“Polylactic acid-polyethylene glycol-hydroxyapatite composite”
An efficient composition for interference screws

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ABSTRACT
Interference screws are commonly used for the treatment of ruptured ligaments. The interference screws are often constructed from polylactic acid (PLA). In this study, a melt blend of PLA, polyethylene glycol (PEG) and hydroxyapatite (HA) was investigated for use in interference screws. For this purpose, mechanical properties, differential scanning calorimetry (DSC), degradation rate, pH change, water contact angle, morphology, cytotoxicity, and cell adhesion on the specimens were investigated. According to the tensile test results, by mixing various levels of PLA, PEG, and HA, mechanical properties of the resulting composite can be kept constant or even improved in comparison with pure PLA. DSC proved the miscibility of components and provided a softer product after adding PEG to the mixture. The weight loss of samples was investigated over a period of 7 months and the results indicated an increase in the degradation rate by increasing PEG level. pH changes were also investigated indicating no significant change in pH. The contact angle test showed an increase in the hydrophilic nature of all specimens with increasing PEG and HA levels. Surface morphology was studied by scanning electron microscope (SEM) and the results showed an increase in toughness with increasing PEG level. 2μm HA particles and HA agglomeration in some areas were clearly observed in the SEM micrographs. According to the MTT test, none of the samples caused cell death, and results also showed good and spread cell adhesion to the specimens.

1. Introduction
Ligament is a tight, yet flexible tissue fiber that its two ends attaches to two joint-forming bones to prevent them from separation [1]. Sometimes, forces exerted on a joint tend to bend it in an incorrect direction. If these forces are very strong and exceed ligament strength, ligament rupture will occur. Ligaments are vein-free tissues and ligament ruptures are not self-healed without an external intervention. Suturing the ligament is not a usual treatment and autografts and allografts ligaments are usually used to treat such ruptures [2]. Interference screws are used to graft this new ligament to the bone. The interference screws are placed in holes previously made by a drill in femur and tibia to hold the new ligament around the joint [3, 4].

Due to the high strength and acceptable biocompatibility of some metals, primary interference screws were made of metals such as titanium [5]. However, metals had their own limitations such as...
stress shielding, interference with magnetic resonance imaging (MRI) and computed tomography (CT) imaging, tendon rupture, and permanence. For these reasons, absorbable polymers such as polylactic acid (PLA) and polyglycolic acid (PGA) replaced metals and have been used in interference screws. These polymers do not interfere with imaging techniques and have a modulus close to the bone. They are also hydrolyzed via a simple process and decomposed into relatively safe components. During degradation, these polymers lose their strength, and load is gradually transferred to the bone, helping the repair to take place faster [6, 7]. Glycolic acids form a sterile cyst on the site of injury due to rapid degradation. Accordingly, PLA with a lower degradation rate is used. PLA takes about 5 years to be completely degraded [3, 8]. Some companies use lactic acid and glycolic acid copolymer (PLGA) to reduce the rate of degradation and adapt it to the bone reconstruction rate up to 1 year [9]. Moreover, Esmaeilzadeh et al. used the PLA/polycaprolactone blend to improve the toughness of PLA so that the screw comprising this material would show less fracture during application [8]. However, polymers have also some disadvantages; for example, these polymers do not induce bone formation and cannot make good connections with the bone. For this reason, resorbable polymer composites with bioactive fillers were designed. Fillers such as hydroxyapatite (HA), bioactive glass, β-tricalcium phosphate, etc. have been used in different studies [3, 6, 8, 10].

Bearing in mind these considerations within a wide research project aiming at “providing a combinatorial composite of PLA/PEG/HA for interference screws,” we conducted the present study to enable appropriate mechanical strength while maintaining a faster degradation rate compared to the previous studies. In particular, we controlled the degradation rate by integrating PLA and PEG, which increased the degradation rate of the composite while sustaining appropriate mechanical strength and toughness. To the best of our knowledge, no study has evaluated the degradation rate by mixing PLA with PEG with the simultaneous use of these three polymers. In fact, we used this composite for application of interference screws, but other researchers used them for other purposes like scaffolds [11–14]. Moreover, we applied HA to increase biocompatibility and induce bone regeneration and improve adhesion of interference screws to the bone.

2. Materials and methods

2.1. Materials

Poly-lactic acid (PLA) with a density of 1.25 ± 0.05 g/cm³ and a melting point of 170–180 °C was purchased from Hisun Co., China. Polyethylene glycol (PEG) with a molecular weight of 6000, and a melting point of 58–65 °C was obtained from Merck Co., Germany. HA with a particle size of 2 μm and a density of 0.8 g/cm³ was purchased from DK Nano Co., China.

2.2. Sample preparation

First, four samples of PLA and PEG containing 0, 2.5, 5, and 7.5 wt.% PEG were selected. Before mixing, the polymers were dried in an oven (ValadkHAni Co.) at 35 °C for 10 h. For homogeneous mixing, the samples were blended in an internal mixer (Brabender W50, Germany) at 180 °C and 80 rpm for 15 min. For each PEG level mixed in the previous stage, 2.5 and 5 wt.% HAs were selected. In this way, six other samples were prepared. The melt blending process was performed for the samples containing PLA, PEG and HA in the same way. After melting and mixing PEG and PLA, HA particles were added and mixed for 5 min.

To perform mechanical and biological tests, the samples were made in sheets of 1 mm in diameter. To this end, a hot-pressing machine (Toyo Seiki WCH (2002)) at 190 °C and 50 kPa was used for 5 min. The samples were then cold pressed at 27 kPa for 5 min.

2.3. Tensile test

Specimens with a length, width, and thickness of 110, 20, and 1 mm were prepared by a fret saw according to ASTM D638. The test was performed by GT7010-D2E (GOTECH, Taiwan) at a rate of 5 mm/min and a jaw distance of 50 mm.

2.4. Differential scanning calorimetry (DSC)

DSC 200 F3 (NETZSCH) was used to perform DSC tests. The temperature program was set from 25 to 220 °C with a rate of 5 °C/min. 10 milligram of each
sample was placed in the pan and the test was carried out in accordance with ISO 13781:2017 standard.

2.5. Degradation test

The specimens were prepared as strips of approximately 20 x 1 x 2 mm in size according to the ISO 13781:2017 standard. The specimens were then placed in 50 ml of phosphate buffered saline (PBS) with an approximate pH of 7.4 at 37 °C in the incubator (PBU-405, PECO Co.). The weight loss was measured within 7 months at intervals of two weeks. For this purpose, the specimens were removed from the buffer solution at specified times and washed with distilled water. The specimens were then dried in an oven at 45 °C for 5 h and weighed by a scale with a precision of 0.1 mg to calculate weight loss percentage.

2.6. pH changes

pH of all samples was measured during degradation according to ISO 10523:2008. For this purpose, strips of approximately 20 x 1 x 2 mm in size were cut and placed in 50 ml PBS with an approximate pH of 7.4 at 37 °C. The pH changes of the samples in PBS were measured within 7 months at intervals of 2 weeks at specified times by Sana pH meter (SANA SL-901).

2.7. Contact angle test

Contact angle test was performed according to ISO 15989:2004 to measure the hydrophobicity and hydrophilicity of the samples. For this purpose, the angle of a water droplet (4 μl) on the polymeric sheets was measured by a system equipped with a CCD camera capable of taking images from droplets. The images were then analyzed by Image J.

2.8. Morphological study

To determine the distribution of HA particles and PEG and their impact on the surface morphology, small pieces of the specimens 1, 5, and 7 were placed in a liquid nitrogen tank and then fractured. Half of the specimens 5 and 7 were placed in 6 M HCl for 12 h to remove HA particles. All specimens were gold coated by sputtering. The fracture surface was then examined by scanning electron microscope (SEM, Phenom-proX, Netherlands). The morphology of acid-washed samples was examined by AIS2100 (Seron Technologies, South Korea).

2.9. Cytotoxicity test

Cytotoxicity test was performed by 3-(4,5-dimethylthiazol-2-Yl)-2,5-diphenyltetrazolium bromide (MTT) method on extracts of the samples to measure the survival of cells according to ISO10993-5. For extraction of the HA-containing sample and a pure PLA sample, 1 cm² (1 cm x 1 cm) of the polymeric films sterilized by ethylene oxide gas was cut under the laboratory hood in sterile conditions. The approximate weight of the samples was 16 ± 0.5 mg. The samples were then placed in 24-well plates and 500 μl of sterilized PBS physiologic buffer was added to each sample. The samples were then kept at 37 °C for 24 h with constant stirring at 50 rpm. The extracts of the samples were used in cytotoxicity tests. The MTT test was used to determine the toxicity of the samples on the human osteosarcoma cell line (G292). First, the G292 cells were cultured in a 96-well plate, with 10,000 cells in each well. The test for each sample was repeated three times. The culture medium was replaced with serum- and antibiotic-free medium after 24 h. Then, extracts of various samples were added to the pure culture medium on the wells. After 24 h of exposure of cells to extracts, MTT (5 mg/ml) was added to each well, not more than one-tenth of the volume of the culture medium. The samples were then returned to the incubator at 37 °C for 4 h. The culture medium was then drained and 100 μl DMSO was added to each well. The plate was shaken at a low speed for 15 min until the formazan dissolves. The absorbance of each well was recorded at 570 nm on an ELISA microplate reader (μQuant and power wave Sx2, BioTek Inc.). It should be noted that no extract was added to the cells in the control wells, and they only contained a pure culture medium.

2.10. Cell adhesion test

The cell adhesion test was carried out to ensure that the cells are adhered to the samples and to observe the behavior of cells. Small pieces of 1 cm x 1 cm in size with a weight of 16 ± 5 mg were cut from HA-containing samples and a pure PLA sample, which were previously sterilized by ethylene oxide gas. The pieces were then placed in a 24-well plate. Thereafter, Human osteoblast-like cell lines G-292 were cultured in each well containing 5 x 10⁴ cells in an incubator. After 24 h, the culture medium was drained and washed with PBS to remove cells that do not adhered or loosely adhered to the surface. It was then stabilized with glutaraldehyde 2.5% for 4 h and washed with deionized water. The samples were dehydrated in 30–100% alcohol and their morphology were investigated by SEM (AIS2100, Seron Technologies Co., South Korea).
3. Results and discussion

3.1. Morphology

To evaluate the effect of PEG and HA on morphology, the fracture surface of the specimens 1, 5, and 7 were examined by SEM. As seen in Figure 1, surface roughness increases by adding PEG. Unlike angular edges and brittle fracture in PLA, there are less sharp edges in the specimen 5 and a less brittle fracture occurs in this case. Similar changes can be found in other articles. So one can conclude that PEG is well-mixed with PLA and has also been able to improve roughness [15–18].

Morphological study of the specimen 7 did not provide detailed information on the distribution of HA particles. To determine particle distribution, the specimen was placed in a 6M hydrochloric acid solution for 12h to remove HA particles dissolved in the acid [19]. In Figure 2a, we can observe the 2-μm spherical HA particles and cavities of agglomerated particles that were washed. Moreover, in Figure 2b, we can clearly see an 18-μm agglomerated HA particle (based on the given scale). Similar results were observed in another study [20].

3.2. Tensile test

The results of the tensile test on all the specimens are shown in Figures 3 and 4. As can be observed, by applying force to specimens containing 2.5, 5, and 7.5 wt.% PEG, the strain at break increased whereas the stress at break was reduced as a result of increasing the PEG content, as compared to pure PLA. In our investigations, the tensile strength of pure PLA was 51 MPa. However, by adding 5 wt.% PEG, it decreased to 46.3 MPa, while the strain of pure PLA increased from 4.5% to 6.2%. Similarly, Baiardo et al. showed that the stress of pure PLA increased from 66 to 53 MPa whereas its strain decreased from 1.8% to 3.5% via 5 wt.% PEG addition [21]. A similar behavior was reported in other studies [22–24].

This is due to the decreased PLA concentration and increased PEG in the blend. Because of the difference in the chemical structure of PLA and PEG, PEG typically acts as a plasticizer in the blend so that the blend shows interstitial properties [15]. This is why smaller PEG molecules are located between PLA molecules and weaken their strong molecular
forces. As a result, it helps increase the flexibility and plasticity of the composite, but decreases its mechanical strength [25].

According to the literature, by increasing the HA level in the mixture, we expected to observe a reduction in the stress and strain at break [19, 26]. However, as shown in Figures 3 and 4, the tests represented a turning point in the stress and strain of the specimens containing 2.5% HA. In other words, by adding 2.5% HA to pure PLA, the tensile strength was improved from 46.3 to 52.7 MPa and the strain increased from 6.2% to 9%. However, by adding 5% HA, the stress and strain reached 46.8 MPa and 8%, respectively, which is decreased in comparison to the previous. The same results were obtained when Diao et al. applied a wide range of HA from 1% to 20%. At lower HA content (1% and 3%), the stress at break was higher than pure PLA and a significant increase was observed in the strain. However, both the stress and the strain decreased at 3 wt.% HA and further decreased at 5 wt.% HA [27].

The reason is that in the composite containing 2.5% well dispersed HA, the force applied to the matrix was more effectively transferred to the HA particles, leading to an increase in the stress tolerance and the strain. As observed in the SEM images, a further increase of HA particles led to HA agglomeration and weak points, thereby reducing the stress and the strain.

Since the interference screw is going to be screwed in the bone to make a junction between

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**Figure 3.** Tensile strength of samples.

**Figure 4.** Strain at break of samples.
Figure 5. DSC curves of samples (a) samples containing various levels of PEG. (b) Samples containing 2.5%PEG and various levels of HA. (c) samples containing 5%PEG and various levels of HA. (d) samples containing 7.5%PEG and various levels of HA.

Figure 6. pH changes after 7-month investigation.
ligament and bone; an increase in mechanical strength makes it less likely to break while being screwed in the bone.

### 3.3. Differential scanning calorimetry (DSC)

The DSC test indicates the thermal properties of materials. It can also provide information about the miscibility of components in a blend. Figure 5 shows melting point ($T_m$), glass transition temperature ($T_g$), and cold crystallization peak ($T_{cc}$). As seen in Figure 5, the melting point remained about the same with increasing PEG level and only marginally dropped from 176 to 174 °C, but $T_g$ decreased slightly from 93 to 73 °C. Moreover, the $T_g$ peak intensity decreased and disappeared. This phenomenon was also observed in Sheth et al. [22].

The presence of smaller PEG molecules between PLA molecules may develop physical bonds such as hydrogen and bipolar–bipolar bonds. As a result, strong PLA–PLA homogeneous bonds are converted into heterogeneous PLA–PEG bonds. Due to its plasticizing properties, PEG causes easier movement of PLA molecules and thus lowers $T_g$. The single $T_g$ peak indicates miscibility of the two materials [17].

As seen in Figure 5, addition of HA to the mixture did not affect $T_m$, $T_g$, and $T_{cc}$, as reported by Ferri et al. [19].

The $T_g$ and $T_{cc}$ peaks gradually disappear with increasing the PEG level for samples containing 5% and 7.5 wt.% PEG. In other words, the addition of PEG to PLA increases crystallization due to the crystalline nature of PEG, and also, enhanced nucleation points and mobility of PLA chains [28]. The peaks appear again with increasing the HA level. This could be explained by the fact that the presence of HA leads to a decrease in the crystallinity of PLA as the presence of these particles limits the mobility of PLA chains and decreases the orientation of polymer chains by increasing their degree of disorder [29]. This chain immobilization in the interphasial region results in a $T_g$ peak in the DSC curve for HA-containing samples [26].

### 3.4. pH changes

With the degradation of the specimens in PBS over time, we expected to observe a decrease in pH, leading to the development of an acidic culture medium due to the degradation of PLA and formation of lactic acid. Before weighing the degraded specimens, the pH of the PBS solution was measured. The results of experiments showed that the pH changes were negligible and below 0.2%. In other words, no change was found in the pH of the specimens within seven months. The pH changes are shown in Figure 6. Of course, the observed slight changes in pH were higher than pure PLA due to the dissolution of PEG in PBS. This can, in turn, slightly change pH. According to Hile et al., no significant change was found in pH after the first 6 months. However, the pH of the medium containing pure PLA decreased significantly after 1 year. In the case of the PLA/HA composite, no change was observed in pH after 1 year [30].

### 3.5. Degradation test

The degradation rate of resorbable implants such as polymeric interference screws should match the rate of bone growth. Otherwise, if the screw degrades faster than bone growth and loses its strength, the implant fails and the surgery should be repeated. Alternatively, in the case of a lower degradation rate,
bone growth is not completed and the screw residues remain in the body. Therefore, the degradation rate of the polymeric compound needs to be taken into consideration. PLA takes about 5 years to be completely degraded. To increase the rate of degradation, some manufacturers use PLA-PGA copolymer which degrades up to 1 year [9, 31, 32].

As shown in Figure 7, the degradation rate increased to 7.5% with increasing the PEG level to 7.5%. This is why hydrophilic PEG absorbs water in
Figure 10. G-292 cell line attachment on samples.
the buffer, accelerates the PLA degradation rate, and dissolves in water by hydrolytic degradation process. Sheth et al. in their study drawn the same conclusion. They reported that by adding 10% PEG to PLA, the weight loss could increase from 1.97% to 12.91% in hydrolytic degradation [22]. Thus, the degradation rate of the implant can become closer to the PLGA degradation rate and can be adjusted to the bone growth rate by combining various PLA and PEG levels.

Since the degradation and weight loss of the specimens occur because of surface degradation and PEG dissolution in water, the share of PEG on the surface appears to decrease by adding HA to the mixture. As a result, the solubility of PEG in water and resulting weight loss decrease. This results in a lower degradation rate for HA-containing samples.

3.6. Contact angle test
PLA is a relatively hydrophobic polymer, and cells have a lower affinity to adhere to its surface than more hydrophilic polymers [33]. On the other hand, PEG and HA are both hydrophilic, and a decrease in the contact angle can be expected by adding hydrophilic materials to pure PLA. The current blend composition has not been utilized before, and they only applied combinations of two of them like PLA/PEG or PLA/HA. For instance, Sheng et al. studied the contact angle by adding PEG to PLA, which decreased the angle from 72.5 to 68.3 [33]. Moreover, Kutikov and Diao et al. showed that by adding HA to pure PLA, the contact angle of the blend was reduced [13, 27]. As shown in Figure 8, this expectation also achieved in our system, and the contact angle was gradually reduced by increasing the level of hydrophilic materials in the composite.

3.7. Cytotoxicity test
The MTT assay is one of the most common colorimetric methods to examine the effect of toxicity on cellular life. This is studied by the reduction capacity of yellow MTT after penetrating into living cells by the mitochondrial succinate dehydrogenase enzyme and its conversion into purplish formazan crystals. After dissolving these crystals in DMSO, the absorbance of the solution at 570 nm was related to the number of viable cells.

The survival rate of the G292 cell line in the presence of extracts of polymeric films 1, 3, 4, 6, 7, 9, 10, and the control sample (untreated sample) is shown in Figure 9. As observed, by increasing HA and PEG levels, no significant difference was observed between the test and the control samples in terms of cell survival rate with regard to statistics and standard deviation. It means that none of the percentages had toxic effects on cells. Sheng et al. showed cell viability of PLA/PEG nanoparticles between 75% and 115%, and that it did not create any cytotoxicity or cell death, meaning that the polymer was biocompatible [33]. Similarly, Kutikov et al. MTT tests on did not show any cytotoxicity [13].

3.8. Cell adhesion test
Images of osteosarcoma cells of the G292 cell line after 24 h of culture on the polymeric films are shown in Figure 10. As expected, the cells had a diameter of about 20 μm. Cell adhesion was observed in all the specimens. The attachment between the cells and the polymeric films indicated cellular activity. In general, one can conclude that the designed specimens have the potential for adhesion, diffusion, and creation of appropriate cellular shapes. As observed in the images, the cells were more uniformly distributed on the specimens 9 and 10 due to more hydrophilicity than other specimens. The cells adhered spherically, and then, began to spread. Seyfoori et al. cultured the same cell line on the surface of a magnesium implant. The morphology of cells growing and spreading is like images taken from the cells on our composite surface [34].

Based on the suitable adhesion of bone cells to the composite surface, it can be assumed that interference screws constructed from this composite show good bioactivity and low rejection rates.

4. Conclusion
The present study mainly aimed at fabricating a new appropriate tailor-made composite that can be used effectively for interference screws. To this end, we attempted to improve the mechanical characteristics of pure PLA so that potentially less failure will occur while fixing it in place. We also intended to increase the PLA degradation rate so that it fits the rate of bone growth. Moreover, we aimed at increasing PLA biocompatibility with bone cell lines showing better growth and adhesion to its surface due to the presence of HA.

The results obtained from various tests are summarized in this section. According to the tensile test, the strength decreased, and elongation increased by increasing PEG level in the composites. A turning point in the mechanical properties was also observed by adding HA to the mixture. By adding 2.5% HA to the mixture, both strength and elongation first increased and then
decreased by increasing HA level to 5%. By adjusting the level of three components in the mixture, it is possible to obtain the properties required for the preparation of interference screws. DSC results indicated the miscibility of the components so that $T_g$ decreased by increasing PEG level. However, $T_g$ and $T_{cc}$ appeared again by adding HA to the mixture due to seeding of crystals. According to the results of the degradation test, addition of PEG led to greater diffusion of fluids in the polymer mixture and thereby an increase in the degradation rate. By adding HA, degradation slightly decreased due to reduced share of PEG on the surface. The results of pH measurements showed no statistically significant difference considering a maximum increase of 0.2% than the pH of human body. In other words, the degradation of the prepared polymeric composites did not change the pH of the media. According to the contact angle test, with increasing hydrophilic PEG and HA levels, the resulting polymeric composite turned more hydrophilic. This in turn accelerated degradation process. As seen in SEM micrographs, the roughness of the fracture surface increased by adding PEG to the mixture while losing brittleness. Distribution of spherical HA particles with a diameter of 2 μm was well seen in the samples. According to the results of cytotoxicity tests on HA-containing samples, no significant difference was found in the rate of cell survival by changing the level of components in the polymeric mixture. In other words, all samples supported cell survival. After 24h culture of G292 cells on samples and stabilization, SEM micrographs showed that the cells began to adhere and spread on all specimens.

Disclosure statement
No potential conflict of interest was reported by the author(s).

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