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Research Article

An Injectable Composite Gelatin Hydrogel with pH Response Properties

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On account of minimally invasive procedure and of filling irregular defects of tissues, injectable hydrogels are increasingly attractive in biomedical fields. However, traditional hydrogel formed by simple physical interaction or in situ crosslinking had inevitably some drawbacks such as low mechanical strength and lack of multifunctional properties. Though many investigations had successfully modified traditional injectable hydrogel to obtain both mechanical and functional properties, an acetalated β-cyclodextrin (Ac-β-CD) nanoparticle composite injectable hydrogel designed in the research was another effective and efficient choice to solve the drawbacks. First of all, gelatin derivative (G-AA) and Ac-β-CD were synthesized to prepare hydrogel and nanoparticle, respectively. In order to ensure good compatibility between nanoparticle and macromonomer and provide crosslink points between nanoparticle and macromonomer, G-AA was simultaneously functionalized onto the surface of Ac-β-CD nanoparticle during the fabrication of Ac-β-CD nanoparticle using one-step method. Finally, injectable composite hydrogel was obtained by photoinitiated polymerization in situ. Hydrogel properties like gelation time and swelling ratio were investigated. The viscoelastic behavior of hydrogels confirmed that typical characteristics of crosslinked elastomer for all hydrogel and nanoparticle in hydrogel could improve the mechanical property of hydrogel. Moreover, the transparency with time had verified obvious acid-response properties of hydrogels.

1. Introduction

On account of minimally invasive procedure and of filling irregular defects of tissues, injectable hydrogels are increasingly attractive in biomedical fields [1, 2]. Generally, the properties of biocompatibility, biodegradability, mild solidification conditions, and nontoxic initiating system were fundamental requisites for biomaterials including injectable hydrogels [1, 2]. As for hydrogels, their highly hydrated structure can mimic the natural extracellular matrix (ECM) of body and lead to the ease of exchange of gas, nutrients, and metabolite substances [3]. Besides biocompatibility, natural polymers like polypeptide and polysaccharide have innate biodegradability, which gives these materials suitable characteristics for injectable hydrogels [4]. To date, many natural macromolecules such as collagen, gelatin, chitosan, alginate, and hyaluronic acid (HA) are fabricated into the injectable hydrogels [5–11]. Among these materials, gelatin is a hydrolysis product of collagen and contains bioactive sequences, which lead to its widespread applications in tissue engineering and drug delivery [5, 6, 8]. Despite these merits, injectable gelatin cannot be formed by only interactions between molecules or simple crosslinking, which is also a common drawback of natural polymers. For this reason, gelatin was modified with reactive functional groups like vinyl groups, acetenyl groups, and thiol, and injectable gelatin hydrogel was fabricated by photoinitiated polymerization or click chemistry in previous research. In the research, gelatin was functionalized with acrylic acid (AA) and photoinitiated polymerization was used to fabricate injectable hydrogel in view of its effectivity and efficiency.

However, traditional hydrogels have also some drawbacks like low mechanical properties and multiresponse deficiency due to unicity of polymer network [9]. Another injectable carrier (particles with a size ranging from nanometer to micrometer) possesses flexible properties due to adjustable structure,

which is just able to compensate for drawbacks of hydrogel [12–15]. Therefore, combining hydrogel with particles is an optimized method to fabricate a novel injectable material. Recently, an injectable scaffold of poly(lactic-co-glycolic acid) microparticles/chitosan hydrogel and a pH-sensitive injectable nanoparticle composite hydrogel was prepared for tissue engineering and anticancer drug delivery application [9, 16]. The previous research work has proven that composite hydrogels had better properties when nanoparticle could be crosslinked or have strong interaction with hydrogel in the process of hydrogel formation [8, 9, 16].

Among the applied particles, low pH-triggered particle attracts increasing interest based on the fact that pH value in infectious and inflammatory sites and in tumor tissue exhibits weak acid environment [17]. Synthesized ester polymers or copolymers could degrade in acid environment, which makes them be primary materials for low pH-triggered nanoparticles [15, 18]. But the biocompatibility of either synthesized ester polymer or its degraded product is not ideal for biomedical application. The recent emerging of acetalated cyclodextrins (Ac-CDs) changes the situation [17, 19–22]. Ac-CD could be prepared to be low pH-triggered nanoparticles by microemulsion method under the stability of emulgator [17, 19–22]. In view of the strong interaction between hydrogel network and Ac-CD nanoparticles, double carbon functional Ac-CD nanoparticles were needed for the fabrication of injectable composite gelatin hydrogel. Considering the amphiphilic property of gelatin and the fact from previous report that emulgator was inevitably absorbed on the surface of nanoparticle stably in the process of nanoparticle formation through microemulsion method, we use above-mentioned AA functionalized gelatin (G-AA) as an emulgator to prepare Ac-β-CD nanoparticles in the research. Finally, an injectable composite gelatin hydrogel was obtained by compounding of the hydrogel with Ac-β-CD nanoparticles, aiming at providing pH response properties for hydrogel and improving the hydrogel mechanical strength.

2. Experimental Section

2.1. Materials. β-Cyclodextrin (β-CD), 2-methoxypropene, pyridinium 4-toluene sulfonate, dimethyl sulfoxide (DMSO), dichloromethane (DCM), and gelatin were obtained from Shanghai Chemical Industries Co., Ltd. (China). 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) were obtained from Sigma. 2-Hydroxy-1-[4-(hydroxyethoxy)phenyl]-2-methyl-1-propanone (Irgacure 2959) was obtained from Ciba Specialty Chemicals. Acrylic acid (AA) was purified via distillation under reduced pressure. All other chemicals and reagents were used as received.

2.2. Synthesis of G-AA and Ac-β-CD. Acrylic acid modified gelatin (G-AA) was obtained by amidation under catalyzation of EDC. Briefly, 500 mg EDC and 200 mg NHS were successively added to 1.6% AA solution with pH value of 4.0–5.0 and adjusted by NaOH to activate carboxyl group. After 30 min, 50 mL 2% gelatin solution was added to the mixture to continue the reaction for the following 10 h at room temperature. Finally, G-AA was obtained by dialyzing of the resulted mixture and freeze-drying.

Acetalated β-cyclodextrin (Ac-β-CD) was synthesized by acetalization. Briefly, 50 mM β-CD and 5 mM pyridinium p-toluene sulfonate were orderly dissolved in anhydrous DMSO under nitrogen atmosphere, into which 40 molar times of 2-methoxypropene were dropped. After the reaction had been conducted at 30°C for 6 h, Ac-β-CD was precipitated from basic water, collected by filtration, and lastly lyophilized to a white powder.

The products were characterized by nuclear magnetic resonance hydrogen spectrum ($_1$H NMR, BRUKER AV500).

2.3. Fabrication of Ac-β-CD Nanoparticle. Ac-β-CD nanoparticles were prepared by microemulsion evaporation method using G-AA as multifunctional emulsifier. Briefly, 1 mL of 10% w/v Ac-β-CD/DCM solution was emulsified via probe sonication (Scientz, JY92-II) into 6 mL of 3% w/v G-AA aqueous solution. The obtained emulsion was immediately added to 20 mL of 1% w/v G-AA solution to evaporate DCM under magnetic stirring. Finally, Ac-β-CD nanoparticles were collected by centrifugation (14000 rpm, 10 min) after 10 h. The collected nanoparticles were washed several times with basic water, lyophilized, and characterized by Fourier-transformed infrared spectroscopy (FTIR, Nicolet IS10) and scanning electron microscope (SEM, S8100). The solubility of nanoparticle was characterized by transparency using UV spectroscopy (Cary 50).

2.4. Preparation of Injectable Composite Hydrogel. The collected nanoparticles were suspended with 15% (w/v) G-AA aqueous solution to obtain homogeneous suspension, to which Irgacure 2959 (photoinitiator) with final concentration of 0.05% w/v was added and incubated at 37°C for 5 min. 200 μL of the mixtures was injected into circle models, covered with coverslip, and irradiated by 365 nm UV light with a power of ~10 mW/cm^2. Gelation time was recorded when the solution lost its fluidity.

2.5. Characterization of Injectable Composite Hydrogel. After being irradiated for 30 min, hydrogels were obtained, freeze-dried, and weighed (W_0). The dried hydrogel was hydrated in water at 37°C for 24 h. Then the equilibrium hydrated hydrogels were weighed (W_1). The swelling ratio of the hydrogel is defined as W_1/W_0.

For the rheological properties test, hydrogels were prepared using another circular and transparent glass mold (25 mm diameter, 0.22 mm height), setting irradiation time of 30 min. The samples were characterized by rheological measurement in a parallel plate mode using a strain-controlled rheometer (MCR102). Dynamic oscillatory mode (compression mode) was used to measure the storage and loss moduli. All tests were performed at 37°C with a fixed strain of 1%.

In addition, the solubility or degradation of nanoparticle in hydrogel was characterized by transparency using UV spectroscopy (Cary 50) at 400 nm.

2.6. Statistical Analysis. Data were analyzed using t-test for differences. Results are reported as means ± standard deviation. The significant level was set at $p < 0.05$.

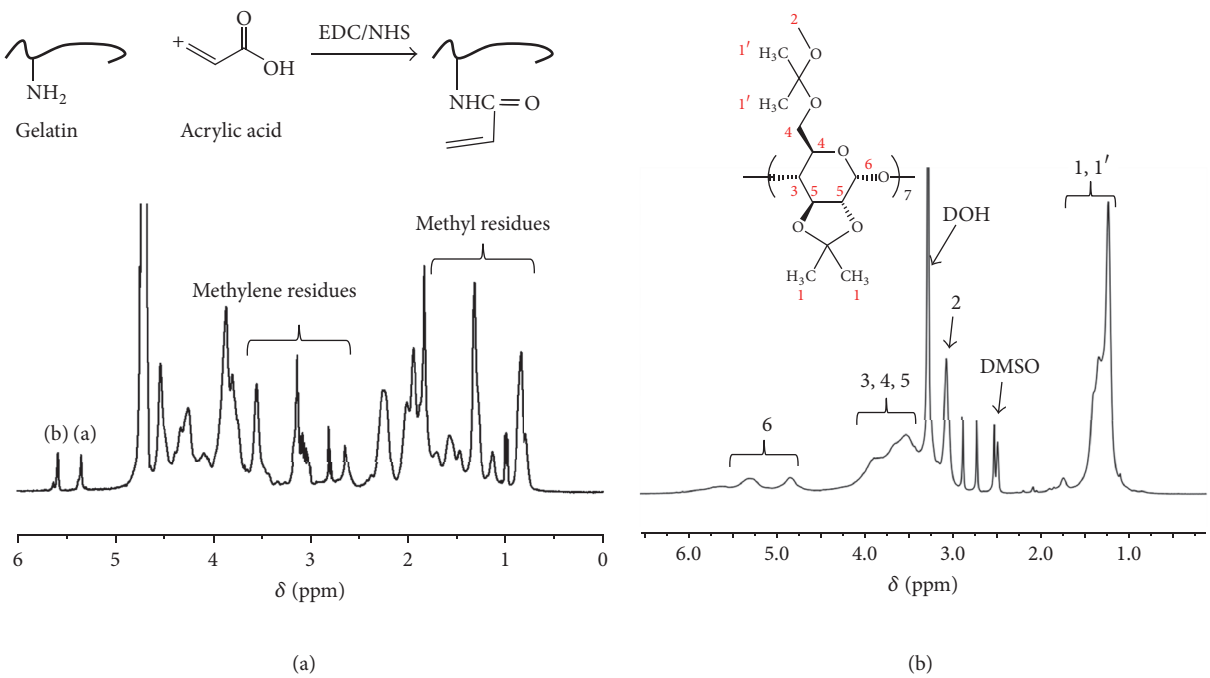

Figure 1: $_1$H NMR spectra of (a) G-AA and (b) Ac-β-CD.

3. Results

3.1. Synthesis of G-AA and Ac-β-CD. The ^{1}HNMR spectra were used for the structural information of G-AA and Ac-β-CD in Figure 1. Firstly, in the ^{1}HNMR spectrum of G-AA (Figure 1(a)), the chemical shifts from 0.6 ppm to 1.7 ppm belong to the protons of methyl residues and the chemical shifts from 2.5 ppm to 3.7 ppm are assigned to the protons of methylene residues, while $\delta = 5.6$ (a) and $\delta = 5.4$ (b) are typical chemical shifts belonging to the protons of $\underline{H_2}$C=C-, which confirms the successful modification of gelatin by AA.

Secondly, the $_1$H NMR spectrum of Ac-β-CD (Figure 1(b)) is analyzed as follows: the chemical shifts at 3, 4, 5, and 6 positions are, respectively, attributed to the protons of pyranose ring, constructed units of β-CD, the chemical shifts from 1.0 ppm to 2.0 ppm belong to the protons of C$\underline{H_3}$-C at 1 and 1′ positions, and $\delta = 3.0$ ppm is assigned to the protons of C$\underline{H_3}$-O at 2 position. From the above analysis, the emergence of chemical shifts at 1, 1′, and 2 positions verified acetalated groups on β-CD molecules. Further, since the number of protons is directly proportional to its relative average area, the degree of substituent (DS) can be quantified according to the relative average area of protons. Given the fact that protons at 3, 4, 5, and 6 positions were fixed, the DS of Ac-β-CD was calculated by average area of 1, 1′, and 2 positions to that of 3, 4, 5, and 6 positions, which was 61%. Ac-β-CD could dissolve in acid solution (pH < 5.5), indicating the pH response property of the β-CD derivative.

3.2. Fabrication of Ac-β-CD Nanoparticle. Figure 2(a) illustrated the fabrication process of Ac-β-CD nanoparticle through single oil-in-water (o/w) emulsion technique. Similar to traditional emulsion technique, nanoparticle was obtained after solvent had been volatilized. But, differently, crosslinkable gelatin (G-AA) was used as an emulsifier in the research. The formed nanoparticle exhibited nearly spherical morphology with slight coarse surface, confirmed by SEM image (Figure 2(b)). Further, the diameter of nanoparticle was 238 ± 61 nm by statistics form SEM images. Moreover, chemical information of Ac-β-CD nanoparticle surface was characterized by FTIR spectrum (Figure 2(c)). At the same time, FTIR spectrum of Ac-β-CD derivative was also detected as a control sample in Figure 2(c). By comparing two spectra, a large amount of change including the obvious shift of absorbance bands from 3433 cm^{-1} to 3320 cm^{-1}, the appearance of absorbance bands at 1446 cm^{-1}, and the obvious enhance of peak at 1640 cm^{-1} and 1560 cm^{-1} emerged in the FTIR spectrum of nanoparticle. Analytically, 3320 cm^{-1} belonged to amide and amino groups, 1446 cm^{-1} is assigned to carboxylic acid peak, and 1640 cm^{-1} and 1560 cm^{-1} are attributed to amide I and amide II characteristic absorption. These differences confirmed the existence of G-AA (typical protein structure) on the surface of nanoparticle.

3.3. Preparation of Injectable Composite Hydrogel. The schematic illustration of injectable composite hydrogel fabrication was shown in Figure 3(a). It was found that Ac-β-CD nanoparticles were compounded with the G-AA solution to obtain stable homogenous solution, which was ascribed to good compatibility between nanoparticle surface and macromonomer (G-AA). In the next step, the mixture was initiated by I2959 to form composite hydrogels. Here 4 types of composite hydrogel were prepared: pure hydrogel without nanoparticle (hydrogel0), composite hydrogel with 2 mg/mL Ac-β-CD nanoparticles (hydrogel1), composite hydrogel with

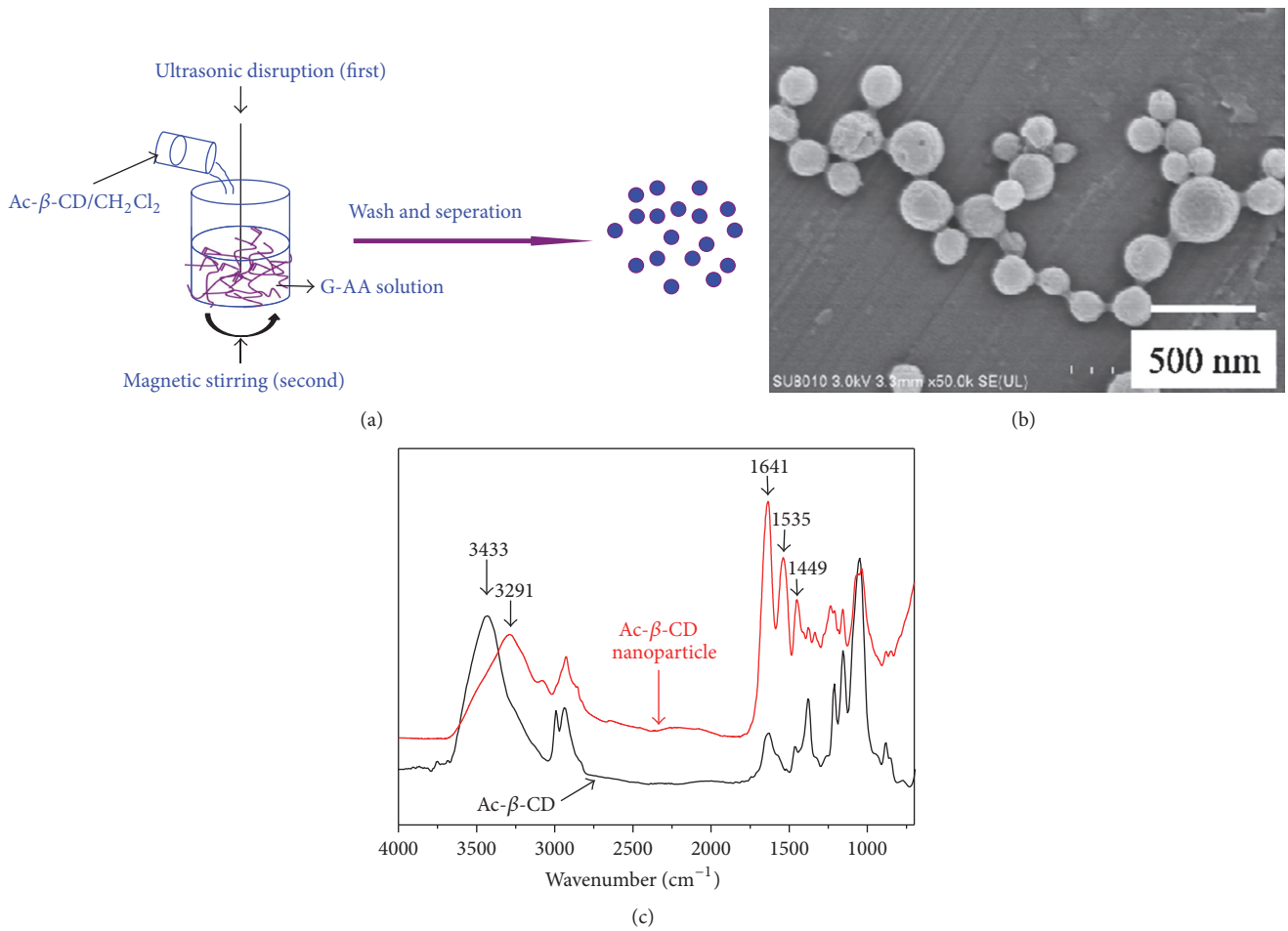

Figure 2: (a) Schematic illustration to show the formation of nanoparticle. (b) SEM image of Ac-β-CD nanoparticles. (c) FTIR spectra of Ac-β-CD and its nanoparticle.

4 mg/mL Ac-β-CD nanoparticles (hydrogel2), and composite hydrogel with 8 mg/mL Ac-β-CD nanoparticles (hydrogel3). As an important evaluation indicator for injectable hydrogel, gelation time of the composite hydrogel was first studied in Figure 3(b). The gelation time showed slight increase with the increase of nanoparticle concentration until nanoparticle's concentration reached 4 mg/mL but without significant difference. Gelation of the G-AA and G-AA composite system, regardless of nanoparticles' concentration, is triggered mainly by crosslinking between the G-AA chains, which makes the solution lose its fluidity upon gelation. Nanoparticles might play a little inhibition for photoinitiated crosslinking reaction but not obvious. Swelling property can reflect the inner structure of hydrogel and influence substance exchange between hydrogels inside and outside environment. Thus swelling ratio of composite hydrogels was characterized in Figure 3(b) which was gradually decreased along with increase of the nanoparticles' concentration but without significant difference. Since the nanoparticle is not water-swelling particle, the mixed nanoparticles contribute only to the dried weight of the composites. Consequently, "apparent" swelling ratio of composite hydrogel showed a slight declined trend with nanoparticles' concentration.

The viscoelastic behavior of hydrogels was investigated in Figure 4. As a whole, storage moduli (Figure 4(a)) of all hydrogels were 1×10^3–5×10^3 Pa, which was 25–100 times higher than loss moduli (Figure 4(b)) of 10–200 Pa over the frequency range of 10^{-1}–10^2 rad/s. The result indicated that all hydrogels had some characteristics of elastomer. With increasing angular frequency, storage moduli showed little change and loss moduli varied gently with no sign of breakage as far as the measured angular frequency range was concerned. Theoretically, for uncrosslinked polymers, polymer chains do not have enough time to relax at high frequencies. Thus the elastic energy has been stored in polymer, which results in a high modulus of polymer. Nevertheless, when the polymer is crosslinked, chain relaxing and chain slipping are inhibited, resulting in relative stable modulus in the measured frequency range. Therefore, it was inferred that all hydrogels had a crosslinked elastomer structure. In further details, along with the increase of nanoparticle concentration, storage moduli were augmented correspondingly, while loss moduli were not varied significantly. This enhancement of storage moduli can be explained by the energy dissipation mechanism, resulting in more uniform distribution of load among the whole network. Under stress, polymer network

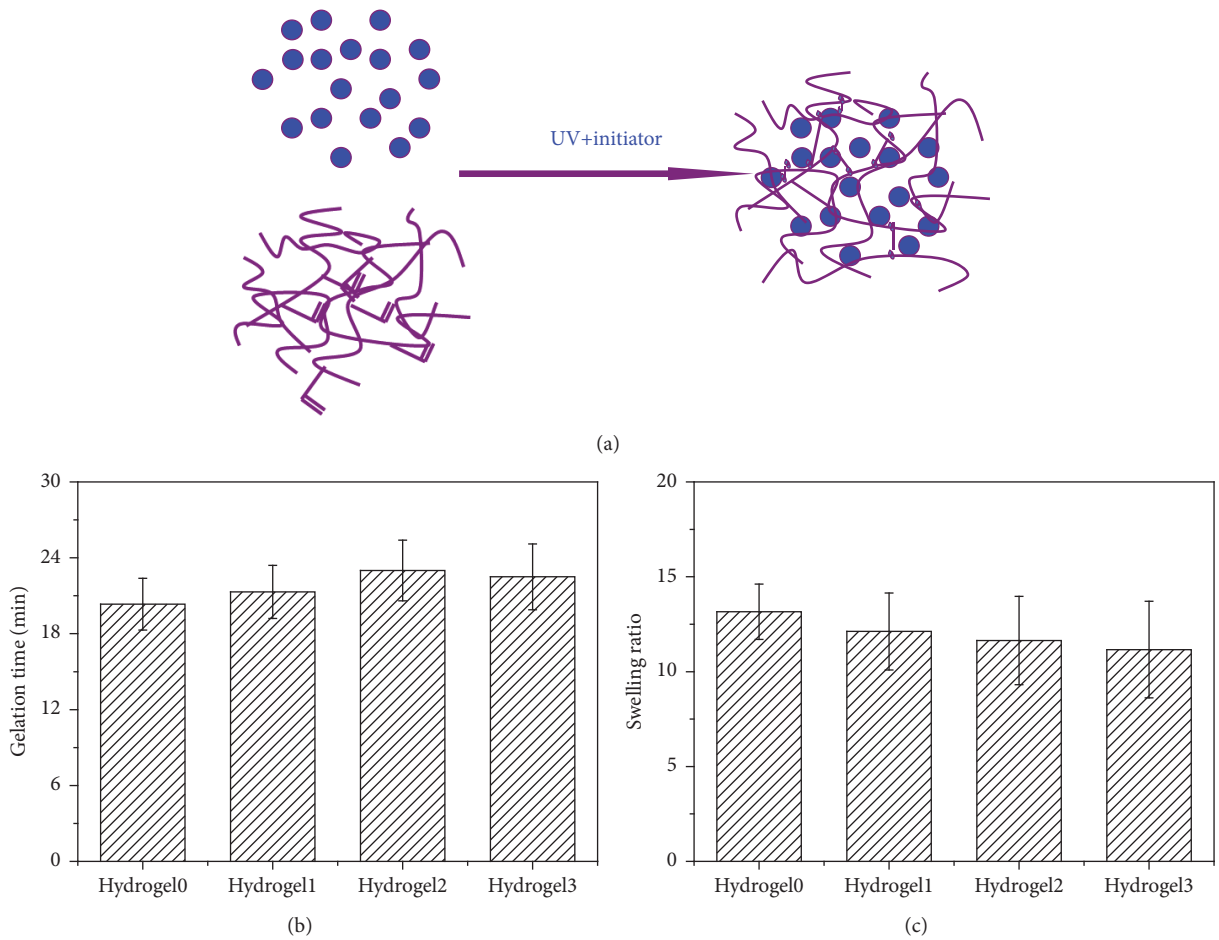

Figure 3: (a) Schematic illustration to show the formation of injectable hydrogel. (b) Gelation time of different hydrogels. (c) Swelling ratio of different hydrogels.

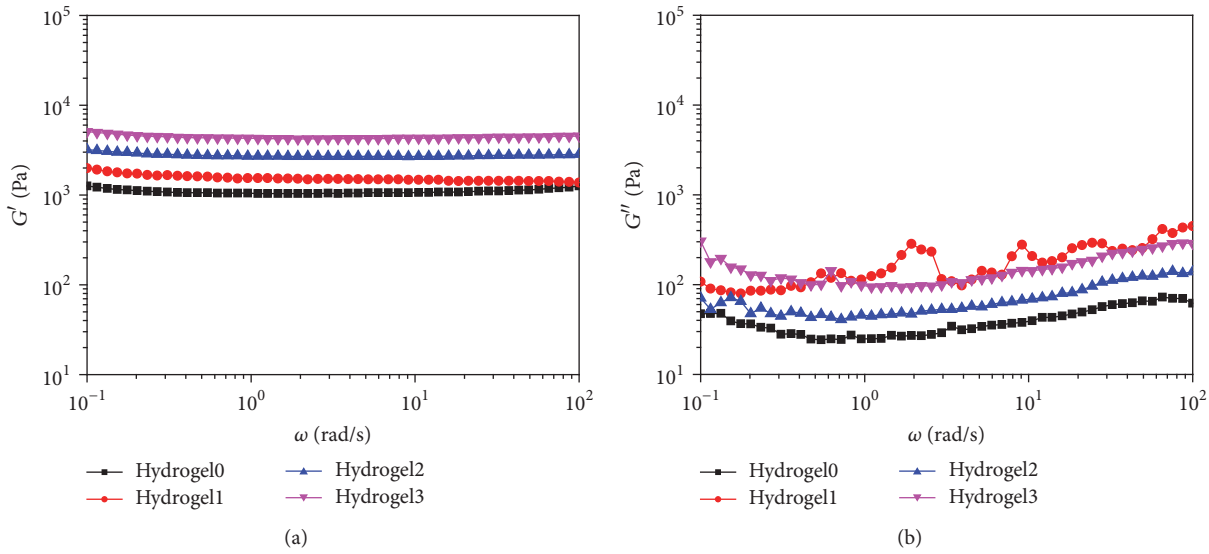

Figure 4: Storage modulus (a) and loss modulus (b) of different hydrogel as a function of compressing frequency (ω). Strain and temperature were set at 1% and 37°C, respectively.

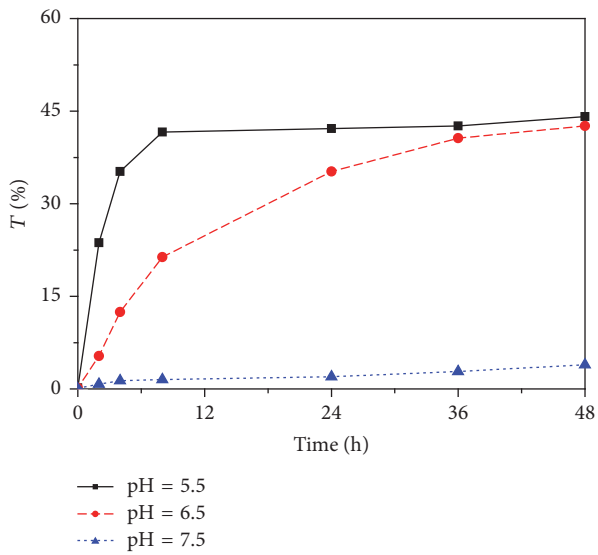

Figure 5: Transparency of hydrogel3 in different medium.

of hydrogel is deformed, dissipating energy to nanoparticles. Not surprisingly, more nanoparticles can endure more stress, resulting in larger storage moduli. In addition, since G-AA was stably absorbed on the surface of nanoparticle in the research, the polymer chain was inevitably crosslinked with nanoparticle surface during the process of hydrogel formation, which ensured effective energy delivery under stress. When it comes to loss moduli, factors of contribution to loss moduli became viscous, which is mainly decided by the continuous phase, namely, crosslinked gelatin network of hydrogel. Therefore, no obvious trend was found for effects of nanoparticle concentration to loss moduli.

In order to evaluate the pH response properties, the transparency of hydrogel3 along with time in different medium was tracked in Figure 5. When pH of outer solution was 5.5, the transparency of hydrogel3 increased quickly in first 6 h, indicating the quick dissolution of Ac-β-CD nanoparticles at acid environment. When pH of outer solution was 6.5, the transparency of hydrogel3 gradually increased in 36 h, implying relative slow degradation of Ac-β-CD nanoparticles in faintly acid environment. When pH of outer solution was 7.5, the transparency of hydrogel3 increased little during the detected 48 h, showing that the Ac-β-CD nanoparticles in hydrogel could exist stably in alkalescent environment. The transparent property of hydrogel is relevant to the degradation of nanoparticle. This pH-controlled degradation could induce the control release of drug/bioactive factor in previous reports. In view of the above-mentioned results and analysis, it can be deduced that the composite hydrogel had obvious acid-response properties, which would broad the injectable materials in biomedical application.

4. Conclusions

An injectable composite hydrogel with pH response properties was designed and prepared for biomedical application. Firstly, double carbon functionalized gelatin (G-AA) and acetalated β-cyclodextrin (Ac-β-CD) with pH response property were successfully synthesized as macromonomer/surface modifier and original material for nanoparticles, respectively. Secondly, G-AA functional Ac-β-CD nanoparticles with diameter of 238 ± 61 nm were conveniently prepared by one-step emulsion method. Finally, injectable composite hydrogel was obtained by photoinitiated polymerization in situ. The gelation time and swelling ratio showed slight increase and gradual decrease along with the increase of nanoparticle concentration, respectively, but without significant difference. All investigated hydrogels in the research had typical characteristics of crosslinked elastomer. Along with the increase of nanoparticle concentration, storage moduli were augmented correspondingly, while loss moduli were not varied significantly. Moreover, the transparency with time had verified obvious acid-response properties of hydrogels.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

Acknowledgments

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