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Hydrogels of dihydroxypropyl chitosan crosslinked with irradiation at paste-like condition

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ABSTRACT

In present study, a series of environmentally friendly hydrogel films were prepared from dihydroxypropyl chitosan (DHP-chitosan) using irradiation technique without any bifunctional crosslinking compounds. DHP-chitosan irradiated at high concentrated solution state (more than 10%, paste-like state) was found to introduce crosslinking structure. Crosslinking behavior, mechanical property, morphology, and swelling behavior of the hydrogel films were studied. It has been found that a concentration of 40% solution is the most effective for crosslinking. The hydrogel films of DHP-chitosan exhibited controllable mechanical property and typically pH-sensitive character in their swelling behavior. A preliminary biodegradation study confirmed that DHP-chitosan hydrogels also undergo biodegradation by enzymatic degradation test.

1. Introduction

Biodegradable polymers and their hydrogels are used for a variety of applications such as biomedical, cosmetic, agricultural, and superadsorbent materials. The hydrogels derived from nature polymer such as polysaccharides have attracted much attention due to their commercial availability, good biodegradability, and biocompatibility (Crescenzi et al., 1997; Dumitriu, 1996; Rosiak & Yoshii, 1999; Yoshii et al., 2003). Chitosan, a copolymer of glucosamine and *N*-acetylglucosamine units linked by 1–4 glucosidic bonds, is obtained by *N*-deacetylation of chitin, which is one of the most abundant natural amino polysaccharide, and has been reported to have a variety of applications (Dodane & Vilivalam, 1998; Dumitriu, 1996; Majeti & Kumar, 2000; Suh & Matthew, 2000). The hydrogels based on chitosan and their derivatives have also been studied widely.

Chitosan and their derivatives have been used as a cationic segment in the synthesis of hydrogels to introduce pH response and improve the gel strength (Mitsumata et al., 2003; Nho & Park, 2002; Shim & Nho, 2003; Zhao, Mitomo, & Yoshii, 2008). Recently, certain chitosan derivatives are becoming increasingly important polymers due to their unique structure, distinctive properties (Majeti & Kumar, 2000). Among them, dihydoxypropyl chitosan (DHP-chitosan) is a highly-hydrophilic polymer, used in practical applications because of its easy preparation, non-toxicity, biocompatibility, antibacterial activity, and biodegradability (Kobayashi et al., 2002; Maeda, Matsumoto, & Kondo, 1997). Therefore, hydrogels based on DHP-chitosan are appealing functional materials and will be expected to meet various demands from the applied scene.

Chemical crosslinking of chitosan derivatives has been studied widely for the synthesis of hydrogels. However, in this method, addition of crosslinking agent such as glutaraldehyde is necessary to initiate the process. It is well known that glutaraldehyde is not preferred because of its physiological toxicity limit the application of products. A new method for the synthesis of hydrogels has been proposed, using ionizing radiation. Compared to other methods, radiation-crosslinking method is the lack of any additives to start the process, hence the final product contains only polymer in its structure. Moreover, ionizing radiation usually allows the combination of the synthesis and sterilization of polymeric materials in a single technological step, which reduce cost and production time. Therefore, ionizing radiation is an excellent tool in fabrication of materials for biomedical and sanitary applications.

In our previous works, we firstly found that some water-soluble chitosan derivatives such as carboxymethylchitosan (CM-chitosan) can be induced to be crosslinked at high concentrated solution state under high energy radiation (Zhao, Mitomo, Nagasawa, Yoshii, & Kume, 2003). Though, DHP-chitosan appears to be good performance in many application fields. However, compared to CM-chitosan, it is hardly soluble in water because of the strong intermolecular hydrogen bonding. Very recently, a successful ap-

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proach was proposed to improve the solubility of DHP-chitosan in water by adding diluted acid as a subversive of hydrogen bonding. It is found that the presence of water in polymer system can relent macromolecular conformation and cause an acceleration of radiation-initiated chemical reactions by the action of intermediate products of water radiolysis (Zhao & Mitomo, 2008). Although the radiation effects on the DHP-chitosan has been reported as short note in our previous work, detailed properties of the crosslinked products such as swelling behavior, mechanical properties, and biodegradability have not been revealed yet; thus, as a continued work, this work completed the above subjects.

2. Experimental

2.1. Materials

DHP-chitosan (M_w 134,000) used in this study was obtained from Dainichiseika Color and Chemical Mfg. Co. Ltd., Japan, which has a deacetylation degree of 85%. The degree of substitution of dihydroxypropyl groups was 1. The chitosan enzyme, from *Bacillus pumilus*, was obtained from Wako Chemical Co. Ltd., Japan. All other materials were of analytical-reagent grade purity. Deionized water was used to prepare all solutions.

2.2. Sample preparation and irradiation

2% Lactic acid aqueous solution was used to dissolve the DHP-chitosan in this work. A high concentrated DHP-chitosan sample (more than 10%) was mixed homogeneously by Keyence HM-500 hybrid mixer. Prepared samples were kept for 2 days in order to ensure complete dissolution and homogeneous distribution. After that, the samples were pressed (200 kPa) for about 45 min to obtain thin film (1 mm thick) and then sealed in polyethylene bags to ensure air-free conditions after degassing using vacuum apparatus. For irradiation by electron beam, a 2-MeV scanning electron accelerator with Cockcroft-Walton type DC power supply (NISSIN Electronic Co. Ltd., Japan) was used at the following irradiation parameters: current = 1 mA, voltage = 2 MeV, and the dose per pass = 1 kGy. The irradiation was carried at room temperature.

The gel fraction of the crosslinked DHP-chitosan was determined gravimetrically. After irradiation, the crosslinked samples were put into water for 72 h at room temperature to remove the soluble part. The gel fraction was calculated according to the following equation:

$$\text{Gel fraction } (\%) = \frac{G_d}{G_i} \times 100 \tag{1}$$

where G_i is the initial mass of the sample and G_d is the mass of dried gel after extraction.

2.3. SEM measurements

Morphology of the gel samples was studied by JSM-5600 scanning electron microscope (SEM) of JEOL, Japan. To preserve the network structure after drying, the hydrogels in equilibrium state was immersed into liquid nitrogen and then frozen dried in vacuum at −20 °C. The dried samples were coated with gold using an ion coater prior to observation. The cross-sections of the gel sample were then photographed.

2.4. Swelling of hydrogel

Hydrogel samples were immersed in distilled water for different times at room temperature. After the excessive surface water was removed with filter paper, the weight of swollen gel was measured at various time intervals. The procedure was repeated until there was no further weight increase. The swelling ratio was determined according to the following equation:

$$\text{Swelling ratio} = (W_t - W_d)/W_d \tag{2}$$

where W_t is the weight of the gel after swelling and W_d is the weight of dried gel before swelling. The equilibrium degree of swelling was also calculated by this equation changing W_t to W_e which was the equilibrium weight of swollen gel.

Effect of some factors such as acid, base, as well as inorganic salt on swelling behavior of the hydrogels also performed by determining the swelling ratio of samples at above condition.

2.5. Mechanical properties

In order to estimate the mechanical property of irradiated samples, the gel films were examined in relaxed state (after irradiation with the original water content). The gel films were cut into dumbbell (ASTM D-1822-L), and then tensile strength and elongation at break were measured by Strograph-R1 Material Tester (Toyoseiki Co. Ltd., Japan) at a crosshead speed of 50 mm/min. At least five measurements for each sample were recorded and a mean value was calculated.

2.6. Biodegradation of hydrogels

Enzymatic degradation was carried out using a chitosan enzyme from *B. pumilus* in an acetate buffer solution of pH 5.6. After removing the sol part, 10 mg dry gel film samples were dipped into enzyme solution for a given time. Concentration of the enzyme in buffer was 0.2 mg/ml. Tests were performed at 40 °C with shaking. After incubation, the samples were washed with distilled water and dried at 35 °C under vacuum. The results of the enzymatic degradation are expressed as percentage of the weight loss:

$$\text{Weight loss } (\%) = G_e/G_d \times 100 \tag{3}$$

where G_e and G_d denote the weights of films after and before enzymatic tests, respectively. As a control experiment, DHP-chitosan hydrogels were also performed without enzyme. It is believed that only hydrolytic degradation occurs in the control experiment.

3. Results and discussion

3.1. Synthesis and morphology of hydrogel films

Very recently, the effects of electron beam radiation on the DHP-chitosan in solid state and solution state have been communicated briefly (Zhao & Mitomo, 2008). Degradation and crosslinking of polymer under ionizing radiation occur simultaneously, and the one, which predominates, determines the final reaction products (Chapiro, 1962; Zhao & Mitomo, 2008). DHP-chitosan underwent degradation at solid state and diluted solution (below 10%). The restricted mobility during irradiation in solid state is the primary factor of scission. In low concentrated solution, the concentration of polymer macroradicals formed under irradiation is too low to combine with each other. EB radiation-induced crosslinking of DHP-chitosan was observed only in the system of a high concentrated of polymers, in so called “paste-like state”. Radiation-induced crosslinking of DHP-chitosan in its paste-like condition (20–60%, at 100 kGy) is shown in Fig. 1. It has been found that a concentration of 40% solution is the most effective for crosslinking. The influence of DHP-chitosan concentration and adsorbed dose on the gel fraction of DHP-chitosan hydrogels has been described detailedly in our previous work (Zhao & Mitomo, 2008). The effect of polymer concentrations on gel formation in terms of gelation dose

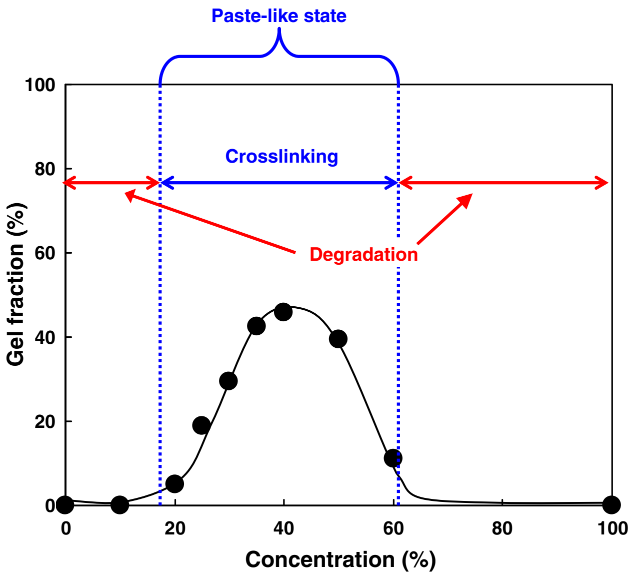

Fig. 1. Radiation-induced crosslinking of DHP-chitosan in paste-like condition.

(Dg) was calculated from Charlesby–Pinner equation and listed in Table 1. The most low Dg also appeared at a concentration of 40% solution. As a result, such crosslinked DHP-chitosan hydrogels could be considered as "green" materials that can be degradable to natural products. The radiation process is also quite simpler and effective, and believed to be mass-produced for industrial products.

The morphology of a crosslinked DHP-chitosan (prepared from 40% concentration, at 100 kGy) is shown in Fig. 2. It can be seen that the crosslinked samples formed a porous morphological structure during the fabrication. The porous structure is advantages to micromolecules to diffuse into interior of the hydrogels, and the size of porous structure will depend on the concentration of polymer solution and irradiation dose used in the process of crosslinking.

3.2. Swelling property of hydrogel

The capacity of hydrogel to swell and hold significant amounts of solvent in its network structure is one of the most important features. Fig. 3 shows the equilibrium swelling ratio of DHP-chitosan hydrogels prepared at different doses and in various concentrations. The swelling curves indicate a typical swelling-dose relationship. The degree of swelling decreases with an increasing dose in each concentration, and the gel made from low concentration solution shows higher swelling ability in water than that made from high concentration solution. It can be suspected that the degree of swelling is controlled by changes in the crosslinking density. Higher irradiation dose increases the number of intermolecular crosslinks, which leads to the decreasing of the degree of swelling. In this study the hydrogel made from the DHP-chitosan shows the maximum swelling ratio of 120. From the practical point of view, DHP-chitosan hydrogels with different swelling capacities can be easily prepared by varying the irradiation dose and polymer concentration. Consequently, the novel hydrogels could meet some specific demands for the uptake and release of compounds.

Table 1
Dg of different DHP-chitosan hydrogels.

	20 wt%	30 wt%	40 wt%	50 wt%
Dg (kGy)	36.6	18.38	9.71	12.58

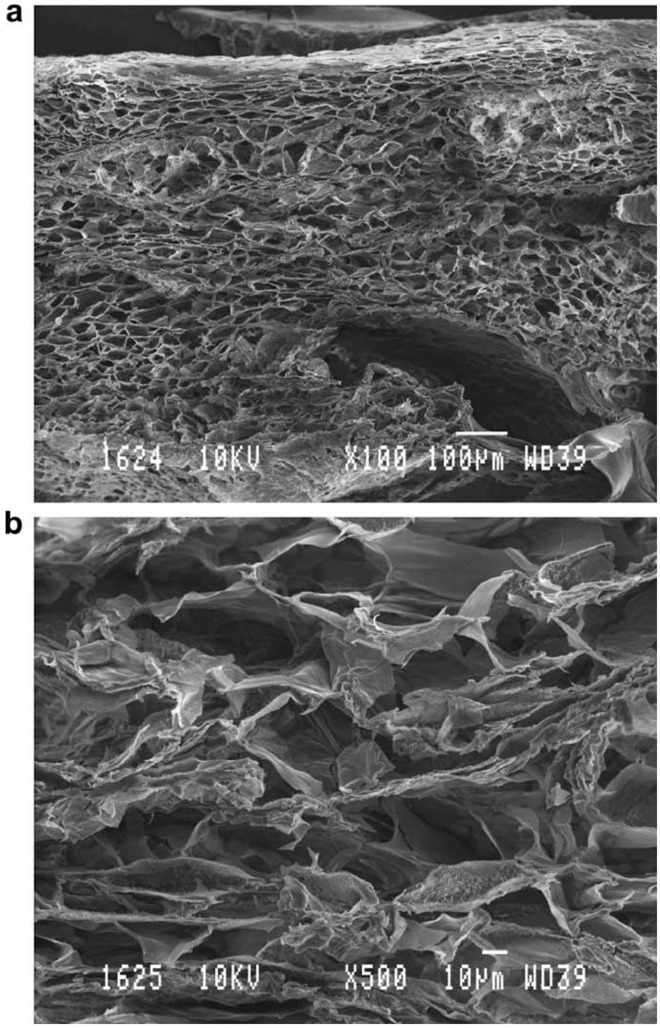

Fig. 2. SEM micrographs of DHP-chitosan hydrogel films. (a) Interior morphology at 100× magnification; (b) interior morphology at 500× magnification.

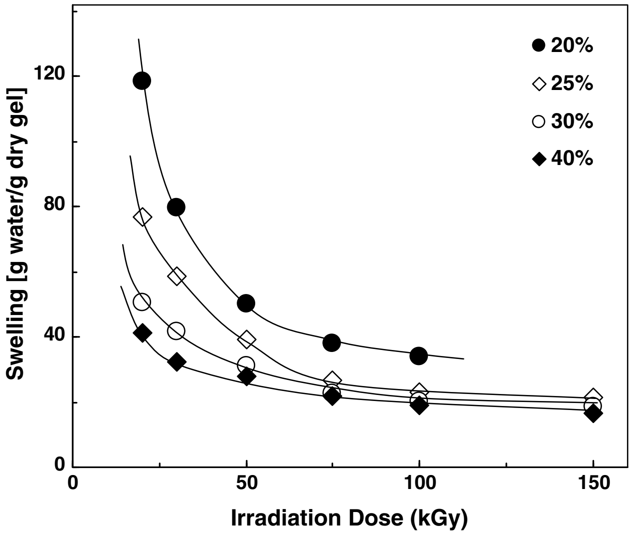

Fig. 3. Swelling of DHP-chitosan hydrogels in distilled water.

The hydrogels prepared from 40 wt% solution at 100 kGy were chosen to do further investigation of swelling behavior. The kinetic of swelling in different solvents was monitored by the weight increase as a function of time and is depicted in Fig. 4. Several typical solvents such as deionized water, 0.9% NaCl solution, acidic buffer of pH 4, neutral buffer of pH 6.86, and basic buffer of pH 9.18, were used here. As shown in Fig. 4, the swelling of DHP-chitosan in these solvents is quick in initial 4 h, and becomes slow gradually. The swelling interval of DHP-chitosan hydrogels to equilibrium is about 24 h. Swelling in acidic solution is significantly higher than that of neutral or basic solution; while swelling in deionized water is somewhat higher than the other media excluding acidic solution. These results are in agreement with the fact that DHP-chitosan is cationic polyelectrolyte.

Second-order kinetics model have been identified as a suitable method to evaluate swelling process in water for radiation-cross-linked CM-chitosan hydrogels (Wang et al., 2008). Similarly, for extensive swelling of crosslinked chitosan derivatives, it is also proposed that the swelling of hydrogels of DHP-chitosan follows the second-order kinetic described by Schott (1992):

$$dS/dt = K_s(S_\infty - S)^2 \tag{4}$$

with initial condition $t = 0$, $S = 0$, it can be got that

$$t/S = A + Bt \tag{5}$$

where K_s is the rate constant of swelling, S is swelling at time t, A and B are constants. Namely, A is the reciprocal of initial rate of swelling and B is identified as the reciprocal of S_∞, the swelling in equilibrium, $B = 1/S_\infty$. Fig. 5 shows the dependence of the reciprocal of the average rate of swelling (t/S) on time. Straight lines were shown for the data of gel swelling in above mentioned solutions. All of the linear correlation coefficients for DHP-chitosan samples are better than 0.995.

The large number, array of different functional groups on the polymer chains, and porous structure will result in relatively complicated swelling process. The simple diffusion model like Fickian diffusion is difficult to describe the swelling process in current case (Crank, 1975). According to the swelling kinetics data, the swelling process is suitable to be explained as a consequence of relaxation rate of the polymer matrix. As a result, the process is not diffusion controlled. The expansion of the hydrogels is limited by the cross-links of network, and the swelling of DHP-chitosan hydrogels is controlled by the polymer relaxation.

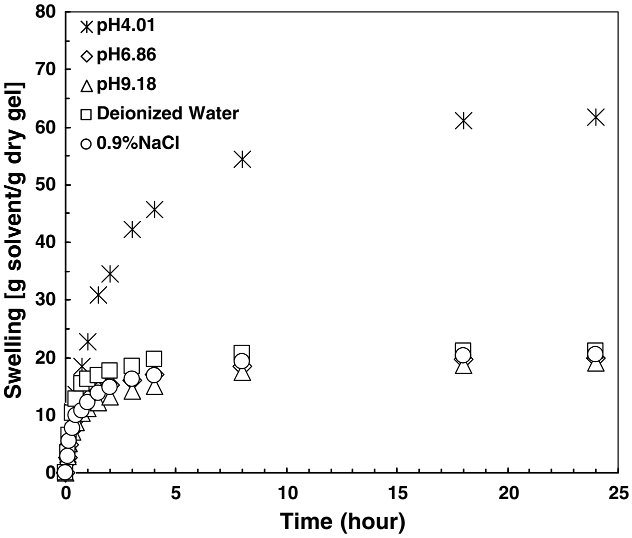

Fig. 4. Swelling kinetics of DHP-chitosan hydrogels in various media.

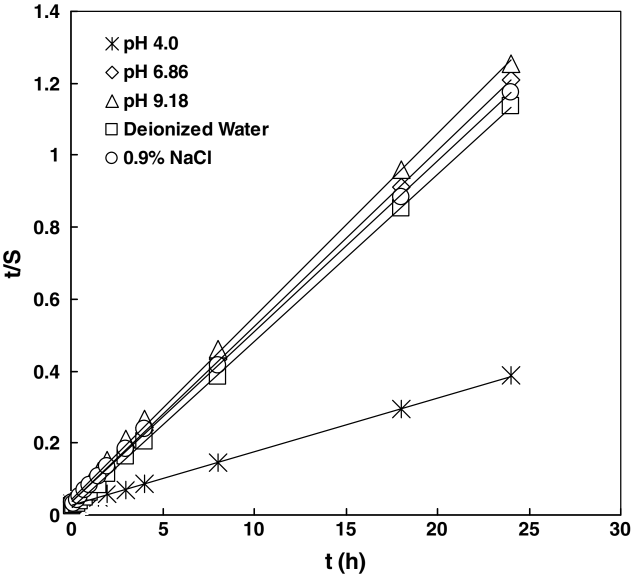

Fig. 5. Swelling dynamics kinetic curves (t/S versus t) of DHP-chitosan hydrogels in various media.

It is well known that swelling and deswelling in response to changes of pH is a typical phenomenon of polyelectrolyte hydrogels. The pH of the external solution has been varied in the range of 1.0–12.0 and the effect on the swelling ratio has been observed. Fig. 6 shows the dependence of swelling ratio on pH of DHP-chitosan hydrogels. The typical swelling characteristics of cationic hydrogel were observed in DHP-chitosan hydrogel. The DHP-chitosan gels swelled at acidic medium and deswelled at neutral or basic medium. The protonation of amino groups of DHP-chitosan takes place at acidic solution. After gel ionization, the increased electric repulsions between positive charged amino groups cause the gel swell. The swelling ratio of the hydrogel thus increases with the decrease of pH. A sharp reduction of swelling was found in the pH range of 3.0–6.0. The pH sensitivity of the DHP-chitosan hydrogels is believed to play an important role in biomedical application.

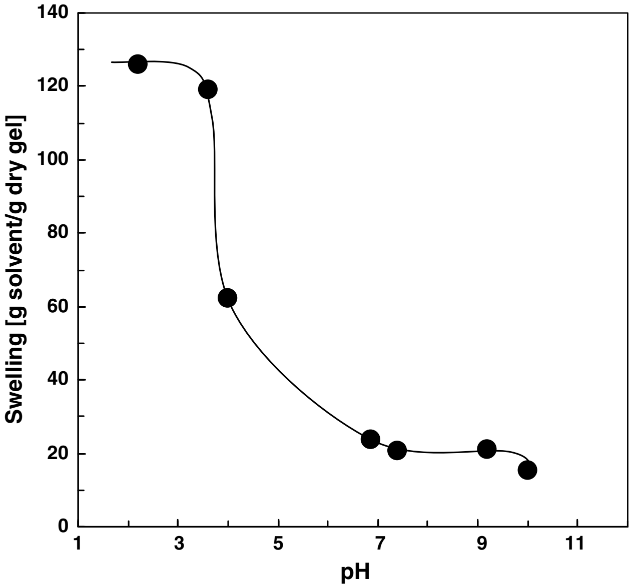

Fig. 6. Swelling of DHP-chitosan hydrogels in aqueous solutions of several pH.

3.3. Mechanical properties of hydrogel

There is a significant need in the biomedical field for hydrogels with suitable mechanical properties. Only a few reports on the evaluation of mechanical property of polysaccharides hydrogels have been found in the literature. Wach et al. initially reported the mechanical property of γ-ray crosslinked CM-cellulose hydrogel (Wach, Mitomo, Nagasawa, & Yoshii, 2003). Zhao et al. discussed the mechanical property of EB crosslinked CM-chitosan hydrogels (Zhao et al., 2003). In their reports, the mechanical property of hydrogels was found to be controllable by change of crosslinking densities. From practical point of view, it is worthy to investigate the mechanical properties of DHP-chitosan hydrogels prepared in this work.

The effect of irradiation dose on mechanical property of DHP-chitosan irradiated by EB in 40% concentration was discussed. Tensile strength of hydrogel film in relaxed state is presented in Fig. 7. Tensile strength was increased with increasing the absorbed dose at early stage, after reaching a maximum and then decreased again. This effect is due to the increasing crosslinking density at early stage, and after reaching a maximum, higher absorbed doses led to degradation and destroy the network structure. Tensile strength of 0.2 MPa at a dose 50 kGy was obtained in DHP-chitosan hydrogels. The gel strength of DHP-chitosan was close to other polysaccharides hydrogels such as CM-cellulose and CM-chitin/chitosan crosslinked by radiation (Wach et al., 2003; Zhao et al., 2003). Elongation at break of crosslinked polymers was decreased with increasing of absorbed dose. This is due to the radiation-induced brittleness of hydrogel film. The mechanical property of radiation-crosslinked DHP-chitosan hydrogels is dominantly controlled by the crosslinking density. The desired elasticity and flexibility of DHP-chitosan hydrogels will be expected to meet various demands from the applied scene of biomedical application, such as wound dressing and tissue engineering.

3.4. Hydrolytic and enzymatic degradation of hydrogel

Degradation is a desirable feature of hydrogels when they are utilized in medicine as controlled drug delivery systems, in agriculture as superabsorbers and other fields. In general, polysaccharides and their hydrophilic derivatives are hydrodegradable and biodegradable. Hydrolytic degradation is always regarded as prerequisite condition for biodegradation. It is well known that enzymatic degradation is a more suitable method of biodegradation testing. Compared to other biodegradation testing methods (e.g. soil burial, microbial attack), the parameters of the conditions can be easily controlled. It is also known that chitosan and their derivatives can be enzymatically degraded by chitosan enzyme, (Fukamizo, 2006; Hutadilok et al., 1995). Therefore chitosan enzyme was carried for the biodegradability test in this work.

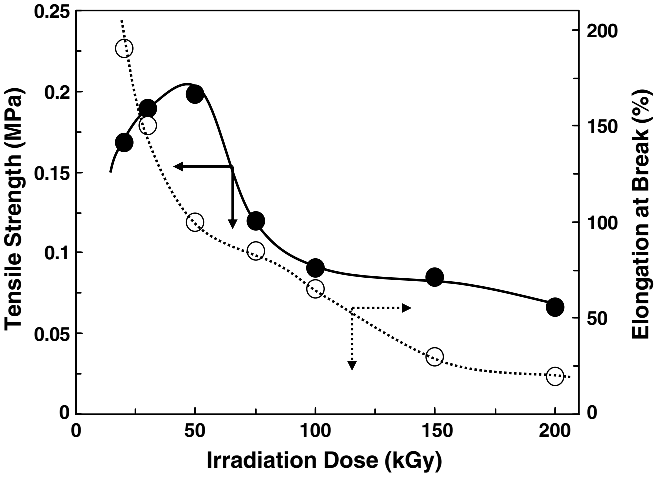

Fig. 7. Tensile strength and elongation at break of DHP-chitosan hydrogels in relaxed conditions.

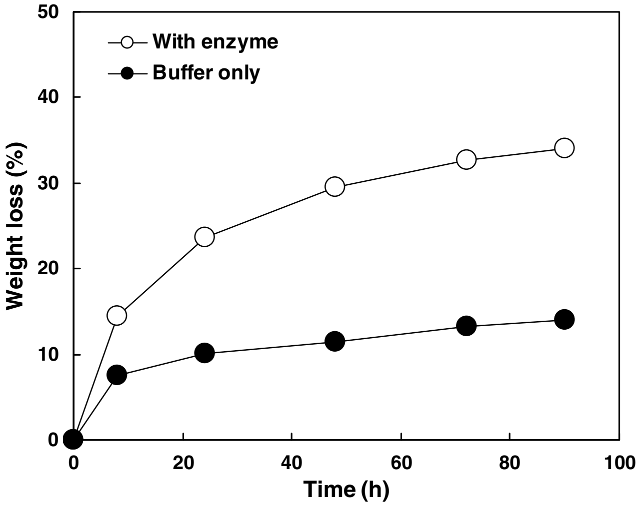

Fig. 8. Biodegradation of DHP-chitosan hydrogels by the chitosan enzyme.

The crosslinked DHP-chitosan hydrogels undergo gradual degradation by chitosan enzyme as shown in Fig. 8. The DHP-chitosan gel samples prepared from 40% DHP-chitosan solution at 100 kGy are used for testing. Hydrolytic degradation of DHP-chitosan in buffer solution is also applied at same condition. It can be seen that the hydrolysis of DHP-chitosan gel reveals lower degradation effect than enzymatic treatment. The chitosan enzyme can enhance degradation yields of DHP-chitosan hydrogels, and DHP-chitosan can be efficiently degraded by enzyme even after its chains were crosslinked. The weight loss of the gel samples with/without the enzyme after 120 h incubation increase to about 33% and 14%, respectively. Sometimes, it is expected that examined samples could possess certain stability against hydrolytic degradation during use; but they are still good for biodegradation after use. According to the above analyses one should find hydrogels of DHP-chitosan prepared with EB irradiation are environmentally friendly material.

4. Conclusions

The novel hydrogels with good quality were successfully prepared from DHP-chitosan with electron beam irradiation at room temperature. Diluted lactic acid was used to dissolve the DHP-chitosan in this work. High concentrated paste-like condition was favorable for gel formation. It has been found that a concentration of 40% solution is the most effective for crosslinking. The hydrogels created from DHP-chitosan, exhibited controllable mechanical property. The swelling of DHP-chitosan gels can be easily controlled by varying the synthesized conditions like irradiation dose and concentration of polymer solution. The hydrogels also displayed typically pH-sensitive character in their swelling behavior. A preliminary biodegradation study confirmed that the hydrogels undergo biodegradation with satisfactory results by enzymatic degradation test. Therefore, the DHP-chitosan hydrogels have great potential for wide utility in the biomedical field and other applications.

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