Preparation and Properties of PVA/PVP Hydrogels Containing Chitosan by Radiation

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ABSTRACT: Radiation can induce chemical reactions to modify polymers even when they are in the solid state or at a low temperature. Radiation crosslinking can be easily adjusted by controlling the radiation dose and is reproducible. The finished product contains no residuals of substances required to initiate the chemical crosslinking, which can restrict its application possibilities. In these studies, hydrogels for wound dressing were made from a mixture of chitosan and polyvinyl alcohol (PVA)/poly-*N*-vinylpyrrolidone (PVP) by freezing and thawing, gamma-ray irradiation, or combined freezing and thawing and gamma-ray irradiation. The physical properties of the hydrogel, such as gelation, water absorptivity, and gel strength, were examined to evaluate the usefulness of the hydrogels for wound dressing. The PVA/PVP composition was 60:40, PVA/PVP–chitosan ratio was in the range 9:1–7:3, and the concentration of, PVA/PVP–chitosan as a solid was 15 wt %. A mixture of PVA/PVP–chitosan was exposed to gamma irradiation doses of 25, 35, 50, 60 and 70 kGy to evaluate the effect of irradiation dose on the physical properties of hydrogels. Water-soluble chitosan was used in these experiment. The physical properties of the hydrogels, such as gelation and gel strength, were higher when the combination of freezing and thawing and irradiation were used rather than just freezing and thawing. The PVA/PVP–chitosan composition and irradiation dose had a greater influence on swelling than gel content. Swelling percent increased as the composition of chitosan in PVA/PVP–chitosan increased.
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Key words: hydrogels; gel; radiation; crosslinking; hydrophilic polymers

INTRODUCTION

The use of dry and wet dressings is well known for the treatment of wounds, including traumatic dermal wounds, wounds caused by removal of skin for dermatoplasty, as well as wound associated with disease. With dry dressings, healing is achieved by maintaining the wounded site dry until a crust is formed. Treatment with wet dressings is directed at creation of adequately wet circumstances to enable floating of the epidermal cells. With the latter method, more rapid healing of the wound is accomplished, less dry necrosis is formed, and a protective effect on the wound surface is produced.

The principal function of a wound dressing is to provide an optimal healing environment. For example, a wound must be isolated from the external environment before healing can begin. A wound dressing covers the wound, mimicking the natural barrier function of the epithelium. To provide an optimal healing environment, a wound dressing should control bleeding, protect the wound from the external environment, prevent further contamination or infection, and maintain

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a moist microenvironment next to the wound surface.

Hydrogels consist of a hydrophilic polymer that forms a three-dimensional network, which contains a lot of water. They are one of the most promising materials for biomedical applications and have several advantages for wound dressing, contact lenses, drug delivery systems, etc. because of their biocompatability with blood, body fluids, and tissue.[1–3] Hydrogels must sustain their physical strength and contain >75% water. Their water adsorption ability is due to hydration, which is related to chemical groups (such as -COOH, $CONH_2$, -CONH-, and SO_3H); capillary effect, and osmotic pressure.[4] These hydrogels also undergo volume change, do not dissolve, and have stable strength, properties that are caused by ionic, hydrophobic, and van der Waals forces. However, the effects of these forces are small; and covalent bonding is prevalent.[5] In fact, hydrogels have been prepared by chemical methods for a long time. However, in recent years, irradiation techniques to produce hydrogels are being used increasingly around the world. This technology is convenient because the physical properties can be manipulated easily by irradiation.[6,7] Ideal hydrogel wound dressings must have basic features, such as absorption of the exudates, prevention of excessive loss of body fluids, good adhesion to the wound, nontoxicity, and prevention of infection.[8]

Chitosan, the partially deacetylated form of chitin, is a material known in the wound management field for its hemostatic properties. Chitin may be extracted from the outer shell of shrimps and crabs, isolated, and then employed in the production of chitosan. In addition to its hemostatic properties, chitosan possesses many other biological properties, including bacteriostatic and fungistatic properties that are particularly useful for wound treatment. Chitosan has therefore been employed in various physical forms for wound treatment; for examples, as a solution/gel, film/membrane sponge powder, or fiber. In general, chitosan with a high molecular weight is not soluble in water but dissolves in acid water solution. To make hydrogels using chitosan in aqueous acid solution, a repeated cleaning process was necessary to neutralize the acid. Water-soluble chitosan was used to simplify the process of making the hydrogels in this study.

In this work, attempts were made to prepare the hydrogels for wound dressing that consisted of PVA, PVP, and chitosan. Hydrogels from a mixture of chitosan and PVA/PVP were made by freezing and thawing, ^{60}Co gamma-ray irradiation, and combination of freezing and thawing and ^{60}Co gamma-ray irradiation. The physical properties, such as gelation, swelling, and gel strength, were examined to evaluate the usefulness of hydrogels for wound dressing.

EXPERIMENTAL

Materials

PVA (MW: 8.5×10^4–1.46×10^3) was supplied by Aldrich Chemical Company (Milwaukee, WI). PVP (average of average molecular weight of 1.3×10^6) was purchased from Sigma (St. Louis, MO) and Aldrich Chemical Companies. These polymers were used without further purification. Distilled water used as a solvent in all experiments.

The water-soluble chitosan, supplied by Zakwang Company, Korea, is manufactured by acid/enzyme, ion-exchange column treatment and membrane treatment. The average MW of chitosan is 300,000. Diethyl ether and kentamine for anesthesia were purchased from Yuhan Company, Seoul, Korea. Povidone iodine topical solution for the disinfection of the skin of rats was purchased from Sung Kwang, Buchon, Korea.

Preparation of Hydrogels

PVA/PVP (60:40 composition) was dissolved in distilled water at 95 °C, and then mixed with chitosan by a physical stirrer at room temperature to give a PVA/PVP–chitosan solution. The solutions were then poured into a Petri dish at room temperature. The solution was kept at room temperature for 24 h to remove air bubbles. Hydrogels from a mixture of chitosan and PVA/PVP were made by freezing and thawing, exposure to ^{60}Co gamma-ray or both freezing and thawing and ^{60}Co gamma-ray irradiation. The PVA/PVP–chitosan ratio was in the range 9:1–7:3, the solid concentration of the total PVA/PVP–chitosan solution was 15 wt %, and the composition of PVA/PVP was 60:40. Water-soluble chitosan was used in this experiment. A mixture of PVA/PVP–chitosan was exposed to gamma irradiation doses of 25, 35, 50, 60, and 70 kGy to evaluate the effect of irradiation dose on the physical properties of hydrogels. Freezing and thawing was repeated up to five times to crosslink the PVA/PVP–chitosan solution physically. Each cycle of freezing and thawing involved lowering the temperature to −30 °C,

standing at this temperature for 1 h, then raising the temperature to room temperature.

Gel Content

The gel content of the hydrogels was measured by extraction in hot distilled water at 50 °C for 72 h and vacuum dried at 70 °C for ~48 h until they reached constant weight. The gel content was defined as in eq 1; where W_d is the dried gel weight after extraction, and W_i is the initial weight of the polymer.

$$\text{Gel } (\%) = \frac{W_d}{W_i} \times 100 \quad (1)$$

Degree of Swelling

The degree of swelling could be described as water absorptivity (Eq. 2) of the hydrogels. The gel samples were immersed in distilled water for 48 h at room temperature until the gel reached the equilibrium state of swelling. After the water on the surface of the swollen gels was removed with cellulose paper, the mass was determined. The dried gels were obtained by drying at 70 °C until they reached constant weight.

$$\text{Water absorptivity } (\%) = \frac{W_s - W_d}{W_d} \times 100 \quad (2)$$

where W_s is the weight of the swollen gels and W_d is the dried gel weight

Gel Strength (Rupture Force and Elongation at Break)

The mechanical properties of the hydrogels were obtained by determining gel strength (eq. 3), which is the peak force (F_B) in grams multiplied by the distance (ΔD) to the rupture measured in centimeters. A test was conducted with a TA-XT2 texture analyzer at room temperature.

$$\text{Gel strength} = F_B \times \Delta D \quad (3)$$

Healing Test of the Hydrogels for Wound Dressing

Rats (200 g) were anesthetized with diethyl ether and kentamine, and then the dorsal fur was removed with electric clippers. The skin was cleansed with H_2O_2. After two wounds of 1-cm diameter in the dorsum were prepared the skin of rats was disinfected with povidone iodine topical solution. One wound was covered with one of the prepared hydrogels (1.5 × 1.5 × 0.3 cm) and the other was covered with a commercially used vaseline gauze as a control. Then, both hydrogels and gauze were covered with Tegaderm (3M). PVA/PVP–chitosan hydrogels made by the two-step method of freezing and thawing and ^{60}Co gamma-ray irradiation were used for the healing test of rats. Each PVA/PVP–chitosan ratio was in the range 9:1–7:3 the solid concentration of the total PVA/PVP–chitosan solution was 15 wt %, and the composition of PVA/PVP was 60:40. Both hydrogels and gauez were replaced with new ones every 3 days.

Healing was evaluated as the percentage of the healed area from the original wound area. The healing test was repeated five times for each case, and then the healing effect was evaluated. At a certain postoperative day macroscopic observation of wound status was made. This observation was repeated daily for 14 days. After all experiments, all the rats were sacrificed with an overdose of kentamine.

RESULTS AND DISCUSSION

Up to and including the late 1950s, it was generally accepted that to prevent bacterial infection, a wound should be kept as dry as possible. However, a variety of studies have questioned this philosophy and found that wounds that were kept moist actually healed more rapidly than those that were left exposed to the air or covered with traditional dry dressings. In a review of the properties of occlusive dressings, Winter[9] reported that dressings that keep wounds moist could increase the rate of epidermal resurfacing by some 40%.

Hydrogels are complex lattices in which the dispersion medium is trapped rather like water in a molecular sponge. Available hydrogels are typically insoluble polymers with hydrophilic sites, which interact with aqueous solutions, absorbing and retaining significant volumes of fluid.

A wider range of polymers can be crosslinked by radiation than by any chemical method. The radiation crosslinking can be easily adjusted by controlling the radiation dose and is reproducible. The finished product contains no residuals of substances required to initiate the chemical crosslinking, which can restrict the application possibilities or can increase the failure rate.

The gelation behavior of the hydrogels that were synthesized by repeated freezing and thaw-

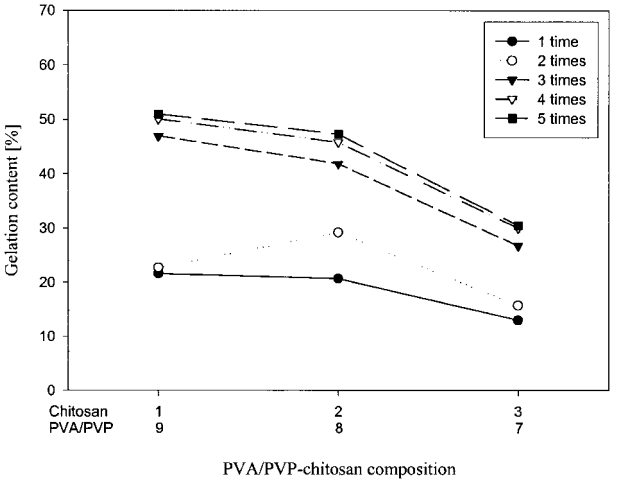

Figure 1 Gelation content of PVA/PVP–chitosan hydrogels versus PVA/PVP–chitosan composition after repeated freezing and thawing without irradiation doses (PVA:PVP = 6:4; solid concentration, 15 wt %).

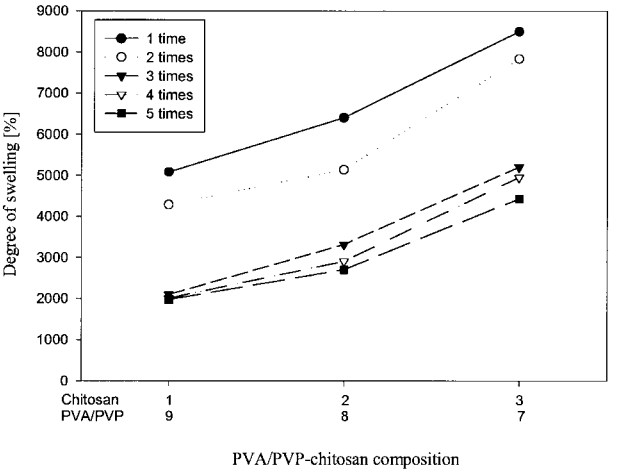

Figure 2 Degree of swelling of PVA/PVP–chitosan hydrogels versus PVA/PVP–chitosan composition after repeated freezing and thawing without irradiation doses (PVA:PVP = 6:4; solid concentration, 15 wt %).

ing are shown in Figure 1. The PVA/PVP–chitosan ratio was in the range 9:1–7:3, and the solid concentration of the total PVA/PVP/chitosan solution was 15 wt %. The composition of PVA/PVP was fixed as 60:40. Gel content increased as chitosan amount in PVA/PVP–chitosan decreased and freezing and thawing was repeated. Freezing and thawing caused the gel content to increase greatly up to four cycles of freezing and thawing; after that, the increase levelled off. It is well known that this procedure of PVA[10] results in the formation of crystallites that serve as physical crosslinks to render the material insoluble in water. Gel content (%) in this experiment was continuously decreased as the amount of chitosan in PVA/PVP–chitosan increased because chitosan is not crosslinked by freezing and thawing. The swelling behavior of the same hydrogels as shown in Figure 1 is shown in Figure 2. The swelling percent was inversely proportional to the gel percent because crosslinking density increases with increasing gelation.

A mixture of PVA/PVP–chitosan was exposed to gamma irradiation doses of 25, 35, 50, 60 and 70 kGy to evaluate the effect of irradiation dose on the gel content (%) and swelling degree of hydrogels (Figures 3 and 4). PVA/PVP–chitosan composition and irradiation dose had a great influence on swelling rather than gel content. The difference between the radiation and freezing and thawing processes used to obtain hydrogels is that the gel content is influenced by PVA/PVP–chitosan composition in the case of the freezing and thawing process, but not greatly influenced by PVA/PVP–chitosan composition in the case of irradiation. This result can be explained by the fact that crosslinking network can be formed between PVA/PVP and chitosan molecules when the irradiation process is used. The gels result from the coupling of the polymer radicals that were directly and indirectly produced from PVA, PVP, or chitosan by gamma rays. The indirect formation of polymer radicals is mainly due to the H· and ·OH radicals arising from water molecules, both of which attract hydrogen atoms to form the

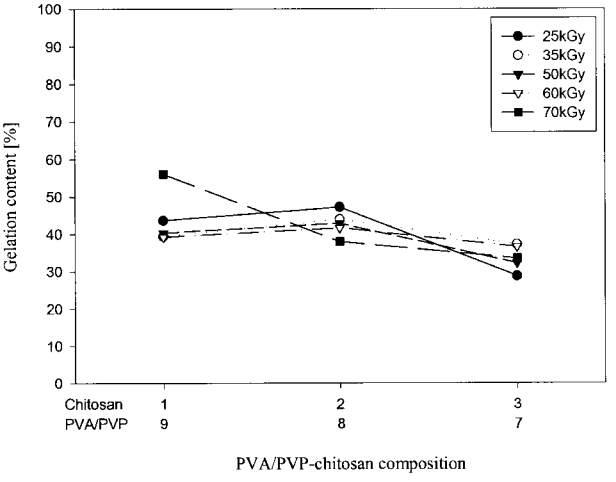

Figure 3 Gelation content of PVA/PVP–chitosan hydrogels versus PVA/PVP–chitosan composition at different irradiation doses (PVA:PVP = 6:4; solid concentration, 15 wt %).

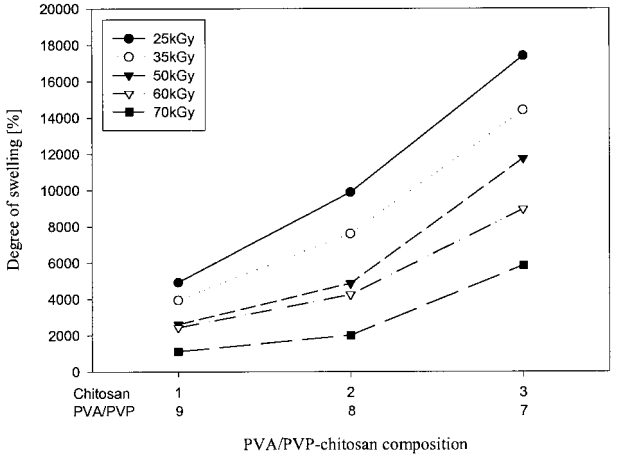

Figure 4 Degree of swelling of PVA/PVP–chitosan hydrogels versus PVA/PVP–chitosan composition at different irradiation doses (PVA:PVP = 6:4; solid concentration, 15 wt %).

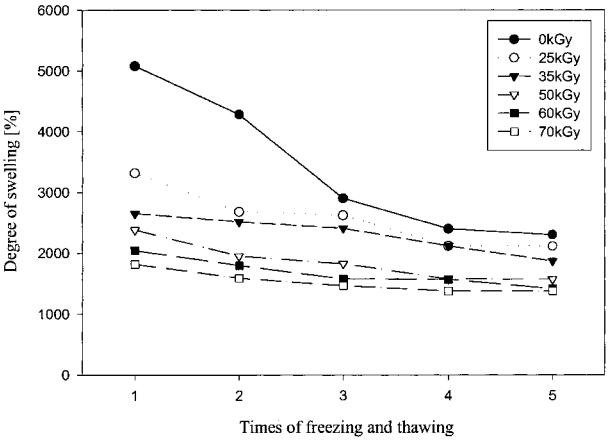

Figure 6 Degree of swelling of PVA/PVP–chitosan hydrogels versus irradiation dose after repeated of freezing and thawing (chitosan–PVA/PVP = 1:9; PVA:PVP = 6:4; solid concentration, 15 wt %).

polymer radicals. There are two types of crosslinking processes; they are, intermolecular and intramolecular crosslinking. The former allows the increase of the MW of crosslinked polymer via the coupling of two or more polymer radicals. The latter does not alter MW, but affects the quantities relating to a polymer chain dimension because the radical coupling reaction should take place within the same polymer chain.[11]

The gelation content and the degree of swelling were examined to evaluate the hydrogels for wound dressing (Figures 5 and 6). Gel percent of hydrogels was higher when two steps of freezing and thawing and irradiation were used than just freezing and thawing. Irradiation of >25 kGy did not have a great effect on gel percent of hydrogels. The swelling degree was greatly influenced by the irradiation dose (Figure 6).

Hydrogels from a mixture of chitosan and PVA/PVP were made by freezing and thawing, ^{60}Co gamma-ray irradiation, or two steps of freezing and thawing and ^{60}Co gamma-ray irradiation. The gel percents of hydrogels are shown in Figure 7. Gel content increased as chitosan concentration in PVA/PVP–chitosan decreased, and when two steps of freezing and thawing and irradiation

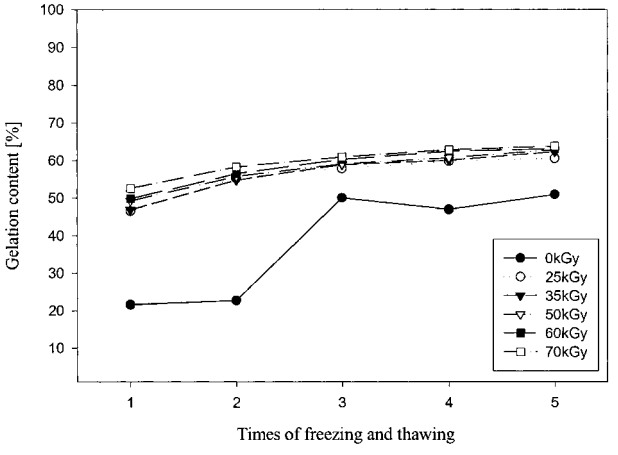

Figure 5 Gelation content of PVA/PVP–chitosan hydrogels versus freezing and thawing at different irradiation doses (chitosan–PVA/PVP = 1:9, PVA:PVP = 6:4; solid concentration, 15 wt %).

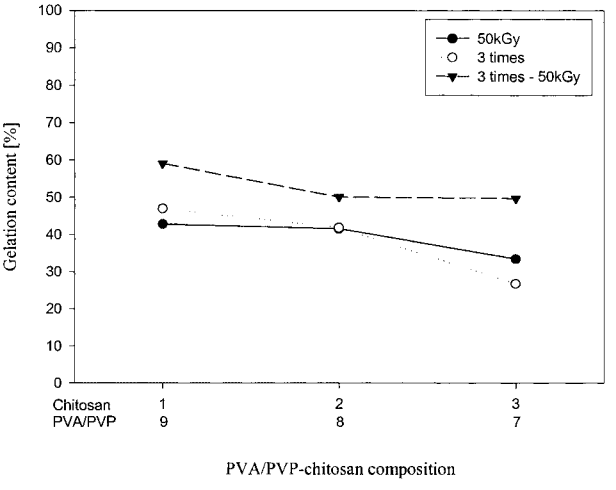

Figure 7 Gelation content of PVA/PVP–chitosan hydrogels versus PVA/PVP–chitosan composition (PVA:PVP = 6:4; solid concentration, 15 wt %).

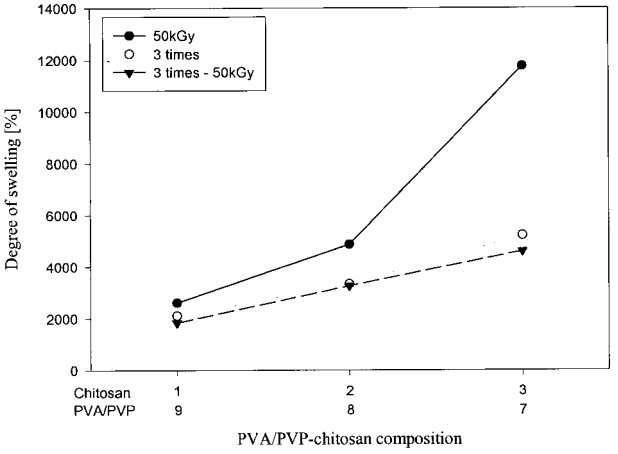

Figure 8 Degree of swelling of PVA/PVP–chitosan hydrogels versus PVA/PVP–chitosan composition (PVA:PVP = 6:4; solid concentration, 15 wt %).

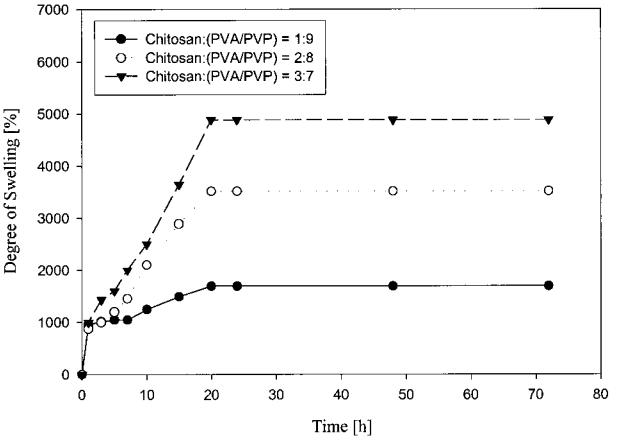

Figure 10 Degree of swelling of PVA/PVP–chitosan hydrogels versus time at 50 kGy after 3 times of freezing and thawing (PVA:PVP = 6:4; solid concentration, 15 wt %).

were used. The swelling percents of hydrogels from Figure 7 are shown in Figure 8. Swelling degree of hydrogels obtained from only the irradiation process was much higher than those obtained from freezing and thawing or the two-step method of freezing and thawing and irradiation. The swelling degree versus immersing time data for the same samples in Figure 7 are shown in Figure 9. The swelling percent increased rapidly up to 1 h, continued to rise steadily up to 20 h, and then levelled off. Miranda et al.[11] reported that swelling of crosslinked PVP occurs at three steps. The first stage at the very beginning includes a very fast absorption due to surface hydrophilicity, and capillarity is observed. The second stage involves the stepwise slowdown of the absorption to almost constant values typical of diffusion mechanism. In the last step, a minor increase in water content based on a very slow network relaxation is detected.

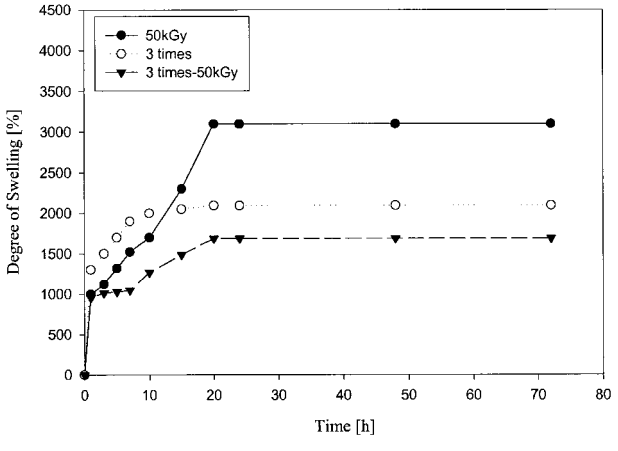

Figure 9 Degree of swelling of PVA/PVP–chitosan hydrogels versus time (chitosan–(PVA/PVP) = 1:9; PVA:PVP = 6:4; solid concentration, 15 wt %).

The swelling behavior of the hydrogels synthesized by the two steps of repeated freezing and thawing and irradiation is shown in Figure 10. The PVA/PVP–chitosan ratio was in the range 9:1–7:3, and the solid concentration of the total PVA/PVP–chitosan solution was 15 wt %. The composition of PVA/PVP was fixed at 60:40. Swelling degree increased as chitosan concentration in PVA/PVP–chitosan increased.

The respective gel strengths of the hydrogels are shown in Figure 11. The gel strength of hydrogels was much higher when two steps of freezing and thawing and irradiation were used than when only freezing and thawing was utilized. The relationship between "the force at break" and "distance at rupture" are shown in Figure 12. Ductile fracture occurred as chitosan concentration in PVA/PVP–chitosan increased. These characteristics can be attributable to a decrease in crosslinking density as the chitosan amount in PVA/PVP–chitosan increased. The relationship between "the force at break" and "distance at rupture" in the irradiation range 25–70 kGy is shown in Figure 13. Gel strength increased in proportion to the irradiation dose.

PVA/PVP–chitosan hydrogels made by the two-step method of freezing and thawing and ^{60}Co gamma-ray irradiation were used for the healing test with rats. The PVA/PVP–chitosan

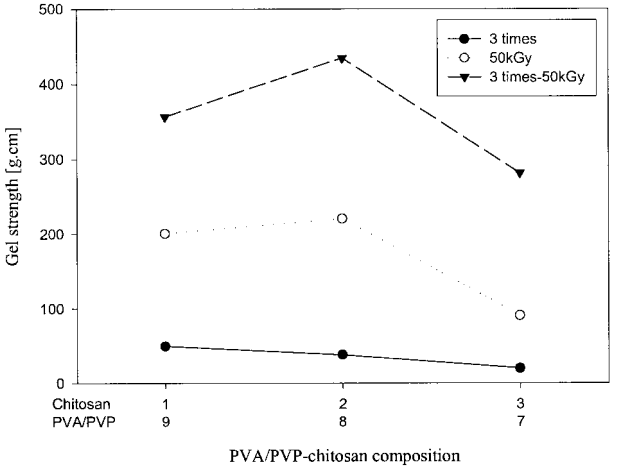

Figure 11 Gel strength of PVA/PVP–chitosan hydrogels versus PVA/PVP–chitosan composition (PVA:PVP = 6:4; solid concentration, 15 wt %).

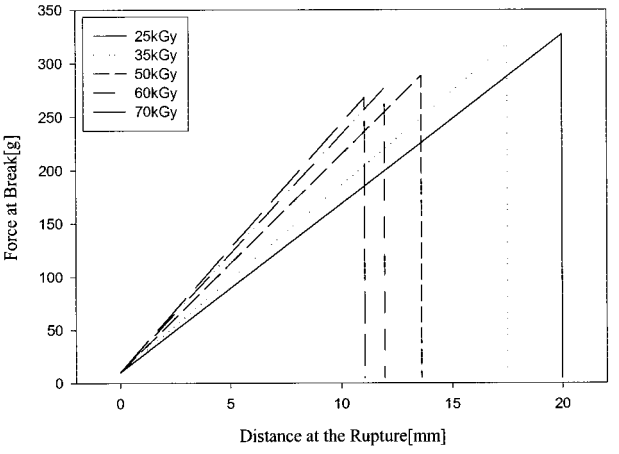

Figure 13 Gel strength of PVA/PVP–chitosan hydrogels versus irradiation dose after 1 time of freezing and thawing (chitosan–(PVA/PVP) = 1:9; PVA:PVP = 6:4; solid concentration, 15 wt %).

ratio was in the range of 9:1, the solid concentration of the total PVA/PVP–chitosan solution was 15 wt %, and the composition of PVA/PVP was 60:40. Wounds of 1-cm diameter that formed on the back skin of rat were covered with the hydrogel samples 0.5 × 1.5 × 0.3 cm) and a vaseline gauze, or a vaseline gauze without dressing. At a designated postoperative day, a macroscopic observation of the wound status was made. The vaseline gauze dried quickly and stuck to the wound of the rat. The PVA/PVP–chitosan hydrogel dressing stopped the bleeding from the wound and had a better curing effect than the vaseline gauze. The observation was carried out for a total of 14 days.

CONCLUSIONS

In this work, attempts were made to prepare hydrogels for wound dressing which consisted of PVA, PVP, and chitosan. The hydrogels were made from a mixture of chitosan and PVA/PVP by freezing and thawing, gamma-ray irradiation, or

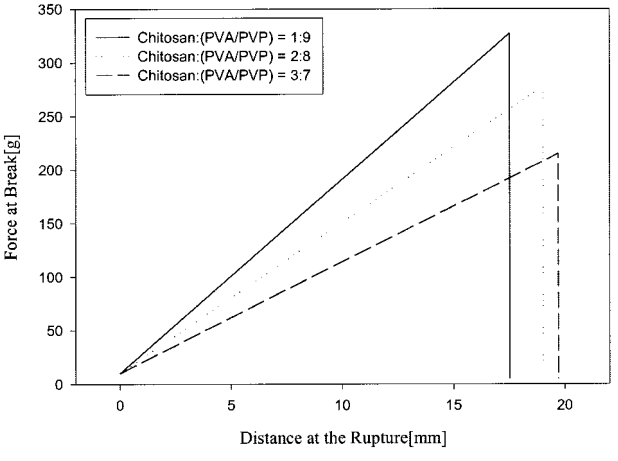

Figure 12 Gel strength of PVA/PVP–chitosan hydrogels versus PVA/PVP–chitosan composition at 35 kGy after 1 time of freezing and thawing (PVA:PVP = 6:4; solid concentration, 15 wt %).

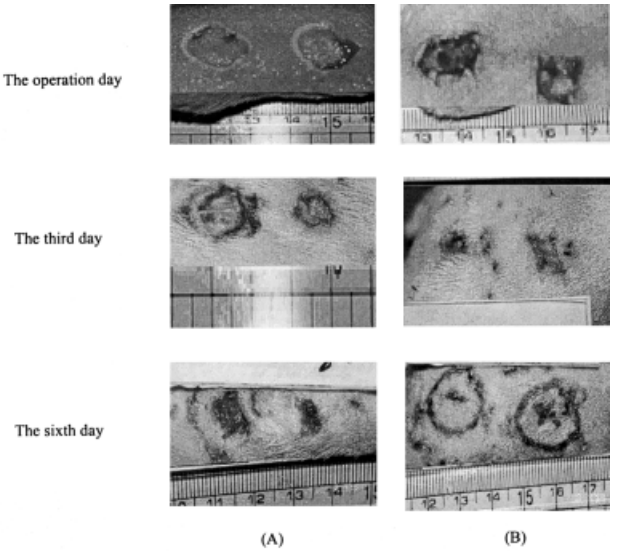

Figure 14 Healing process of wound using (A) no dressing(left)/gauze(right), (B) PVA/PVP–chitosan hydrogel (left)/gauze (right).

a two-step method of freezing and thawing and gamma-ray irradiation. The physical properties of hydrogels, such as gelation and gel strength, were higher when two steps of freezing and thawing and irradiation were used than only freezing and thawing was utilized. PVA/PVP–chitosan composition and irradiation dose had a greater influence on swelling than gel content. Irradiation of >25 kGy did not have a great effect on gel percent of hydrogels. Swelling percent was greatly increased as the composition of chitosan in PVA/PVP–chitosan increased.

Wounds of 1-cm diameter that formed on the back skin of the rat were covered with hydrogel samples (1.5 × 1.5 × 0.3 cm) and vaseline gauze. At the designated postoperative day, macroscopic observation of wound status was made. The vaseline gauze dried quickly and stuck to the wound of rat. The PVA/PVP–chitosan hydrogel dressing stopped the bleeding from the wound and had the better curing effect than vaseline gauze.

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