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Evaluation of the ability of xanthan gum/gellan gum/hyaluronan hydrogel membranes to prevent the adhesion of postrepaired tendons

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ABSTRACT

After tendon-repair surgery, adhesion between the surgical tendon and the synovial sheath is often presented resulting in poor functional repair of the tendon. This may be prevented using a commercially available mechanical barrier implant, Seprafilm, which is composed of hyaluronan (HA) and carboxymethyl cellulose hydrogels. In a rat model, prepared membranes of various compositions of gellan gum (GG), xanthan gum (XG) and HA as well as Seprafilm were wrapped around repaired tendons and the adhesion of the tendons was examined grossly and histologically after 3 weeks of healing. Certain formulations of the XG/GG/HA hydrogel membranes reduced tendon adhesion with equal efficacy but without reducing the tendon strength compared to Seprafilm. The designed membranes swelled rapidly and blanketed onto the tendon tissue more readily and closely than Seprafilm. Also they degraded slowly, which allowed the membranes to function as barriers for extended periods.

1. Introduction

The tendon adhesion that occurs after tendon-repair surgery is a physiological phenomenon that results in both the inflammatory response triggered at the site of surgery and the loss of physical separation between the repaired tendon and the surrounding tissue (Potenza, 1962). Postsurgical adhesion in the tendon interferes with the normal gliding function of tendons and nerves and causes pain and greatly restricts motion; if these effects are severe and prolonged, ischaemia and nerve injury can develop. Tendon healing is a slow process that lasts for months, during which the continuity and strength of the tendon fibre are re-established (Hagberg, Tengblad, & Gerdin, 1991). Moreover, tendon healing frequently results in the formation of scars that restrict the full range of motion of tendons, and the repaired tendon fails to recover its original strength.

Commercial medical products that exhibit antiadhesive properties are currently available; in these products, films, gels, membranes, or fluids are used. One of the products available is Dynavics, which is a clear and absorbable gel designed for coating tissues that are injured as a result of tendon or peripheral-nerve surgery. A Seprafilm adhesion barrier (Genzyme, Cambridge, MA, USA) is a bioresorbable membrane composed of chemically modified sodium hyaluronate (HA) and carboxymethyl cellulose (CMC), which is rapidly degraded and cleared after placement in the body. In clinical practice, Seprafilm has been observed to hydrate to form a lubricious gel coating within 24–48 h when applied on the surface of tissues. The barrier is resorbed from the site of application within 7 days and, thus, a second operation for removing the barrier is not required (Genzyme). The safety and efficacy of Seprafilm have been demonstrated, and the barrier has been used for preventing adhesion after abdominopelvic surgery (Altuntas, Tarhan, & Delibas, 2002; Vrijland et al., 2002; Becker et al., 1996; Tsapanos, Stathopoylou, Papathanassopoulou, & Taingounis, 2002; Beck et al., 2003) and cardiovascular surgery (Ballore, Orru, & Nicolini, 2000; Kudo et al., 2004). In a preclinical study, Seprafilm was used to prevent adhesion after tenolysis of the flexor digitorum tendon in chickens (Karakurum, Buyukbebeci, Kalender, & Gulec, 2003). The tendons covered with Seprafilm were observed to exhibit a substantially improved gliding excursion profile and a diminished incidence of adhesion when compared with controls. However, the use of these products is limited by shortcomings such as their high cost and rapid degradation, their nondeformability, and the difficultly involved in wrapping the barriers around a tendon, and

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the inability of the barriers to function in certain circumstances, such as when bleeding or infection occurs and after anastomotic surgery. These shortcomings adversely affect patient management and intervention after surgery and increase healthcare costs.

Xanthan gum (XG), a polysaccharide secreted by the bacterium *Xanthomonas campestris*, belongs to a family of substances known as hydrocolloids. XG can form a gel and bind many times its weight in water, which makes XG a valuable food additive and rheology modifier in cosmetic products. One particularly noteworthy property of XG is its ability to substantially increase the viscosity of a liquid when added at 0.5 wt%. XG is extremely stable over a wide temperature and pH range. XG is also used in numerous nonfood products and applications because it is nontoxic and exhibits high thickening capacity (Sharma & Maffulli, 2005; Chang, Haung, Yang, Kuo & Lee, 2012).

Gellan gum (GA) is a linear, anionic polysaccharide secreted by *Pseudomonas elodea*. GA is also a food additive that functions as a stabiliser, thickening agent, and gelling agent in a wide variety of foods. Recently, GA has been investigated for its use as a drug-delivery agent, cell carrier, guided bone-regeneration material, and wound-dressing material in biomedical engineering because of the biocompatibility and low cytotoxicity of GA.

Following all surgical incisions, adhesions develop as a part of the normal healing process that occurs in response to tissue trauma. Adhesions occur within the first 3–5 days after surgery and are composed of sticky, fibrous scar tissues. If the development of adhesions can be interrupted, several potential complications associated with surgery can be avoided. In this study, for use as antiadhesive membranes, we prepared XG/GA/HA (XGH) hydrogel membranes featuring various formulations of XA, GA, and HA. We used a rat model to evaluate the ability of these membranes to reduce adhesions in repaired Achilles tendons and to compare this with the efficacy of Seprafilm, an FDA-approved antiadhesive barrier that contains chemically modified HA.

2. Material and methods

2.1. Fabrication of XGH hydrogel membranes

Four membranes featuring distinct weight ratios of HA, XG, and GG were prepared and their ability to prevent postsurgical tendon adhesion was evaluated (Table 1). XG, GG, and HA were dissolved in 10 mL of deionised water and heated to 85–90 °C to generate a transplant solution. The solution was then poured into a glass dish and evaporated in an oven at 37 °C for 24 h to obtain a dry membrane, which was crosslinked using a solution of 15 mM 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide/N-hydroxysuccinimide (EDC/NHS); the crosslinking was performed for 6 h at room temperature, and the crosslinked membranes prepared using distinct formulations (denoted as A, B, C, and D in Table 1) were washed with 95% ethanol three times to remove any residual unreacted EDC/NHS and then dried at room temperature.

Table 1
Various compositions and weight ratios (%) of the XGH hydrogel membranes in different formulation's groups.

Formulation content (100%)	HA	GG	XG
A	33.3	33.3	33.3
B	38.4	30.8	30.8
C	42.8	28.6	28.6
D	40	26.7	33.3

HA: hyaluronon; GG: Gellan Gum; XG: Xanthan Gum

2.2. Characterisation of XGH membranes

2.2.1. Water-content measurement

The water content (WC) of the XGH membranes was determined by swelling the membranes in a pH 7.4 phosphate-buffered solution (PBS) at room temperature. After the membranes were equilibrated with PBS, the wet membranes were blotted using filter paper to remove the water adherent to the membrane surface. The WC of the membranes was calculated as

$$\mathrm{WC}(\%) = (W_w - W_d)/W_d \times 100\%$$

where *W*w and *W*d are the weights of the wet and dry membrane, respectively. The experiment was conducted three times and the WC mean and standard deviation were calculated.

2.2.2. Mechanical-strength measurement

The Seprafilm sample swelled considerably in solution and, thus, could not be mounted firmly onto the load-cell used in measurements; therefore, we conducted the mechanical-strength test under dry conditions and compared the strengths of Seprafilm and the other membrane samples. The membranes were cut into pieces (1 × 6 cm) and the tensile strengths of the membranes were measured up to the point at which they broke. The mechanical parameters of the membranes were calculated and recorded automatically by using a material-testing system (MTS; Eden Prairie, USA) at a crosshead speed of 5 mm/min.

2.2.3. In vitro degradation test

The *in vitro* degradation of the prepared membranes was tested by incubating the membranes in 10 mL of PBS (pH 7.4) in a vial and placing the vial on a shaker set at 40 rpm and 37 °C. At predetermined times, the membrane was removed from the incubation medium, washed with distilled water, dried, and weighed, after which another 10 mL of fresh PBS was added into the vial and the degradation test was continued. The degradation profiles were obtained as the cumulative weight losses of the membranes. The surface microstructure of the membranes was examined using a scanning electron microscope (SEM); all the samples were dried and sputter-coated with gold before being examined under the SEM (JEOL, JSM-5300, Japan).

2.3. Cell-viability assay

The cytocompatibility of the prepared membranes was measured using the MTT assay. The membranes were sterilised by applying ^{60}Co gamma irradiation at a dose of 15 kGy and then were placed in 24-well bacterial-grade dishes, with each well containing 5×10^4 L929 fibroblasts; 2 mL of culture medium was added to each well and the samples were incubated at 37 °C in a 5% CO_2 atmosphere for 24 h. After incubation, 20 μL of the MTT solution (5 mg/mL) was added to each well and the cells were incubated for an additional 3 h. The formazan precipitate formed was dissolved in 200 μL of DMSO, and the solution was mixed vigorously to dissolve the dye. The 570-nm absorbance of the sample in each well was measured using a multiplate reader. To generate a standard curve, the spectrophotometer (Multiskan Co., Thermo Scientific, USA) was first calibrated to zero absorbance by using a cell-free culture medium. All the experiments were repeated three times, and the absorbance values measured in the MTT assay were converted to cell numbers/well.

2.4. Animal studies

In this study, we used eighteen 8-week-old male Sprague-Dawley rats that weighed 250–300 g. The rats were anaesthetised

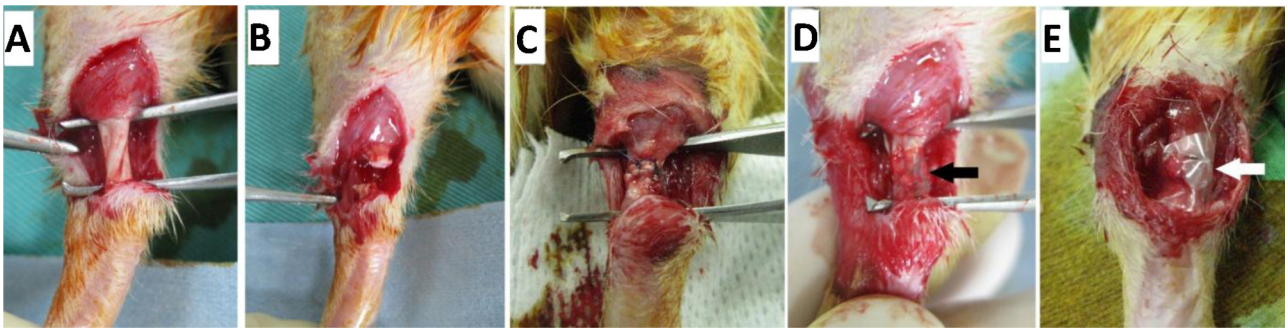

Fig. 1. Animal model setting (A) Sharp dissection was used to expose the Achilles tendon. (B) Achilles tendon was transected at mid-point. (C) The tendon was repaired with 5-0 Prolene sutures (D) Post-repaired tendon was wrapped with XGH hydrogel membrane, which presented fit smoothly on the tendon (indicated by black arrow). (E) Seprafilm was irregularly deformable for fitting on the tendon (indicated by white arrow).

using transabdominal injections of Zoletil 50 (a 1:1 mixture of Tiletamine and Zolezepam) at a dose of 0.2 mL/200 g bodyweight. The hind leg was shaved and then sterilised by using 70% alcohol, betadine, and 70% alcohol sequentially. A midline incision was made on the posterior side of the ankle in each hind leg. By performing a sharp dissection, the Achilles tendon was exposed and transected at its midpoint. The transected tendon was repaired using a modified Kessler technique (Kim et al., 2010) in which we used 5-0 Prolene sutures (Ethicon, Somerville, NJ, USA), and then the tendon was wrapped with Seprafilm or XGH hydrogel membranes prepared using Formulations A, B, C, or D (Fig. 1). The 36 hind legs of the 18 rats were assigned randomly to six groups containing six legs each: the control group, Seprafilm group, and Groups A, B, C, and D. In the control group, the transected tendon was not wrapped with any membrane. After completing the surgical procedure, the skin was closed using 4-0 monofilament nylon sutures (Ethicon) and the hind limb was wrapped in petroleum gauze and immobilised using a casting tape. The animals were then returned to their cages and allowed to heal for 3 weeks, during which they were checked daily for signs of appetite change, wound infection, and swelling of the legs. After 3 weeks, the animals were sacrificed by overdosing them with isoflurane (10%) and then gross evaluation, histological assessment, and biomechanical-strength tests were performed on the tendons. All procedures and the handling of the animals were in accordance with the Guide for Animal Use Protocol published by the Institutional Animal Care and Use Committee of I-Shou University (IACUC-ISU-101013).

2.4.1. Gross evaluation

To perform gross evaluation, three legs in each group were chosen randomly ($N = 3$). After sacrificing the animals, a midline incision was made in the hind leg to expose the repaired Achilles tendon. The gross severity of the adhesion around the repaired tendon was evaluated using an adhesion-scoring system (Liu et al.,2013; Ishiyama et al., 2010) that contained five grades: Grade 1, no marked adhesion; Grade 2, filmy adhesions that could be readily separated using blunt dissection; Grade 3, $\leq$50% of the adhesion areas could be separated using only sharp dissection; Grade 4, 51%–97.5% of the adhesion areas could be separated using sharp dissection; and Grade 5, >97.5% of the adhesion areas could be separated using sharp dissection. All gross evaluations were performed by an investigator who was blinded to the groups.

2.4.2. Histological evaluation

For histological examinations of repaired tendons, the heel tendon site of the other three legs in each group ($N = 3$) were harvested from the tendon insertion of calcaneal bone to parts of the gastrocnemius and soleus muscle complex. The specimens were immersed in 10% buffered formalin for 24 h, dehydrated using an ascending graded series of ethanol solutions, and then embedded in paraffin wax. The specimens were sectioned sagittally and stained with Masson trichrome for use in histological examinations, in which the adhesions were assessed based on four grades: Grade 1, no adhesions; Grade 2, mild adhesion (<33% adhesion area on the tendon surface); Grade 3, moderate adhesion (34%–66% adhesion area); and Grade 4, severe adhesion (>66% adhesion area) (Liu et al., 2013). Tendon healing was also evaluated in the histological examination and was defined using the following grades: Grade 1, excellent (favourable tendon continuity and smooth epitenon surface); Grade 2, good (intratendinous collagen bundles exhibiting good repair, but epitenon interrupted by adhesions); Grade 3, fair (irregularly arranged and partly disrupted intratendinous collagen bundles); and Grade 4, poor (failed healing or overgrowth of granulation tissue) (Ishiyama et al., 2010).

2.5. Biomechanical evaluation

To measure the breaking strength of the repaired tendons, the tendons after gross evaluation in each group ($N = 3$) were dissected and harvested together with the calcaneal bone and parts of the gastrocnemius- and soleus-muscle complex. Both ends of the specimens were fixed using clamps, and the mechanical strength of the tendons was measured up to the point at which the tendons broke. The mechanical parameters of the tendons were calculated and recorded automatically by using an MTS (QTest/10, MN, USA) at a crosshead speed of 6 mm/min.

2.6. Statistical analysis

Data were presented as mean $\pm$ standard deviation (SD). One-way analysis of variances was used to analyse biomechanical results of repaired tendons, and RT-PCR results of experimental groups compared with control group. Two-way analysis of variance was used to analyse water content of materials, degradation of membranes, and mechanical strengths of membranes across groups. Gross evaluation and histological assessment of tendon adhesion and healing were analysed using Wilcoxin signed rank test. All statistical analyses were performed with SPSS (Statistical Package for Social Science; version 17.0; SPSS, Chicago, IL, USA). A p value < 0.05 was considered significant.

3. Results and discussion

3.1. Basic properties of antiadhesion membranes

A key behaviour that antiadhesive membranes should exhibit is that they must reach steady hydration equilibrium within a few minutes. As shown in Fig. 2A, the water content of the

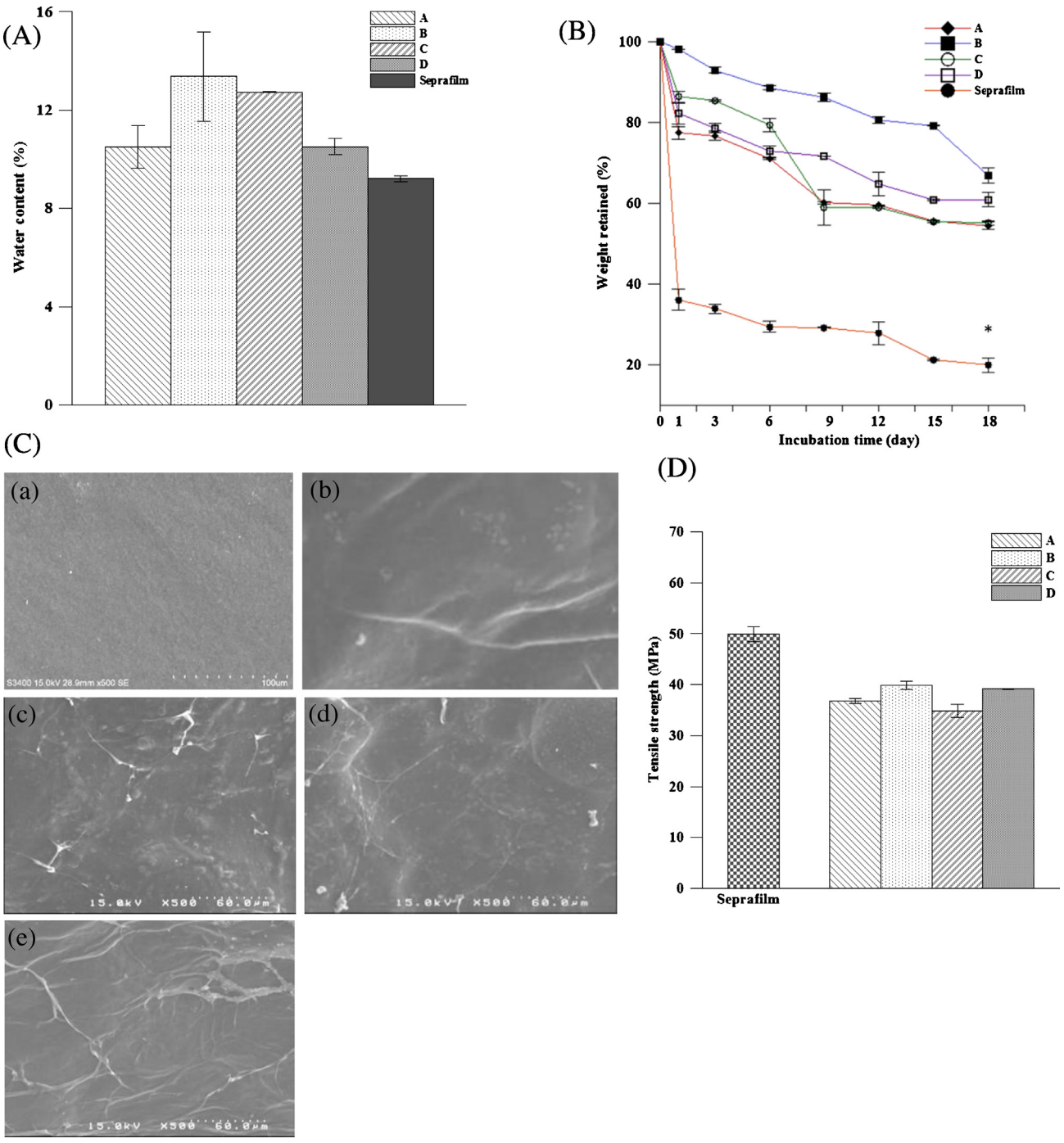

Fig. 2. Basic properties of anti-adhesion membranes. (A) Water content of XGH hydrogel membranes and Seprafilm in pH 7.4 solution in 60-min period of experiment. (B)The degradation profiles of anti-adhesion membranes in PBS solution, pH 7.4.(C) SEM images of the XGH hydrogel membrane-group C after 0–18 days of shaking in PBS solution (surface section). (a) 0-day, (b) 1-day, (c) 6-day (d) 12-day and (e) 18-day. (D) Mechanical strengths of the anti-adhesion membranes. The significant differences are based on comparisons with the XGH hydrogel membranes group, $^{*}p < 0.05$. The experiments were conducted in triplet ($N = 3$).

membranes increased by approximately 10% in a 60-min experimental period. The water content of XGH hydrogel membranes was higher than that of Seprafilm, although the difference was not statistically significant. Notably, the XGH hydrogel membranes reached an equilibrium state of swelling and became soft after immersion for 3 min in PBS, whereas Seprafilm required 60 min to reach a similar state as the XGH hydrogel membranes and this barrier could not be readily deformed for application on surgical sites (Fig. 1E). The rapid swelling exhibited by the XGH hydrogel membranes might facilitate their clinical manageability and use in surgical procedures; the membranes could be easily applied on surgical sites and affixed smoothly (Fig. 1D).

To be used in clinical applications, another requirement is that antiadhesive membranes must degrade within a suitable period. When membranes are used as antiadhesive barriers after abdominopelvic surgery, they must typically maintain a certain level of barrier function for approximately 1 week to ensure that the antiadhesive effect is exerted. However, the barrier membranes must degrade slowly while maintaining their function in tendon-related surgery, because tendons heal slowly. As shown in Fig. 2B,

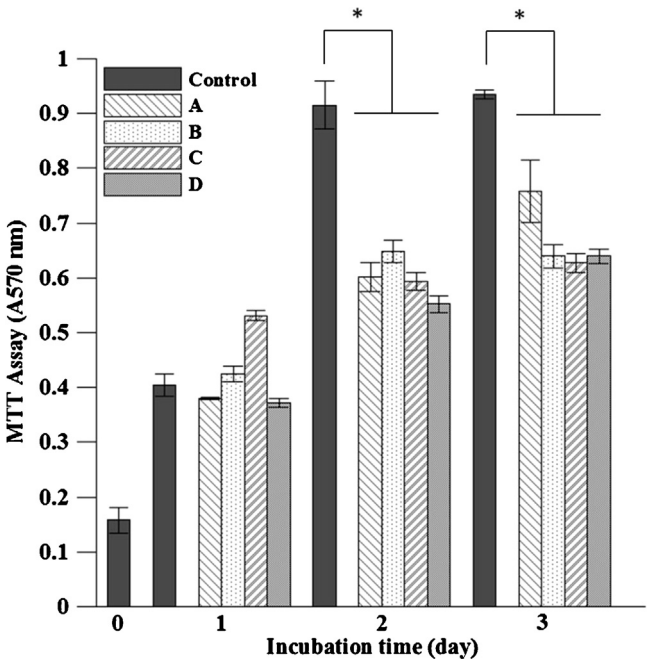

Fig. 3. Cell toxicity tests of the prepared XGH hydrogel membranes. Control group: tissue culture grade Petri dish. The significant differences are based on comparisons with the control group, $^{*}p < 0.05$.

all the XGH hydrogel membranes degraded slowly and gradually and lost 30–40% of their initial weight after an 18-day shaking test. However, Seprafilm degraded extremely rapidly on the first day and then lost approximately 80% of its initial weight after the 18-day shaking test. The material of an antiadhesive membrane must exhibit a degradation rate that matches the timeframe in which tissues are remodelled during regeneration. Although the resorption process can be facilitated or influenced by enzymatic digestion in clinical applications, our results suggest that the membranes prepared in this study can meet the degradation requirements placed on the antiadhesive membranes used for healing tendons. Fig. 2C presents SEM images of Membrane C as an example; the detailed composition is listed in Table 1. The images were obtained after the membrane was used in the 18-day shaking test. The XGH hydrogel membrane exhibited an irregular surface that maintained favourable integrity, albeit signs of degradation were also detected on the surface. However, Seprafilm did not retain an intact structure (data not shown), which could be attributed to its high HA content (nearly 66 wt%) and the rapid and substantial degradation of Seprafilm in aqueous solutions.

Because the swollen membranes could not be firmly mounted on the MTS load-cell, the mechanical-strength tests were conducted under dry conditions. As shown in Fig. 2D, the Young's modulus of the XGH hydrogel membranes and Seprafilm ranged from 35 to 50 MPa and these values exhibited no statistically significant differences. As observed from Fig. 3, the MTT assay values increased as culture continued from day 1 to day 3, on the XGH hydrogel membranes, which demonstrated the cells proliferated slowly and the results of the MTT assay indicated that all the prepared XGH hydrogel membranes were nontoxic to cells.

3.2. *In vivo gross observations*

Fig. 4 shows representative gross views of repaired rat Achilles tendons after 3 weeks of healing. Severe adhesions were characterised by the presence of massive, dense adhesive bundles between the tendon and the surrounding tissues in the control group (Fig. 4A). In the case of the tendons of the Seprafilm group and Groups A and B, filmy adhesion bundles were present that loosely bridged the tendons and the surrounding tissues (Fig. 4B–D). The adhesion area could be separated easily using blunt dissection. By contrast, more severe peritendinous adhesions were observed in Groups C and D than in the Seprafilm group (Fig. 4E–F); in Groups C and D, fibrous bundles bridging the tendons and the surrounding tissues were observed, which could be separated using only sharp dissection. Moreover, a few XGH hydrogel membrane residuals were observed in the area surrounding the repaired tendon in Groups B, C, and D. By contrast, the Seprafilm membrane was not detected and, thus, appeared to have degraded fully, which demonstrated that the XGH hydrogel membranes degraded more slowly *in vivo* than Seprafilm did. This result agrees with the results of the *in vitro* degradation test. The gross adhesion scores measured for Groups A and B and the Seprafilm group were significantly lower than those measured for the control group, but the differences between these experimental groups were not statistically significant (Fig. 5A).

3.3. *In vivo histological assessments*

Histological assessments of the tendons of the various groups are shown in Fig. 6. The repair site of the untreated tendon exhibited an irregular peritendinous surface and massive fibrous adhesion scars were present at the surrounding sites, which demonstrated adhesion between the tendon and neighbouring tissues (Fig. 6A & B). A mild fibrous scar was observed between the epidermis and the repaired tendon that had been treated using Seprafilm. However, numerous residual Seprafilm materials existed and occupied the epidermis and tendon which due to the fast degradation of Seprafilm membrane (Fig. 6C & D). Compared with corresponding sites in the control and Seprafilm groups, the repaired sites wrapped with XGH hydrogel membranes of A and B groups exhibited a clear gap between the tendon and epidermis, together with the presence of a few loose bundles of fibrous tissue and residual materials (Fig. 6E–H). These results can potentially be attributed to the slow degradation of XGH hydrogel membranes, which yields a superior antiadhesion outcome, compared with that produced by Seprafilm. In contrary, massive fibrous tissues and adhesions were observed between the epidermis and the repaired tendon that had been treated with XGH hydrogel membranes of C and D (Fig. 6I–L). In addition to exhibiting basic antiadhesive function, the material used in an antiadhesive membrane must not invade injured tissues or influence the normal healing of these tissues. In this study, we used a grading system to evaluate tendon adhesion and healing based on histological observations. As shown in Fig. 5B, the transected tendon wrapped with the XGH hydrogel membranes of Groups A and B and with Seprafilm exhibited a lower adhesion grading; thus, adhesion was prevented to a greater extent in the tendons in these groups than in the tendons of the control, C, and D groups. Moreover, the tendon-healing grades of Group A and the Seprafilm group (approximately 2) were lower than those of the other groups, which indicated the superior healing of the tendons in these groups compared with that in the other cases; however, the differences between the six groups were not statistically significant (Fig. 5C). Collectively, the results of gross examination and histological observations indicated that the XGH hydrogel membranes that were prepared using Formulations A and B exerted an effective antiadhesive effect on the repaired tendons but did not influence the healing of the injured tendons.

3.4. *Biomechanical analysis*

Biomechanical testing supported the histologic findings (Fig. 5C). Fig. 7 shows the biomechanical strengths of the tendons

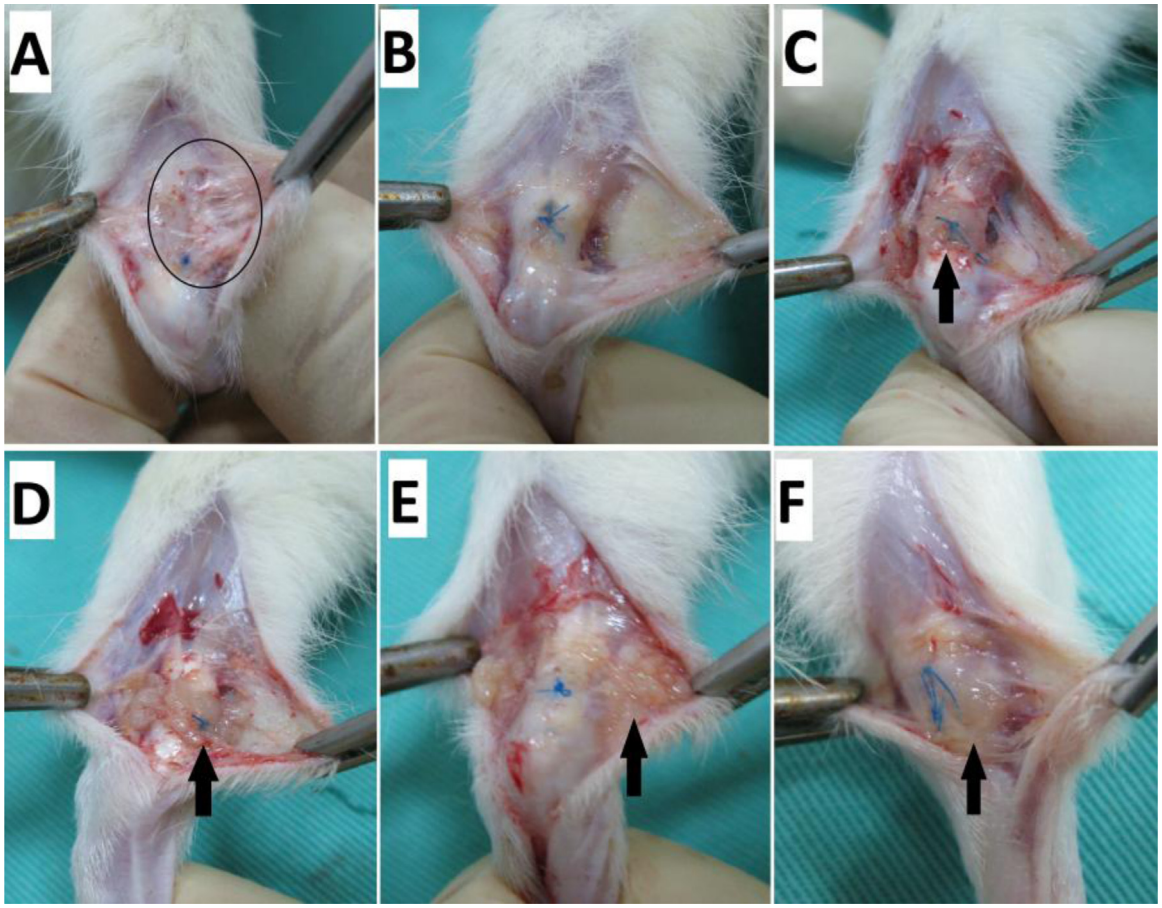

Fig. 4. Gross evaluation of repaired Achilles tendon after 3-week healing in a rat model. (A) control group; (B) Seprafilm group; (C) group A; (D) group B; (E) group C and (F) group D, respectively. Black circle indicated massive dense adhesive band. Black arrow indicated the residual membranes.

calculated based on the required breaking force. The breaking force of the repaired tendons that were wrapped with the membranes of Groups A and D was slightly lower than that of the tendons of the other groups. The tendons wrapped with Seprafilm required the highest breaking force. All the transected tendons that were wrapped with antiadhesive membranes healed and their breaking force recovered to the level exhibited by the normal tendon. No statistically significant differences were observed in the breaking force of the repaired tendons of the six groups.

The low cost and ease of production of XG and GG could make them extremely useful in a clinical setting. GG can remain at a repair site for several weeks, which is a major advantage of using this material when considering the tendon-healing timeframe. XG, another component of the XGH hydrogel membrane, is used to moderate the characteristics of hydrogel membranes. HA, which is a biodegradable mucopolysaccharide that is recognised to be one of the main components of synovial fluid, has been used previously to prevent peritendinous adhesion. However, unlike XG and GG, HA is rapidly degraded by hyaluronidase and disappears from the repair site within 72 h.

To evaluate whether these XGH hydrogel membranes can be used as antiadhesive materials, we compared them with a commercially available product, Seprafilm. Seprafilm is challenging to handle during certain surgeries, particularly when wrapping a tendon, because Seprafilm loses its integrity and strength during hydration, which was shown by our results in Fig. 1. Seprafilm

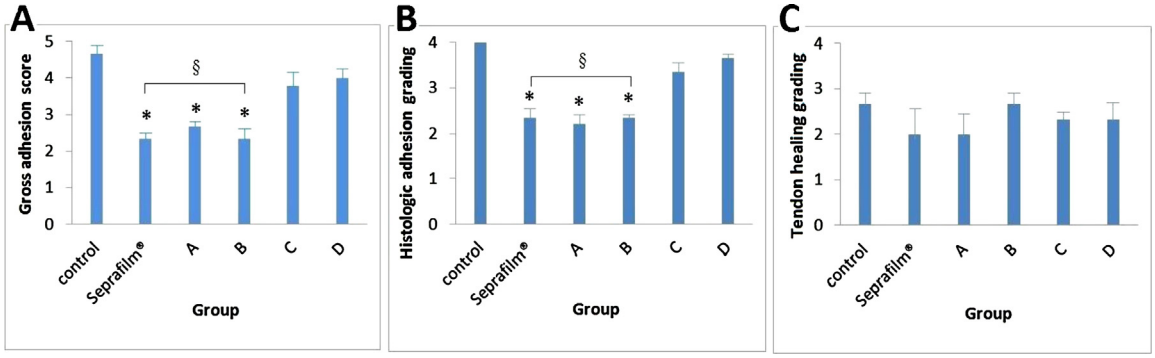

Fig. 5. Gross and histologic evaluation of groups. (A) Gross adhesion score. (B) Histologic adhesion grading. (C) Histologic tendon healing grading. $^{*}p < 0.05$ compared with control group, §: no statistically significant difference between groups.

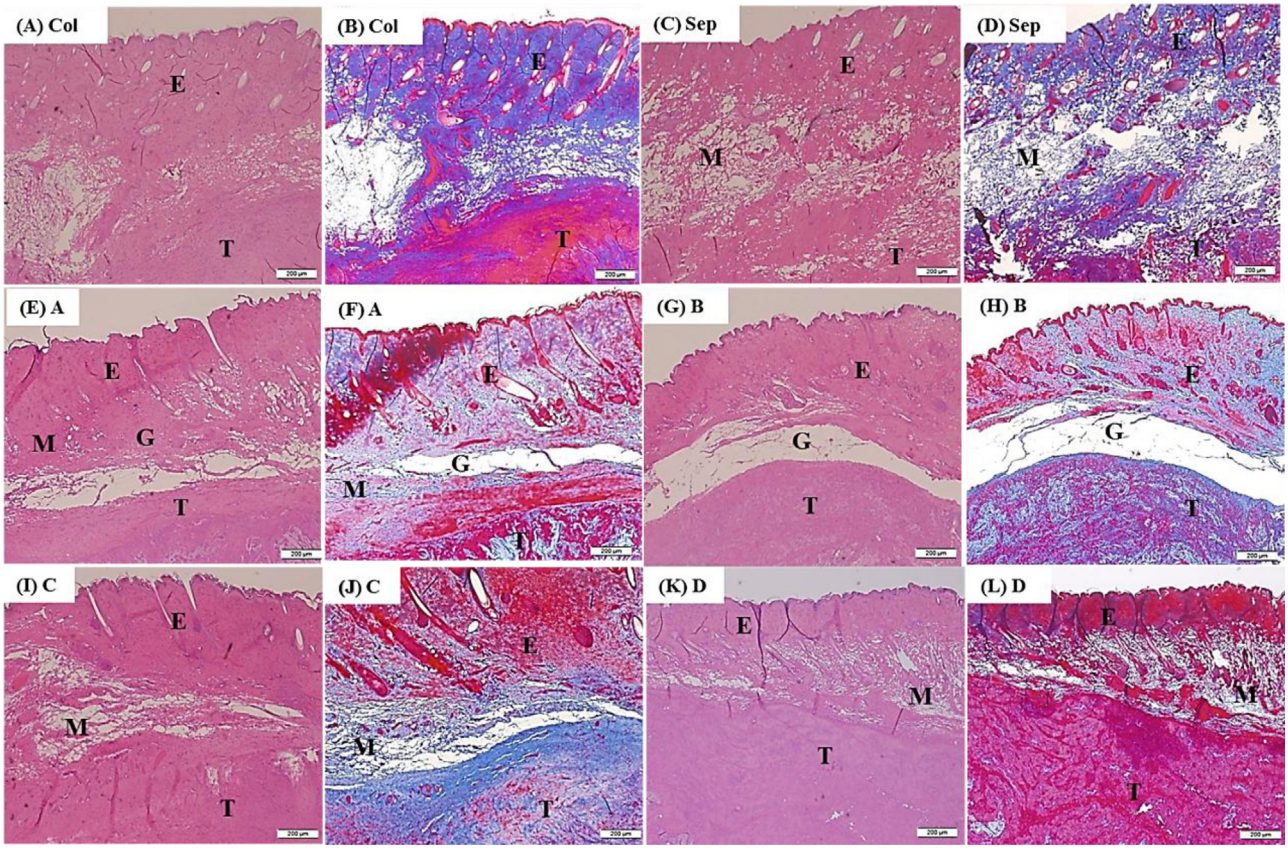

Fig. 6. H&E staining and Masson's trichrome staining of repaired tendon. (A, B) Control group: massive adhesion fibrous scar between epidermis and repaired tendon. (C, D) Seprafilm group: similar and massive fibrous scar was observed between the epidermis and the repaired tendon. (E–H) Group A and Group B: clear interface space and loose bundle of fibrous tissue within the space between of epidermis and tendon. Residual un-degraded material (denoted as M) could be found above the tendon. (I–L) Group C and Group D: more fibrosis scar and residual un-degraded materials were detected within the epidermis and tendon space. Some adhesions were detected within the interface.
E: epidermis; T: Achilles tendon area; M: residual material; Col: control group; Sep; seprafilm.

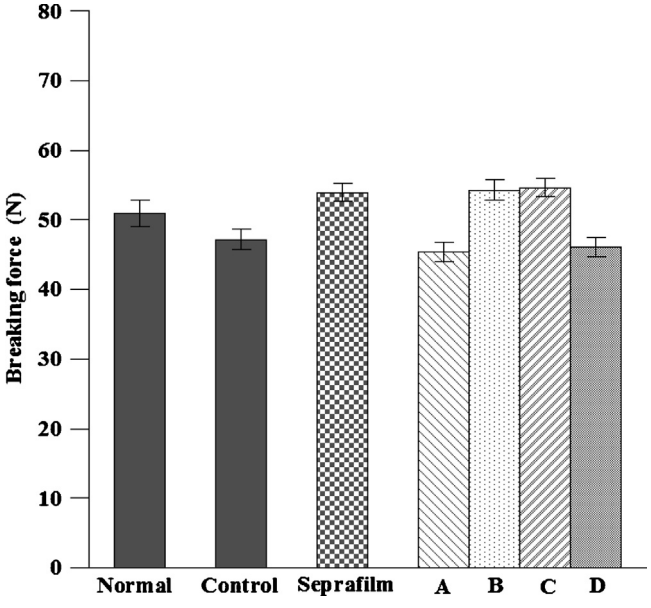

Fig. 7. Biomechanical strength was evaluated by determining the breaking force of the tendons. Data are expressed as mean ± SD for three tendons/group. Normal: without transection; control: with transection but without wrapping membranes. No statistical difference.

can form a lubricious gel in 24–48 h at the application site and can act as a physical barrier; however, the barrier degrades rapidly and lasts only for a period *in vivo* that is often too short to bridge the critical 5–7-day period required for adhesion-free healing to occur (Liu, Shu, & Prestwich, 2006). In this study, we determined that XGH hydrogel membranes degraded *in vivo* more slowly than did Seprafilm, and this property was contributed by the GG component of the XGH membranes. In animal studies, we observed several residues of XGH hydrogel membranes covering the repaired tendon after 3 weeks, especially in the cases in which GG was used at high weight ratios (Groups A and B). By contrast, almost no Seprafilm membrane was detected after the same experimental period. Although the antiadhesive effects exerted by the XGH hydrogel membranes did not differ in a statistically significant manner from the effect of Seprafilm in the rat model, XGH hydrogel membranes remained at the application site and prevented tendon adhesion for longer periods than did Seprafilm. Seprafilm is approved by the FDA for use in reducing postoperative intraabdominal and pelvic adhesions. In preventing the adhesion of peritoneum, the critical period is the initial 3–5 days after a surgical procedure and before the completion of remesothelisation (Diamond, Burns, Accomando, Mian, & Holmdahl, 2012). Seprafilm can remain at a target site for approximately 1 week, which is adequate for preventing postoperative peritoneal adhesion. However, the residence time of Seprafilm might be too short to permit the adhesion-free healing of tendons because, in humans, the critical period of adhesion formation during tendon healing is longer than that of adhesion formation during peritoneum healing. A prolonged

residence time of a physical barrier is likely to critically affect its ability to prevent adhesion formation after tendon-repair surgery in humans because tendons heal slowly. In certain clinical studies, Seprafilm was reported to be less effective in preventing adhesion after surgery compared with other antiadhesive products, the half-life of which *in vivo* was longer than that of Seprafilm (Trew, 2006; Liu et al., 2006).

4. Conclusion

Preventing peritendinous adhesion after tendon-repair surgeries remains a major clinical challenge. This study suggests that the use of XGH hydrogel membranes might help reduce the incidence of postoperative tendon adhesion, and concurrently enable tendon healing and preserve the mechanical strength of the healing tendon as effectively as the commercially available product Seprafilm. The XGH hydrogel membranes degrade more slowly than Seprafilm does and, thus, might function for a longer period than Seprafilm can as a barrier in preventing the adhesion of repaired tendons. The XGH hydrogel membranes swell rapidly, which can also facilitate their clinical application and manageability. Based on our results, we conclude that the XGH hydrogel membrane can potentially be used for reducing the formation of adhesions following the surgical repair of tendons. Compared with Seprafilm, the XGH hydrogel membranes prepared in this study are (i) less expensive and more elastic; (ii) easier to handle and they maintain their integrity more effectively after hydration; and (iii) degraded more slowly. All of these features combined indicate the possibility that in addition to Seprafilm, XGH hydrogel membranes can be used as effective anti-adhesive barriers after performing tendon surgeries; however, this should be confirmed by performing clinical trials in humans.

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