooled to 45 °C. Subsequently, Na-alginate was dissolved in obtained aqueous solution, the mass ratio of agar to Na-alginate was shown in Table 1. Then Indomethacin (25 wt%, relative to the weight of Na-alginate), a common anti-inflammatory drug, was added and dispersed homogeneously. The mixed solution was extruded dropwise using a syringe needle into cold oil (4 °C) resulting in beads because of the coagulation of agar. After 30 min, the beads were separated and washed with 1.0% solution of tween-80, and then these gel beads were immersed into 3% (w/v) aqueous solution of $CaCl_2$ under gentle stirring. The obtained beads were repeatedly rinsed with deionized water for three times to remove the drug attached on the surface of beads. Finally, samples were dried in air overnight and then vacuum drying to constant weight at 40 °C for 24 h.

2.3. Characterizations

The dry samples were characterized by Fourier transform infrared (FTIR) spectroscopy. FTIR spectra within the range of 500–4000 cm^{-1} were recorded with a Bruker Tensor 27(German). The morphological characterization of the sample beads was observed by using SEM (FEI Quanta 200). Before the observation of SEM, the dried samples were fixed on the aluminum sheet using adhesive and were coated with an approximate 100 Å layer of gold using a vacuum evaporator [13].

2.4. Swelling measurements

2.4.1. Evaluate the swelling degree of pH response

The classical gravimetrical method was used to measure the swelling degree (SD_t) and equilibrium swelling degree (SD_{eq}) of the hydrogel samples. The dried beads were accurately weighed and immersed into 30 mL phosphate buffer solution (PBS, pH 7.4) or HCl solution (pH 2.1) at 37 °C, respectively. At a predetermined time interval (30min), the beads were taken out and then weighed after absorbing the excess surface water with filter paper. This procedure was continued until the weight of swollen beads reached a constant value. The SD_t and SD_{eq} were calculated from the following