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BIOCOMPATIBILITY STUDIES

Original Research

In-vivo evaluation of a partially resorbable poly l-lactic acid/ braided bioactive glass fibers reinforced composite for load bearing fracture fixation

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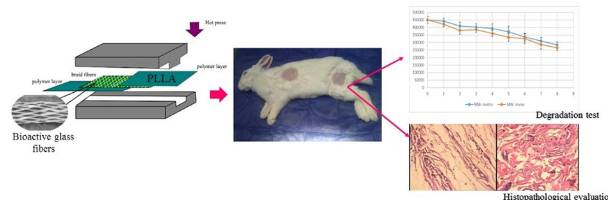
Abstract

Our previous studies have been focused on the design, optimization and manufacture of a partially resorbable composite bone plate consisting of a poly l-lactic acid matrix reinforced with braided fabrics bioactive glass fibers (PLLA/BG). In the present study, the response of the composite samples, the degradation rate, the inflammatory response, fibrous capsule formation and tissue-implant bonding to the in-vivo environment were assessed via implantation in the rabbit subcutaneous tissue. Despite the presence of both enzymatic degradation and hydrolysis processes within the body, the rate of the molecular weight loss as an indicator of degradation did not show a significant difference with the in-vitro conditions. It was predicted that strength loss would show the same trend since it was a consequence of molecular chain disruption and the loss of molecular weight. Inexistence of chronic inflammation, as confirmed by our previous results on the controlled degradation rate, also showed the maintenance of the physiological pH in the peripheral environment of the implant. Moreover, lack of the fibrous capsule tissue around the implant indicated that the implant was bioactive. In addition, given the composition of the bioactive glass fibers, that could be bonded to soft and hard tissues, tissue bonding with the PLLA/BG composite samples was also observed, thereby confirming the bioactivity and biocompatibility of the proposed bone plate.

Graphical Abstract



1 Introduction

Metallic bone plates are commonly used for long bone fracture fixations due to their proper strength. However, as they have some shortcomings, researchers have been trying to develop non-metallic types [1].

Fiber reinforced composites could be designed to achieve the intended mechanical behavior by the proper selection of a matrix and reinforcement materials, as well as volume fraction, direction and aspect ratio of the fibers. By using bioabsorbable materials, some advantages could be obtained, such as elimination of the traditional metallic bone plate drawbacks. The main benefits of bioresorbable composite bone plates are the gradual decrease in the mechanical strength and also, their young modulus, which

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is near the cortical bone [1]. These properties lead to the bone growth and prevent the osteoporosity followed by stress shielding since shielding delays callus formation, which can decrease the bone healing rate [2]. Other advantages of biodegradable implant include no tissue reaction originating from the released metallic ion and corrosion, no artifacts on the computed tomography and finally, no need for a second surgery for the purpose of removal [1].

Bioabsorbable plates made of biodegradable polymers, such as PLA, polyglycolic acid (PGA), poly-l-lactic acid (PLLA), polylactic co glycolic acid (PLGA), polycaprolactone (PCL) and polydioxanone, (PDS), have been proposed to overcome the mentioned problems. Although they have enough strength to support the craniofacial bone fractures, they show some problems including inflammation due to the acidic intermediate product of the degradation process and also, the control rate of degradation. Moreover, they could not be used in load bearing applications [3]. Therefore, biodegradable composites have been considered by the researchers to achieve the optimized degradable bone plates. In this case, the biodegradable polymers have been used as a matrix and bioactive ceramics such as phosphate glass fibers, hydroxyl apatite and tetra calcium phosphate have been commonly applied as the reinforcements. The degradation rate of biodegradable polymer matrix composites could be easily controlled by changing the composition and fabrication techniques or adding coupling agents and fiber treatments. Moreover, a wide range of mechanical properties could be obtained by controlling the volume fraction and the arrangement of the reinforcements [4].

Our previous research was focused on the design and fabrication of a biodegradable composite bone plate consisting of poly L-lactic acid (PLLA) as the matrix and bioactive glass (BG) fibers as the reinforcement. Finite element analysis revealed that using the 45% volume fraction of the reinforcement in the matrix, with a braided arrangement of the fibers with the longitude direction in 15° degrees, elastic modulus, and tensile and bending strength of the bone plate would be near to those of the cortical bone [5]. Previous studies have of PLLA, but its resistance to hydrolysis is rather poor; so, in the aqua environment, the mechanical properties of the composite would be decreased in the PLLA/BG composites, and a chemical bond could be formed between the silanol groups of the BG fibers and the carboxyl or hydroxyl groups [6]. By using the aminopropyl silane as a coupling agent, some covalent bonding between PLLA matrix and BG fibers was formed and load transferring from the matrix to the reinforcement occurred perfectly. So, the fabricated PLLA/BG composite bone plate showed the tensile strength and elastic modulus of 195 MPa and 22 GPa, respectively, which were close to those of the cortical bone [7]. Since, in the real life condition, more analysis was performed to assess the load capacity of the PLLA/BG composite bone plate under real life conditions, the results showed that the PLLA/BG composite bone plate could tolerate physiological loading in the normal movement and support fracture site [8].

Another important role of the coupling agent is the prevention of water penetration through the fiber and matrix interface. This prevention can postpone the degradation process and decrease the strength loss rate. Therefore, the biodegradable composite bone plate could fix the fracture site completely in the first weeks of treatment. Then, it could be degraded slowly, and the load would be gradually transferred to the bone [9].

Since the degradation of PLLA is slightly different from that in the in-vitro to in-vivo environment due to enzymatic degradation, the aim of this research was to evaluate the synergic effect of the hydrolytic and enzymatic process on the degradation rate and tissue response. Our previous study revealed that the pH change from 7.4 to 8 when the PLLA/BG samples were immersed in PBS and they were only under hydrolytic degradation, it was predicted to neutralize the acidic product of PLLA degradation; so, it could play a significant role in reducing the degradation rate. However, the in-vivo evaluation of biocompatibility and inflammation reaction of the PLLA/BG composite bone plate was necessary to be assessed. This article documents the biocompatibility and usefulness of our PLLA/BG bone fixation system through in-vivo experiments.

2 Materials and methods

2.1 Materials

The polylactic acid (PLLA)/ bioactive glass (BG) composite consisted of PLLA as the matrix and bioactive glass fibers (13-93, 6Na2O, 12K2O, 5MgO, 20CaO, 4P2O5, 53SiO2; wt%) as the reinforcement. PLLA with an average molecular weight (M_w) of 200,000 and an inherent viscosity of 3.3–4.3 dl/g was supplied by Boehringer Ingelheim Pharma, Germany (Resomer® L 210 S); also, BG fibers were purchased from MO-SCI Corp, USA. γ-aminopropyltriethoxy silane (γ-APS) coupling agent with the purity of 99% was purchased from Sigma-Aldrich Corporation, USA. Phosphate buffer saline (PBS) and simulated body fluid (SBF) solutions were the products of Sigma-Aldrich. This information was supported by the results of a previous study [10].

2.2 Materials preparation

The BG fibers were modified by adding γ-APS. To put it briefly, a solution with 95% ethanol (C_2H_5OH) and 5%

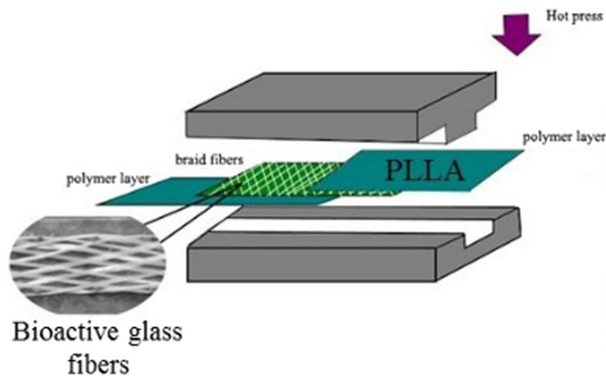

Fig. 1 Schematic of three layers composite and stainless steel hot press machine

deionized (DI) water was prepared. A hydrolyzed γ-APS solution was prepared by adding 1 wt% of γ-APS to 99 wt% of the prepared solution and shaken vigorously; then it was kept at room temperature for 5 min. BG fibers were immersed into a hydrolyzed γ-APS solution for 2 h and dried at room temperature. The BG fibers were re-dried in an oven at the temperature of 110 °C for 10 min to improve the surface functional groups.

The pulling method was used to coat the BG fibers with polymer; this enabled further processing and improved the mechanical properties of the fibers [11]. For the formation of tows, modified bioactive glass fibers with an average weight of about 0.100 ± 0.010 grams were coated by the PLLA solution. The solution was prepared by dissolving PLLA in the chloroform solvent (50 w/V). Braided textures were fabricated with a braiding angle of 15 degrees, as shown in Fig. 1a. The braided texture was re-weighed to determine the amount of the coated polymer. Weight fraction (w_f) was computed according to Eq. (1). and the volume percent of the fibers was 45%:[5]

$$w_f = \frac{\rho_f v_f}{\rho_f v_f + \rho_m v_m} \tag{1}$$

where ρ_m is the density of PLLA, ρ_f is the density of BG, V_f is the Volume fraction of the BG fibers (0.45), and V_m is the volume fraction of the matrix polymer (0.55).

PLLA was dissolved in the 10% w/v chloroform solution and stirred for 3 h at 40 °C to obtain a uniform solution. One-half of the uniform solution was poured into a Teflon mold with the dimensions of 100 mm × 10 mm × 1 mm (length × width × height). Braided bioactive fibers were hand laid up into the solution; then the remaining solution was added into the mold and dried at the ambient temperature for 48 h.

As shown in Fig. 1, three single layers composite were transferred from the Teflon mold to a stainless steel mold with the dimensions of 100 × 10 × 3 (mm). The stainless steel mold was placed in a hot press machine, and a pressure of 10 MPa at 130 °C was applied to the mold for 1 h and slowly cooled down to the ambient temperature in the mold. This led to the proper crystallinity in the polymer matrix and established the appropriate bonding between the matrix and the reinforcement. The implantable samples were produced with the dimensions of 10 × 10 × 3 (mm).

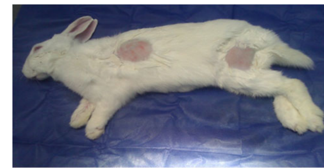

Fig. 2 Preparation of the implantation sites

2.3 In-vivo study

The surgical procedure was performed according to ISO 10993-6:2016 (Biological evaluation of medical devices, Part 6: Tests for local effects after implantation). All animal experiments were performed at Isfahan University of Medical Sciences Laboratories, according to the National Institutes Health guide for the care and use of Laboratory animals, the 8th ed.

The prepared PLLA/BG composite samples were disinfected in Deconex for 15 min and then completely washed with the normal saline. To leave the probable deconex residue, the specimens were sterilized in the normal saline for 15 min.

Eighteen mature male New Zealand white rabbits with the initial weight of about 2.0–2.5 kg were under a diet of pellets and fresh lettuce. These rabbits were acquired from the Pasteur Institute of Iran. The animals were kept in a purpose-designed room for experimental animals and observed for ten days to confirm their health, such as behavior pattern, faces, activity and other clinical signs. Rabbits were under anesthesia by the intramuscular injection of acepromazine (0.07 mg/kg), xylazine (5 mg/kg) and ketamine (30 mg/kg) combinations and had a subcutaneous surgical rupture. Three areas of the body, including the two sides of the chest and left femora, were entirely shaved and scrubbed with alcohol, chlorhexidine and betadine three times, as presented in Fig. 2.

A 10 mm longitudinal skin incision was made over the left femora. Afterward, with a cut on the skin and the removal of the fascia under the skin, a sample was subcutaneously inserted through the incision using a particular trocar in contact with the muscle and sutured with the non-absorbent 3-0 nylon stitch. Figure 3 shows an implant on the muscle and the final stage of the surgery. Rabbits received the intramuscular injections of Penicillin G potassium

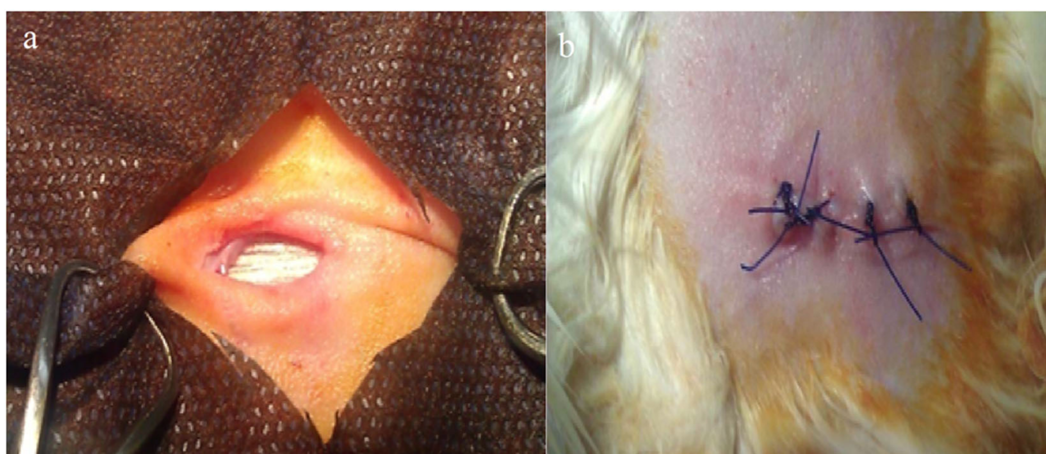

Fig. 3 **a** implantation of the PLLA / BG specimen in subcutaneous tissue and **(b)** final stage of the surgery

Table 1 Inflammation degrees

Without inflammation (grade 0)	Mild inflammation (grade1)	Moderate inflammation (grade 2)	Severe inflammation (grade 3)
Without inflammatory cells	Presence of macrophage and plasma cells	Presence of macrophage and plasma cells	Necrosis
Fibroblast cells >30	Inflammatory cells >30 Fibroblast cells 10-30	Aggregates of lymphocytes and Granulocyte cells	High density of inflammatory cells

(22,000 U/kg, IV, every 8 h) for 5 days and Flunixin Meglumine (1.1 mg/kg, IV, every 8 h) for 3 days as a postoperative analgesia. The study lasted 8 weeks. At the end of this time, the samples were removed and the adjacent tissue's response was evaluated. The in-vivo degradation rate of the samples during the period of implantation was also investigated.

2.4 In-vivo evaluation of the PLLA/ BG samples degradation

A total of eight rabbits were selected randomly for the in-vivo degradation evaluation. The implants were retrieved from the implantation site from 1 to 8 weeks with a 1-week interval after surgery (three samples at each time point were evaluated). The specimens were washed with cold physiological saline and vacuum dried to keep the weight constant. For M_w measurement, the dried samples were dissolved in a 2 ml chloroform solution in separate containers and injected into the Gel Permeation Chromatography (GPC) cells (Nawr company, Germany). M_w for each sample was measured as a function of time by GPC. The in-vivo degradation rate was calculated by determining the Mw changes during 8 weeks and compared with the in-vitro one. For this purpose, the PLLA/BG samples were immersed in PBS and their Mw changes during 8 weeks (three samples at each time point) were evaluated. The percentage of M_w loss was calculated as follows:

$$\text{Mw Loss\%} = \left[(M_{w0} - M_{wt})/M_{w0}\right] \times 100, \quad (2)$$

where M_{w0} and M_{wt} are the initial molecular weight and the molecular weight in each preset time, respectively.

2.5 Inflammatory response and fibrous capsule formation

Ten rabbits were randomly divided into two equal groups. During 4-week and 8-week periods of time, each implant placed with a 1-cm margin around the subcutaneous connective tissue was removed. Each composite specimen was separated from the adjacent tissue, and the tissue was fixed in a 10% neutral buffered formalin solution and prepared for histological examination. The 10% formalin solution was prepared by mixing 100 ml formalin (37% formaldehyde) with 300 ml of distilled water. For histological examination, the tissues were sectioned at a thickness of 10 μm. The samples were stained with Eosin and Haematoxylin for 15 min and then studied and evaluated using optical microscopy.

Tissue inflammation and inflammation process were evaluated based on the inflammatory cells adjacent to the composite implants and the total number of the inflammatory cells. The samples were classified into four groups; without inflammation, mild inflammation, moderate inflammation and severe inflammation, as shown in Table 1.

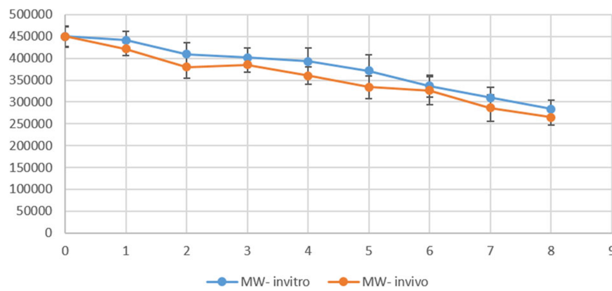

Fig. 4 PLLA/ BG composite molecular weight changes during 8 weeks degradation. (In vivo group: samples were implanted in rabbit subcutaneously, In vitro group: the samples were immersed in PBS.)

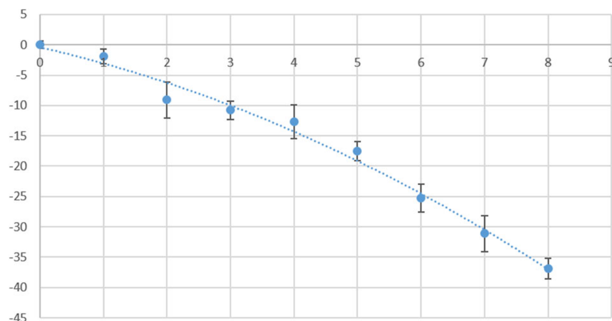

Fig. 5 PLLA/ BG molecular weight-loss percentages over 8 weeks

Cells were counted at the magnification of ×40, and details such as cells type, fibrous tissue formation and collagens condition were determined using a magnification of ×100. All evaluations were done using an optical microscope (Siemens AG, Germany).

2.6 Statistical analysis

All of the results are presented as means ± standard deviation. The one-way analysis of variance was used, and differences were declared as statistically significant at $P < 0.05$.

2.7 Results

2.7.1 In-vivo degradation of the PLLA/ BG samples

GPC analysis of the implanted samples showed the decrease of Mw in both in-vitro and in-vivo groups, as presented in Fig. 4. Mw loss percentages of the in-vivo implanted samples are also presented in Fig. 5. A lower Mw loss rate could be seen in the first week; then the weight loss rate was accelerated slowly and the degradation trend was the same for both groups.

Mw loss was less than 10% in 2 weeks, showing a slow degradation rate. After that, the degradation process was accelerated; so at the end of the 8th week, the Mw loss percentage was 37%. All of the specimens completely preserved their structural integrity during the degradation process, which is one of the important parameters in degradable implants.

2.7.2 Histopathological evaluation

The histopathologic results of 30 samples (10 rabbits, three samples were placed in each), in the 4th and 8th weeks are presented in Table 2. When the PLLA/BG samples were removed from their places, it could be observed that most samples appeared to be mild inflammatory or without any inflammatory responses. In other words, after 4 weeks, 33% of the implanted samples were completely bonded with the surrounding tissue and no inflammation response was observed. In 53% of the samples, a thin fibrous layer was observed; however, the fibrous tissue did not cover the whole sample; also, there was bonding between the tissue and the implant in some areas, showing the mild inflammation. In 13% of the samples, the fibrous tissue covered the samples completely and moderate inflammation could be identified. The average inflammation score was 0.8, that was in the mild inflammation range. In the second stage of the study, after 8 weeks, the inflammation response was observed in a few samples. According to our observation, in 73% of the rabbits, there was no fibrous tissue around the samples and the surrounding tissue was attached to the samples completely; in other words, there was no inflammation response. In 20% of samples, the mild inflammation was observed and only one specimen was covered with a thin fibrous layer. The average inflammation score after 8 weeks was 0.33. None of the samples showed the severe inflammation response through the in-vivo study period of time. Comparing the average inflammation score from the 4th to 8th weeks showed that when the PLLA/BG composite samples were implanted in the subcutaneous position, an inflammation response was initiated; over time, this led to a mild and even elimination inflammation response.

The results of the histopathologic study are presented as the microscopic images of the stained samples in Figs. 6 and 7. The samples with mild and moderate inflammation could be observed, respectively. Giant cells and fibrous capsules are also shown in the Fig. 7. In the samples with moderate inflammation, the thickness of the fibrous tissue and also, its continuety were more than those with mild inflammation. Microscopic images of the mild inflammatory samples revealed that the fibrous capsule did not surround the implant, and there were some regions in which fibroblasts could grow and attach themselves to the implant; on the other hand, around the samples with moderate inflammation response, the thickness of the fibrous capsule after the 8-week implantation was increased that could be due to implant micromovement.

Table 2 Histopathological results of PLLA/ BG samples during 8 weeks in vivo study ($n = 30$)

Inflammation grades	4 weeks	8 weeks	Tissue bonding after 8 weeks
Without inflammation (grade 0)	5	11	Bonding between tissue and sample
Mild inflammation (grade1)	8	3	The bond between sample and tissue, a thin fibrous capsule formation
Moderate inflammation(grade 2)	2	1	No bonding
Severe inflammation (grade 3)	0	0	–

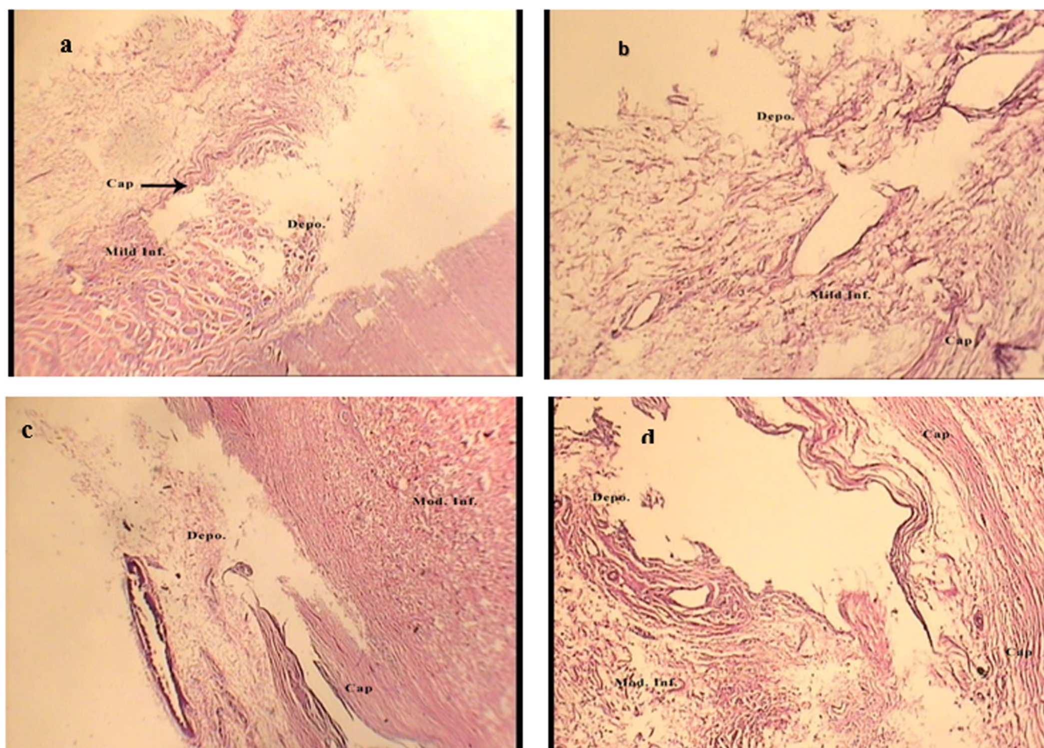

Fig. 6 Microscopic images of the stained samples (**a**) mild inflammation response ×40 magnification. **b** mild inflammation response with ×100 magnification. **c** moderate inflammation response with ×40 magnification. **d** Moderate inflammation response with ×100 magnification. Cap: fibrous capsule. Depo: selected area deposition of samples. Mild inf: mild inflammation. Mod.inf: moderate inflammation

According to Fig. 7, the giant cells were observed to be adjusted to the implant in both mild and inflammation samples; however, they were more in the moderate inflammation ones.

3 Discussion

Fully and parcially resorbable composite bone plates were developed to overcome the shortcoming of metallic ones. It's predicted that at in vivo conditions, simultaneously effect of hydrolytic and enzymatic degradation mechanisms increase the rate of degradation. Since, degradation rate has an important role in elastic modulus and strength loss of the bone plates, accelerating the degradation process will lead to obstacle in fracture fixation and healing processes. In addition, rapid degradation cause the immune system reactions that lead to chronic inflammation and fibrotic capsule formation around the implant and prevent tissue-implant bonding.

Several parameters could be affected degradation rate process such as the ratio of the crystalline to amorphous regions, bonding between the matrix and the reinforcement and controlling the local pH. During degradation, the amorphous regions were preferentially hydrolyzed. In the pure polymer, the hydrolysis of the amorphous chain and subsequently, the auto catalyst effect due to the acidic low-molecular-weight degradation product caused the acceleration of the degradation process [12]. In this research, by using hot press fabrication processing, polymer crystallinity could be increased according to our previous research [13]. Moreover, water would penetrate into the bulk of the composite, reaching the fibers and finally causing the ion release from the composite bulk. This could increase the pH

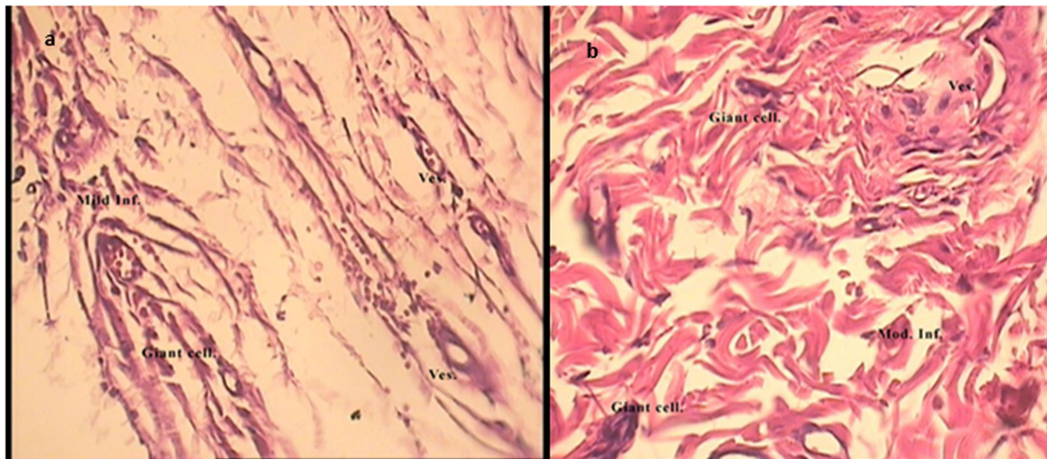

Fig. 7 Microscopic images of stained samples with mild and moderate inflammation. **a** mild inflammation responses with ×400 magnification. **b** Moderate inflammation responses with ×400 magnification. Mild inf: mild inflammation. Ves: Neo vessels

of the solution in the vicinity of the implantation and neutralize the auto catalyst effect [9].

Previous studies have shown that the presence of the bioactive glass affects the polymer matrix degradation, but the rate of degradation could depend on the balance between the autocatalytic effect caused by carboxyl end groups and the buffering effect of the released ions from the bioactive glass.

On the other hand, its SiO_2- and SiO-, that were bioactive solution products, catalyzed the break of the ester bonds by the hydroxyl anions which accelerated the hydrolysis of PLLA [14]. By using the amino propyl silane as a coupling agent, surface silanol groups with hydroxyl end groups of the polymer could make a covalent bond postponing the water penetration and causing the slower degradation rate [15].

Researchers have shown that hydrolysis and enzymatic reaction are two ways by the degradation mechanism of biodegradable polymers is realized; however, for most biodegradable materials, hydrolysis plays the main role in degradation [16]. According to Fig. 4, there is no significant difference in the Mw decrease between the in-vitro vitro in-vivo groups ($p > 0.05$). Therefore, it could be concluded that in-vitro results could strongly predict the in-vivo response of the implant. In other words, previous studies have shown that the strength of the PLLA/BG composite could be decreased only about 5% in 2 weeks; then the degradation process was accelerated slowly, reaching to about 35% of the first strength after 8 weeks of soaking in the PBS. Since the loss of mechanical properties in the degradation process is a consequence of the molecular chain disruption and loss of Mw, it could be concluded that no significant difference between the samples tested under in-vitro and in-vivo conditions in terms of the decrease in the strength. Appropriate initial mechanical properties and also, the good resistance to hydrolysis could represent the biomechanical compatibility of the PLLA/BG bone plates, i.e. the fixation of the fracture and loads bearing in the initial stages of healing and then, the gradual load transfer to the healing bone [16, 17].

When bioactive glass (13–93) was incorporated into PLLA polymer matrices, it caused the implant to bond to the soft and hard tissues, which could be attributed to the higher biocompatibility and bioactivity of the implant and the formation of an HCA layer on the surface in contact with the body fluids [18]. It is an advantage for complex biomechanical applications when the composite implant is placed at the interfaces between the soft and bone tissues [15, 19].

The physiological response of the tissues against implanted materials is one of the most important issues in the development of the medical biomaterials. In the case of polymeric biomaterials, the tissue responses, i.e., inflammatory reactions, partly depend on the chemical structure due to the surface hydrophilic nature of the polymers. Moreover, various studies have shown that implant movement in the subcutaneous region and the injuries caused by it could lead to more inflammatory reactions and the increased encapsulation [14]. Also it was reported that the thickness of the fibrous capsule around the implant is associated with the severity of the inflammatory reaction [20] and this phenomena was observed in present study. For biodegradable polymers, tissue responses are affected by the in-vivo degradation rate and the obtained results. For example, the poly(glycolic acid) that generally undergoes the in-vivo degradation in 2-4 weeks is known as a biodegradable polymer causing the acute inflammatory reaction as the degradation proceeds [21]. It is known that the hydrolysis by body fluids is the major mechanism contributing to the in-vivo degradation of polymeric

biomaterials. Mechanical performance and bioactivity of various composite systems could not be explained except where implant biodegradation and biocompatibility information have been considered. In the PLLA/BG composite implant, modulation of the degradation rate is an important factor in determining the local and systemic tissue response [22]. Slow degradation rate polymers were not induced under inflammatory tissue reactions, as compared to the high degradation rate polymers like PGA [23]. Previous studies have revealed that adding ceramics to polymers could lead to the faster degradation rates and the aggregation of lactic acid in PLLA would cause the capsular inflammation. However, the acidic pH can be compensated by the alkali ions [22]. In the PLLA/BG fiber composite, for bone plate using relatively the high Mw PLLA and also, the bioactive glass (13–93) fibers, the degradation rate and local pH were controlled. Moreover, our previous research showed apatite formation on the PLLA/BG composite surface after 14 days of soaking in the simulated body fluid (SBF) solution, especially when the BG fibers were placed near the surface and coated by a thin layer of PLLA [9]. Therefore, in the present study, we observed that the surrounding tissue was attached to the implant and mild inflammation occurred.

4 Conclusion

In the present study, a biodegradable PLLA/BG composite bone plate was successfully fabricated and implanted in the rabbit subcutaneous tissue. The degradation rate of PLLA/BG was evaluated under in-vitro and in-vivo conditions. After that, the inflammatory response and fibrous capsule formation were studied. There was no significant difference in Mw loss between in-vitro and in-vivo groups, thereby confirming that hydrolysis played the main role in degradation. Moreover, since mechanical performance depends on the degradation rate, it could be predicted that the same in-vitro trend in strength loss would occur the in-vivo one too, in which physiological load would be transferred to the fractured bone about one month after fixation, causing the better healing process. In the tissue response study, we observed that the surrounding tissue was attached to the implant and little inflammation occurred. None of the samples, however, showed severe inflammation responses through the in-vivo study, confirming our previous results on the controlled degradation rate process; the physiological pH was maintained in the peripheral environment of the implant due to the localization of the acidic pH compensation by the alkali ions, as released from bioactive glass fibers. Moreover, lack of the fibrous capsule tissue around the implant indicated that the implant was bioactive. It could be, therefore, concluded that this composite showed a modulated in-vivo degradation rate and also, a significant attachment to the surrounding tissue, which caused better fracture fixation, evidencing the high biocompatibility of the composite bone plate.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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