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All issues

Aniek Setiya Budiatin*, Maria Apriliani Gani, Chrismawan Ardianto, Samirah, Sahrati Yudiaprijah Daeng Pattah, Fitroh Mubarokah and Junaidi Khotib

The impact of glutaraldehyde on the characteristics of bovine hydroxyapatite-gelatin based bone scaffold as gentamicin delivery system

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Abstract

Objectives: Biomaterials are widely used as drug delivery systems targeting bone tissue, such as to treat bone infectious disease. However, the addition of drugs to biomaterials weakens their mechanical properties. Crosslinkers are compounds that improve the mechanical properties of biomaterials. This study aims to determine the effect of glutaraldehyde (GTA) as a crosslinker on the characteristics of bovine hydroxyapatite-gelatin-based bone scaffold with gentamicin as antibiotics (BHA-GEL-GEN-GTA).

Methods: BHA-GEL-GEN-GTA scaffold with GTA solid content ranging from 0.1 to 1.4 wt% was made by direct compression. The compressive strength test was carried out using autograph. Scaffold degradation test was carried out by dissolving the scaffolds in PBS. Scaffold toxicity was performed by MTT assay using BHK-21 fibroblast cells.

Results: There was a significant difference in the scaffolds' compressive strength due to differences in GTA volume. Scaffold crosslinked using GTA with solid content 0.1 and 0.2 wt% in 2 mL solution had higher compressive strength than those in 1 mL solution. Furthermore, GTA with solid content 0.6, 1, 1.2, and 1.4 wt% showed higher compressive strength than those without GTA. Degradation test results showed that GTA increased the percentage of weight loss and swelling of the scaffold. The scaffold exhibited a nontoxic profile in MTT assay.

Conclusions: GTA with optimum solid content shows great compressive strength, stable swelling profile with low percentage of scaffold's weight loss, and is considered as nontoxic.

Keywords: biomaterials; bovine hydroxyapatite; compressive strength test; degradation test; glutaraldehyde; infectious disease.

Introduction

Bone defect is a serious condition mostly caused by local trauma. Every year, more than 2.2 million people need surgical procedures to deal with bone defects [1]. Osteomyelitis is the most common complication due to bone defects. Drug delivery to the bone for osteomyelitis therapy is very challenging in the pharmaceutical and orthopedic fields. This is because the oral route is unable to produce sufficient MIC to the bone tissue. On the other hand, the systemic route is potentially toxic to other organs when antibiotic concentration is too high [2, 3]. Thus, the development of biomaterials as an antibiotic delivery system with direct targets on bone tissue is increasing [3].

Bovine hydroxyapatite (BHA) is one of the biomaterials composing bone scaffold with chemical formula and physical properties similar to human bone hydroxyapatite. BHA has a carbonate substitution group on the apatite that distinguishes it from synthetic hydroxyapatite [4]. The carbonate group is known to increase osteoblast proliferation, thus accelerating the synthesis of new bone matrix [5]. Gelatin (GEL) is a polymer similar to bone organic minerals and is useful for supporting apatite crystal formation in the synthesis of new bone matrix [6, 7]. This makes BHA and GEL widely used as scaffold components for bone tissue engineering. Moreover, the BHA-GEL complex is a potential matrix for antibiotics delivery in the treatment of osteomyelitis [3]. Based on the study of Budiatin et al., matrix containing BHA-GEL is known to sustainably release gentamicin (GEN) to inhibit the growth of *Staphylococcus aureus* in a concentration-dependent manner [3].

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However, the addition of antibiotics to the biomaterial weakens the scaffold's mechanical properties causing premature degradation [8]. Therefore, to improve scaffold mechanical properties, a crosslinker such as glutaraldehyde (GTA) is needed to induce chemical bonds in the biomaterial polymer chain [3, 9]. GTA is a dialdehyde compound which has a very reactive aldehydic group. GTA causes covalent bonds with amine or hydroxyl groups on the polymer biomaterial, which increases the scaffold's mechanical strength [3, 9, 10]. In contrast, there is no enough evidence about the impact of GTA on the characteristics of the BHA-GEL-GEN-GTA scaffold. Thus, this study aimed to determine the effect of GTA concentration in BHA-GEL-GEN-GTA scaffolds on compressive strength, degradation (weight loss and swelling profile), and scaffold's toxicity.

Materials and methods

Fabrication of BHA-GEL-GEN-GTA scaffold

Eight grams of BHA (Airlangga University, Indonesia) with 1 g of GEN (Yantai Justaware Pharmaceutical, China) were stirred in the mortar until homogeneous. Then, 20 wt% GEL (Cartino, Thailand) was added in the mixture. After that, GTA (Merck, USA) with solid content of 0.1, 0.2, 0.4, 0.6, 0.8, 1.0 1.2, and 1.4 wt% from GTA 25 wt% was added on the BHA-GEL-GEN by spraying on the mixture while stirring until homogeneous. After forming a dense mass, the BHA-GEL-GEN-GTA mixture was sifted with a mesh size of 1.0 mm. The granules obtained were then dried at 37 °C for 24 h. After that, as much as 100 mg of granules were weighed and pressed into scaffolds.

Compressive strength test

Before the compressive strength was conducted, the scaffold body's diameter and length are measured using a micrometer to calculate the scaffold's surface area. The compressive strength was measured using a calibrated autograph which previously calibrated (Shiamdzu AG-10 TE, Japan). Compressive strength is calculated based on the formula $\sigma = \frac{4F}{(\pi d^2)}$ [11].

Degradation test

The initial scaffold weight (mi) was weighed before the degradation test was conducted. The PBS solution was prepared by mixing 0.7075 g of Na_2HPO_4, 0.118 g of KH_2PO_4, and 0.9 g of NaCl into 100 mL of distilled water. Furthermore, the pH of the solution was checked using a pH meter (PBS solution has a pH of 7.4 ± 0.2). After that, 2 mL of PBS solution was inserted, each into the 5 mL venoject. The scaffold was then inserted into a venoject containing PBS and incubated (37 ± 1 °C). After 1, 2, 3, 6, and 12 h, the scaffolds were taken and dried with filter paper until the PBS fluid on the scaffolds did not remain. After the scaffolds dry, the scaffolds are weighed (m). Next, the scaffold was returned to the venoject containing the new PBS solution and placed in an incubator at 50 °C for four days. After four days, the final scaffold was weighed (md). The percentage of scaffold weight loss and swelling are calculated based on [12]:

$$\text{Weight loss}(\%) = \left(\frac{\text{md} - \text{mi}}{\text{mi}}\right) \times 100,\ \text{Swelling}(\%) = \left(\frac{\text{m} - \text{md}}{\text{md}}\right) \times 100 \quad [12].$$

Here m is the weight of degraded scaffold measured at t time, mi is the initial weight of the scaffold, and md is the final weight of the scaffold (degraded scaffold after drying at 50 °C for four days) [12].

MTT assay

The cell that used for MTT test was BHK-21 fibroblasts. The BHK 21 suspension was placed into a 96-well (50 µL/well) plate and added with DMEM media as much as 100 µL/well. The 96-well plates filled with cells were then incubated in a CO_2 incubator (temperature 37 °C for 24 h). After 24 h, scaffolds that previously smoothed were inserted into each well (2 mg/well). The 96-well plate that already contained BHK 21 cell and scaffold powder then incubated for 24 h. After 24 h, the remaining powder in the well was removed, and the well washed with PBS. Furthermore, DMEM media was added to the well, followed by MTT (µL/well), cells then were incubated for 3 h. After that, DMSO was added to the well (50 µL/well) and incubated for another 5 min. Furthermore, the absorbance (abs) was read by an ELISA reader (Thermo Scientific, USA) at a wavelength of 620 nm. The cell viability was calculated based on [13]:

$$\text{Cell viability}(\%) = \frac{\text{Abs treatment} - \text{Abs media}}{\text{Abs control} - \text{Abs media}} \times 100 \quad [13].$$

Material is non-toxic when the cell viability is more than 50% [14].

Results

A study about GTA concentration on the compression strength and degradation of BHA-GEL-GEN-GTA scaffolds was done. Before the compressive strength test was carried out, a test was conducted to optimize GTA solution volume. There was a significant difference in the scaffolds' compressive strength due to differences in the crosslinker solution volume. The scaffolds that were crosslinked using GTA with solid content of 0.1 wt% in 2 mL solution showed a higher compressive strength than those with the same solid content in 1 mL solution (One Way ANOVA, $p<0.001$; Figure 1A). Similarly, scaffold crosslinked using GTA with solid content 0.2 wt% in 2 mL solution showed a higher compressive strength than those in 1 mL of solution (One Way ANOVA, $p<0.05$; Figure 1A). Thus, the volume of 2 mL GTA solution was used for the next experiment. Moreover, GTA with solid content of 0.6, 1, 1.2, and 1.4 wt% increases the compressive strength of scaffolds (one way ANOVA, $p<0.01$ vs. BHA-GEL-GEN; Figure 1B).

Furthermore, degradation test was carried out to see the effect of GTA concentration on scaffold degradation.

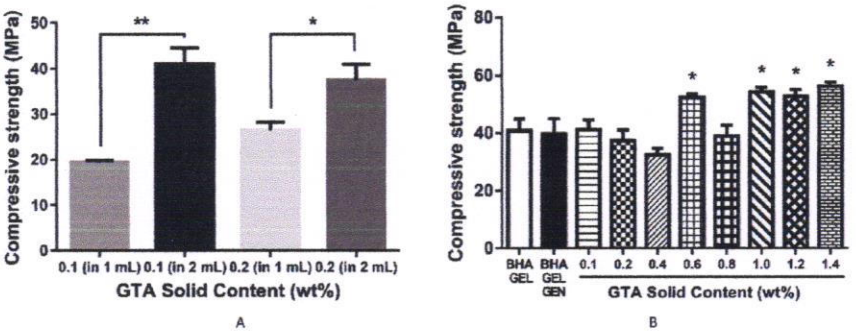

Figure 1: Optimation of the volume of GTA solution on the scaffold's compressive strength. Solid content is the weight of GTA (wt%) to the total weight of the scaffold.
**p<0.001, *p<0.05 (A). The compressive strength test results of scaffolds with different solid content of GTA (all in 2 mL) (B). Each bar represents the mean ± SEM compressive strength of the five scaffolds, *p<0.01 compared to BHA-GEL-GEN. The statistical test used in both figures was ANOVA one way.

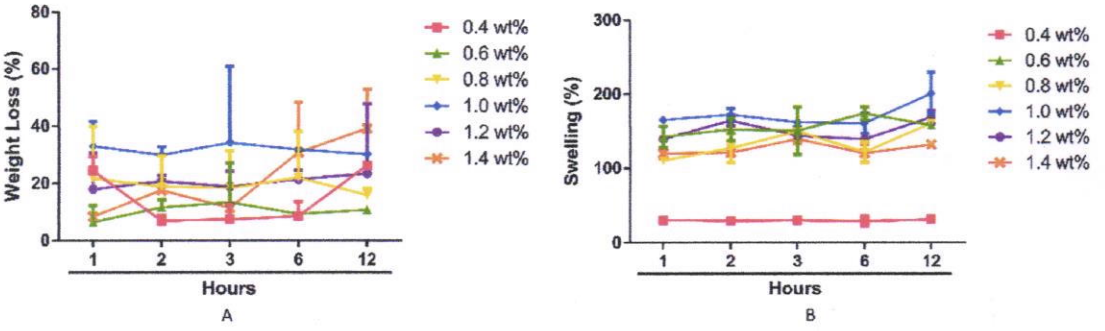

Figure 2: The results of the BHA-GEL-GEN-GTA scaffold degradation test.
Percentage of scaffolds' weight loss (A), percentage of scaffolds swelling (B). Each point shows the mean weight loss or swelling ± SEM of the two scaffolds.

The degradation test results, namely percentage of weight loss and swelling, are shown in Figure 2. Based on the weight loss percentage profile (Figure 2A), the increase in GTA concentration causes an increase in the percentage of weight loss from scaffolds. The scaffold swelling profile shows that the increase in GTA concentration also increases the scaffolds' swelling (Figure 2B).

Considering that GTA is a toxic compound, MTT assay was carried out to examine the effect of GTA concentration on the viability of BHK-21 fibroblast cells. Based on the results, the viability of fibroblast cells in each group was 103.383 ± 7.504, 138.307 ± 8.810, 124.089 ± 11.314, 86.510 ± 2.793, and 96.011% ± 5.588 respectively fot BHA-GEL and BHA-GEL-GEN-GTA with GTA solid content of 0.0, 0.1 and 0.4 wt% (Figure 3).

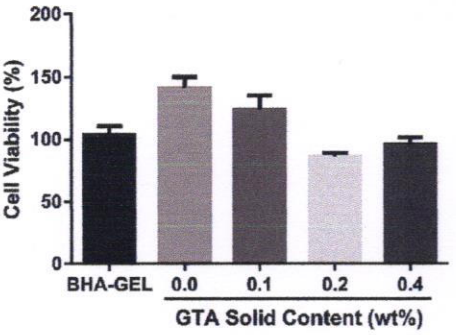

Figure 3: The results of the BHA-GEL-GEN-GTA scaffold toxicity test with different solid content of GTA. All groups tested had cell viability above 50%.

Discussion

GTA is a dialdehyde compound with a very reactive aldehydic group and form covalent bonds with functional groups such as amines and thiols phenols, hydroxyl, and imidazoles [10]. Because of this, GTA is widely used as a crosslinker to increase the mechanical strength of biomaterials [9, 10]. The present study showed that the volume of GTA solution affects the compressive strength of scaffolds, even with the same solid content of GTA. This is possibly because an increase in the volume of solution

increases contact area between the scaffold and GTA, which may speed up the chemical reactions and increase the formation of crosslink. Thus the present data indicates that an increase in GTA solid co[ntent increases the crosslink formed.

The compressive strength test results showed that GTA with solid content of 0.6, 1, 1.2, and 1.4 wt% had higher compressive strength value compared with the group without GTA. This high value in compressive strength may increase the physical performance for clinical use. This is in line with the research conducted by Pinto et al., which states that increasing the concentration of GTA causes an increase in the strength of chitosan-based scaffold [15]. GTA is a compound that highly soluble in water [16]. Therefore, even the compressive strength increase due to the increase in the GTA solid content, does not guarantee the decrease in degradation of the scaffolds in water. Thus, the scaffold degradation test was performed. The test results indicated that an increase in the solid content of GTA led to an increase in the percentage weight loss of scaffolds. Furthermore, the swelling test showed that an increase in GTA's solid content also led to an increase in the percentage of scaffold swelling. This is because an increase in GTA's solid content may increase the volume of water drawn by the scaffold, thereby increasing the percentage of scaffold swelling and weight loss [16]. The swelling capacity of a scaffold is one factor that supports nutrient diffusion and cell adhesion to the biomaterial. However, excessive swelling diminish the scaffold's mechanical integrity, which causes premature degradation before the completion of the new bone matrix synthesis [17]. This may eliminate the scaffold function in bone remodeling. In addition, premature degradation may also be toxic to the bone tissue microenvironment because GTA and the delivered drugs are highly released [9]. In this study, scaffolds that are crosslinked using GTA with solid content of 0.4 wt% had a stable swelling profile with a low percentage of weight loss. Present finding indicates that the scaffold has an excellent capacity to absorb fluid and may not experience premature degradation *in vivo*.

To examine the toxicity of the scaffold, the MTT assay was carried out. Based on the results, the group with 0.0 wt% GTA showed the highest cell viability. This was because there was no GTA present on the scaffold, so the metabolic activity was not disturbed by GTA, thus making cell proliferation run well [10]. Furthermore, the addition of GTA demonstrates cell viability above 50% in the solid content of GTA up to 0.4 wt%. The present data indicates that the addition of GTA to the scaffold may not disturb the activity of cells involved in the bone tissue regeneration. This is in line with the study conducted by Bharatham et al. that the use of 2% GTA as a crosslinker was considered as nontoxic based on MTT assay [18].

Conclusions

The present study found that the increase in GTA solution, the better the efficiency of the crosslink formed. Furthermore, the increase in GTA's solid content leads to an increase in the scaffolds' compressive strength. GTA with a lower solid content showed stable swelling profile with low percentage of scaffold's weight loss. Based on the toxicity test, scaffold with the optimum solid content of GTA is considered as non-toxic. Therefore, BHA-GEL-GEN-GTA scaffold with optimum GTA solid content is potentially investigated in further *in vivo* study with bone infection animal model to test its effectiveness in delivering GEN.

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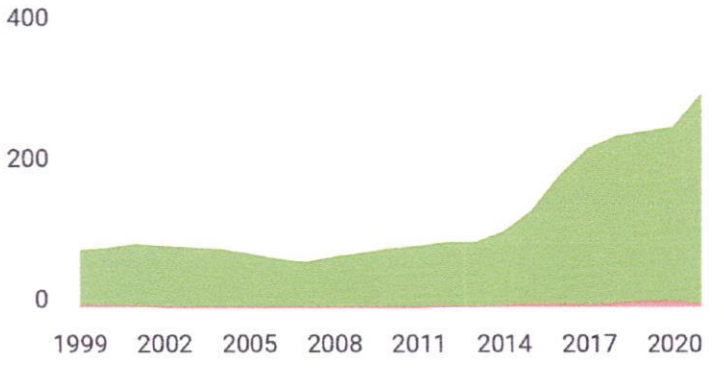

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