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All issues

Samirah, Aniek Setiya Budiatin, Ferdiansyah Mahyudin and Junaidi Khotib*

Fabrication and characterization of bovine hydroxyapatite-gelatin-alendronate scaffold cross-linked by glutaraldehyde for bone regeneration

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Abstract

Objectives: Alendronate are widely used in the treatment of bone disorders characterized by inhibit osteoclast-mediated bone resorption such as Paget's disease, fibrous dysplasia, myeloma, bone metastases and osteoporosis. In recent studies alendronate improves proliferation and differentiation of osteoblasts, thereby facilitating for bone regeneration. The disadvantages of this class are their poor bioavailability and side effects on oral and intravenous application such as stomach irritation and osteonecrosis in jaw. Thus, local treatment of alendronate is needed in order to achieve high concentration of drug. Bovine hydroxyapatite-gelatin scaffold with alendronate was studied. Glutaraldehyde was used as cross-linking agent, increase the characteristics of this scaffold. The objectives of this study were to manufacture and characterize alendronate scaffold using bovine hydroxyapatite-gelatin and crosslinked by glutaraldehyde.
Methods: Preparation of cross-linked bovine hydroxyapatite-gelatin and alendronate scaffold with different concentration of glutaraldehyde (0.00, 0.50, 0.75, and 1.00%). The scaffolds were characterized for compressive strength, porosity, density, swelling ratio, *in vitro* degradation, and cytotoxicity (the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay, shorted as MTT assay).
Results: Bovine hydroxyapatite-gelatin-alendronate scaffold cross-linked with glutaraldehyde showed lower density than without glutaraldehyde. As glutaraldehyde concentration increased, porosity also increased. Eventually, it reduced compressive strength. Swelling ratio and *in vitro* degradation was negatively dependent on glutaraldehyde concentration. In addition, the scaffold has a good safety by MTT assay.
Conclusions: Bovine hydroxyapatite-gelatin-alendronate scaffold was fabricated with various concentrations of glutaraldehyde. The presence of glutaraldehyde on bovine hydroxyapatite-gelatin-alendronate is safe and suitable candidate scaffold for bone regeneration.

Keywords: alendronate; bovine hydroxyapatite; gelatin; glutaraldehyde; scaffold; neglected disease.

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Introduction

Bisphosphonates, a bone resorption inhibitor, are drugs currently used for metabolic bone disease, such as osteoporosis, Paget's disease, fibrous dysplasia, myeloma, and bone metastases [1, 2]. Among bisphosphonates, alendronate (Ale) is a drug that is widely used because it effectively inhibits bone resorption by preventing recruitment and differentiation of osteoclasts. Furthermore, in recent study alendronate also improves the proliferation and differentiation of osteoblast, that can accelerates bone regeneration [3, 4]. In oral administration, alendronate has poor bioavailability (1%). Meanwhile, it is associated with side effects including esophageal irritation and osteonecrosis in jaw [2]. Given these drawbacks, the local administration alendronate through scaffold composite is a promising therapy strategy [1, 5].

Hydroxyapatite (HA) is an inorganic component that naturally present in bone tissue and widely used as a main composite for bone tissue regeneration [6]. Bovine hydroxyapatite (BHA) is a natural HA derived from bovine bone. BHA has carbonates substitution that improved activity of osteoblast [7]. Gelatin is a natural polymer which is similar to the organic components of the bone. Gelatin has biodegradable, biocompatible, and osteoinductive properties [8]. Therefore, BHA and gelatin composite is widely used as scaffolds for bone regeneration. Scaffold composed of BHA and gelatin is easily degraded, therefore need a

crosslink agent such as glutaraldehyde (GA) to improve characteristics of composite [9, 10].

The objectives of this study were to manufacture and characterize of bovine hydroxyapatite-gelatin-alendronate scaffold with various concentrations of GA. The scaffold was characterized for mechanical strength, density, porosity, swelling ratio, *in vitro* degradation and cytotoxicity. The fabrication and characteristic test of the scaffold were carried out to obtain a suitable bone graft candidate for bone regeneration.

Materials and methods

Material

Bovine hydroxyapatite powder was obtained from Teaching Industry of Airlangga University, Surabaya, Indonesia. Alendronate sodium was product of Arshine Technology Co., Limited (Wanchai, China). Gelatin 150 bloom was product from Cartino, Thailand. Glutaraldehyde 25%, KH_2PO_4, Na_2HPO_4, and NaCl were product of Merck Millipore, Germany.

Scaffold fabrication

Eighteen grams of bovine hydroxyapatite was mixed with 200 mg of Alendronate, and a 20 wt% gelatin 150 bloom solution in a warm mortar. After that, the mixture was granulated with a 1 mm sieve in order to obtain uniform size. The granules then were dried in 40 °C oven for 24 h. Then, the dried granules were cross-linked using glutaraldehyde with concentration of 0.00, 0.50, 0.75, and 1.00% for 24 h until the color change to brownish. After that the granules were washed with distilled water to remove the remaining glutaraldehyde, followed with phosphate buffer saline (PBS) at pH 7.4. After that, the granules were dried again in oven 40 °C. Dried granules (100 mg) were weight and pressed into pellets.

Mechanical testing

Mechanical behavior of scaffold cross-linked with glutaraldehyde in different concentration was investigated through compression strength measured using an autograph (Shimadzu AG-10 TE, Japan). The scaffold was pressed with a cross head speed of 5 mm min^{-1} in a cylindrical sample with a diameter of 4 mm and a height of 3 mm. Five samples of each group were used for the compressive strength [11–13].

Density and porosity determination

Density is calculated based on the ratio of dry mass to volume. The porosity of scaffold is determined by weighing the dry mass, then immersing the sample in 5 mL of distilled water for about ±2 min until the sample expands. After that, the filter paper is used to remove the remaining liquid present on the sample. Then the sample is weight again as wet mass. The porosity is the ratio between the difference in wet mass and dry mass divided by the volume of the sample [14].

Swelling ratio

Swelling ability of scaffold was measured based on the previously described method by [15, 16]. The scaffold was immersed in PBS solution (pH 7.4) at 37 °C for 1, 3, 7, 14, and 28 days. Wet samples were wiped with filter paper to remove excess liquid then weighed as wet weight (Ww). After that, the scaffold was dried at 60 °C for 72 h (Wd). Swelling ratio is measured based on equation = (Ww − Wd/Wd) × 100%.

In vitro degradation

Scaffold degradation was carried out by immersing the sample in PBS in order to mimic the body fluids *in vivo*. The initial weight of scaffold is weighed before the degradation test conducted. The degradation test was carried by immersing the scaffold in PBS pH 7.4 at 37 °C for 1, 3, 7, 14, and 28 days. After immersing the scaffold, the scaffold was dried using oven at 60 °C for 72 h. After that, the scaffold was weight as dry weight. Weight loss is the changes of dry weight after immersion and initial weight before immersion [12, 15].

Cytotoxicity test

The MTT assay is used to determine the viability of cells, depend on the cell's ability to metabolically reducing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to formazan. The MTT assay was conducted using Baby Hamster Kidney (BHK)-21 fibroblast cell. Each sample was mixed with 2 mL of media and put into well as much as 50 µL/well. After that, the well then added with culture media of 100 µL/well, and incubated for 24 h (37 °C). Then, samples were washed with PBS and added with MTT solution of 10 µL/well. After incubated for 3 h (37 °C), dimethyl sulfoxide (DMSO) as much as 50 µL/well was added and slowly shaked for 5 min to dissolve the formazan crystals which present in purple. The absorbance was measured with ELISA reader with the wavelength of 620 nm. Cell viability was determined by dividing the viability of treated cells with the controls [17].

Statistical analysis

The data are presented as mean ± standard error of the mean (SEM). The study data were statistically analyzed using software SPSS version 24.0 (SPSS Inc., chicago, IL, USA). The result obtain were submitted to the Shapiro Wilk normality test and One Way analysis of variance (ANOVA). p value less than 0.05 was considered statistically significant. All calculations were performed using GraphPad Prism 6 Software (GraphPad, Inc., San Diego, CA, USA).

Results

Mechanical testing

Mechanical strength is the capacity of a material or structure to withstand loads. Mechanical characterization test using autograph is needed to compress the scaffold until it breaks.

Figure 1 is the compressive test results of scaffold with various concentrations of glutaraldehyde. The compressive strength was 12.080 ± 1.156, 10.666 ± 0.808, 10.449 ± 0.946, 9.122 ± 0.670 MPa for scaffold with GA concentration of 0.00, 0.50, 0.75, and 1.00%, respectively. These results indicated that the presence of glutaraldehyde reduced compressive strength. Increasing glutaraldehyde concentration, reduced compressive test value.

Density and porosity

Density is the ratio between the mass and volume of the substance at a certain temperature and pressure. While porosity is a measure of the empty spaces in a material, that contributes to the cell homing. Based on the porosity and density test, glutaraldehyde concentration affects the scaffold's density and porosity (Figures 2, 3). The density of scaffold with 1.00% GA was significantly different with another scaffold (0.00, 0.50, 0.75% GA) ($p<0.05$). Figure 3 shows the results of the porosity test on the scaffold with different GA concentration. The porosity of the scaffold in GA 0.00, 0.50, 0.75, and 1.00% was 37.837 ± 5.701, 60.914 ± 0.539, 63.306 ± 3.084, and 65.004 ± 4.063%, respectively ($p<0.05$). The result showed that more GA concentration increased the more porosity increased.

Swelling ratio

Swelling ratio is the fractional increase in the weight of the hydrogel due to water absorption. Figure 4 showed swelling ratio of the scaffold with various concentrations of GA after soaking the scaffold in PBS for 28 days. All groups experienced cracks starting on day one, and there was an increase

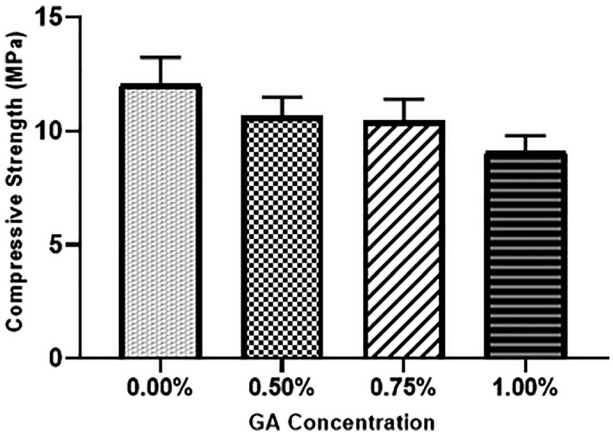

Figure 1: Compressive strength of scaffold with 0.00, 0.50, 0.75, and 1.00% GA.

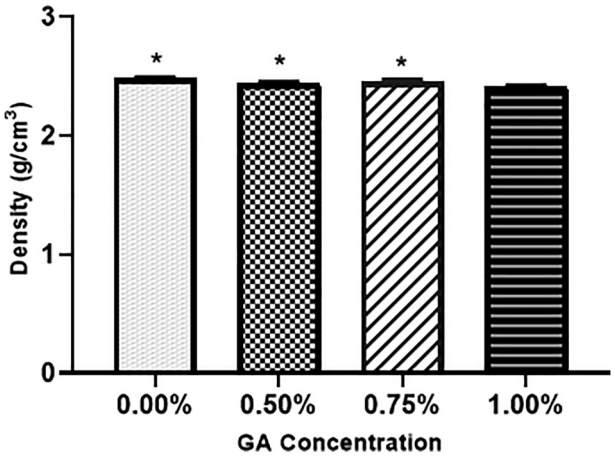

Figure 2: Density of four different scaffold as a function of the addition of glutaraldehyde (GA 0.00%, GA 0.50%, GA 0.75%, GA 1%) (*$p<0.05$ compared with 1.00%).

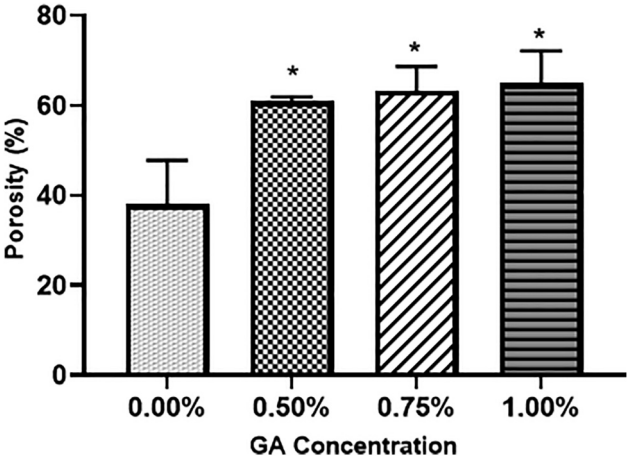

Figure 3: Porosity of four different scaffold as a function of the addition of glutaraldehyde (GA 0.00%, GA 0.50%, GA 0.75%, GA 1%) *$p<0.05$ compared with 0.00%.

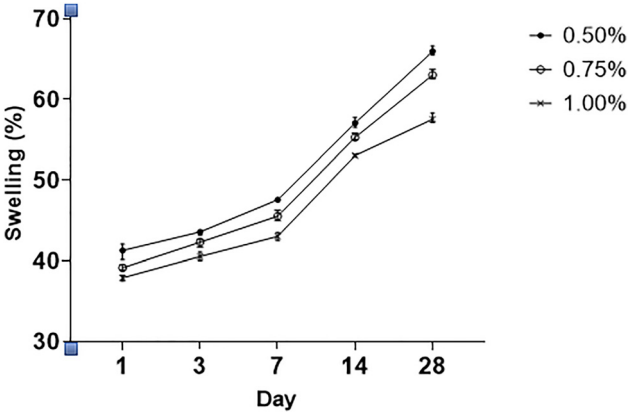

Figure 4: Swelling of scaffold crosslinked with various amount of glutaraldehyde concentration after immersion in PBS pH 7.4 at 37 °C for 28 days.

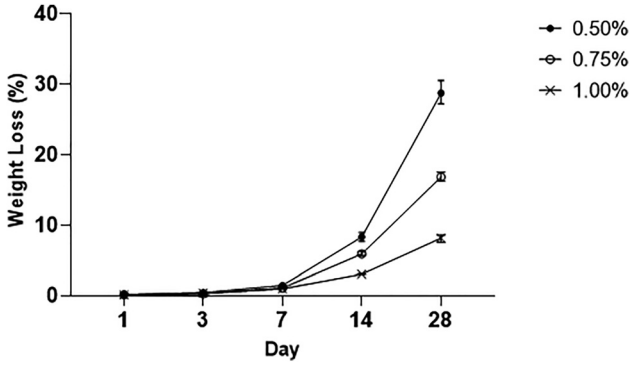

Figure 5: Weight loss of scaffold crosslinked with various amount of glutaraldehyde concentration after immersion in PBS pH 7.4 at 37 °C for 28 days.

after day seven and sharply increased from day 14 to day 28. Scaffold with 0.50% GA showed the highest swelling ratio. Cumulative swelling results on day 28 for scaffold 0.50, 0.75, and 1.00% were 65.963 ± 0.318, 63.040 ± 0.365, and 57.543 ± 0.389%, respectively ($p<0.05$).

In vitro degradation

Degradation is gradual decomposition of a material. Figure 5 showed the scaffold's weight-loss after immersion in PBS pH 7.4 for 1, 3, 7, 14, and 28 days. All samples showed additional weight-loss during the time period. The curves were divided into three groups with different concentrations of GA. In the first group, the weight-loss of scaffold with 0.50% GA increased after day seven of immersion and got sharper after the 14th and 28th days. Another group was GA 0.75 and 1.00% show similar profile with first group. The cumulative weight-loss on day 28 for scaffold with GA concentration of 0.50, 0.75, and 1.00% GA scaffold were 28.727 ± 0.954, 16.800 ± 0.369, and 8.150 ± 0.315%, respectively. The minimum weight-loss was in the scaffold with 1.00% GA ($p<0.05$).

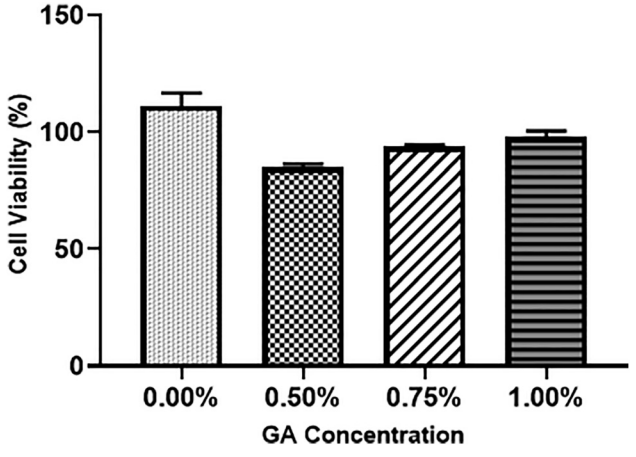

Figure 6: Result of cell viability study (MTT assay).

Cytotoxicity

Cytotoxicity is the property of the chemicals that is harmful to living cells. Figure 6 shows the results of the cytotoxicity test using BHK 21 fibroblasts. The results of cell viability with various GA concentrations showed no toxic effect because the viability was above 50%. The highest cell viability was shown in the sample with GA level of 1.00%. The MTT assay was correlated with cell proliferation and mitochondrial function, the loss of cell viability was indicated by decreased MTT measurement [18].

Discussion

In this study, scaffold bovine hydroxyapatite-gelatin-alendronate containing alendronate with varying levels of GA as crosslink agent was successfully designed. The characteristic properties of these scaffolds were provided. Furthermore, there was a decrease in the scaffold's compressive test, along with the increase in GA concentration (Figure 1). Higher GA concentration allowed gelatin chain to react with more GA molecules that causes more fragile [19]. The compressive test obtained in this study from 9.122 ± 0.670 to 12.080 ± 1.156 MPa, in line with the compressive strength for femoral bone (9.3 ± 4.5 MPa) [8] and compressive strength for spongy bone (4–12 MPa) [19].

As shown in Figures 2, 3, density was negative dependent to the porosity. The porosity of the scaffold with various concentrations of GA ranges from 60.914 ± 0.539 to 65.004 ± 4.063%, this corresponds to scaffold with high porosity of 50–65%. Scaffold without GA have 37.837 ± 5.701% porosity, appropriate to scaffold with low porosity of 35–45% [20]. The density of the scaffold affects mechanical strength, permeability, and the presence of structural defects. Porosity is an important parameter that defines the properties of biomaterials obtained [6]. Increase of porosity caused a decrease in compressive strength otherwise higher density contributes to higher mechanical strength [8]. High porosity provides a biological environment for proliferation, differentiation, and cell function that benefit the scaffold [21]. Therefore, it is necessary to balance between porosity and density of the scaffold to established specific application [8].

In this study, the swelling ratio showed that all samples with GA experienced cracks. The longer scaffold immersed in PBS, the more water absorbed. This could be because during the immersion process, the scaffold formed a lot of capillary

cavities that could cause PBS to enter and disrupt the bonds between the constituent compositions and then decrease the integrity [1, 15]. Swelling of scaffold facilitates cell adhesion, cell internalization and increases nutrient diffusion, which is the basis for enhancing tissue regeneration [21]. Concentration of glutaraldehyde is inversely proportional with swelling ratio. Porosity is a characteristic related to the swelling ratio. In general, when the scaffold has high porosity, the swelling ratio will also increase. However, different things happened in this study; the porosity test results compared the best with the swelling ratio test results. This may happen because of the effect of alendronate in the formulation. Alendronate formed strong chemical bonds through the phosphonate groups and the calcium ions. These chemical bonds might prevent the excessive swelling of the scaffold [22]. Scaffold with GA 1.00% showed the lowest swelling, is the most suitable one for scaffold application. In line with research conducted by Bigi et al. (2001), that the higher the concentration of glutaraldehyde will reduce the amount of water absorbed [23].

The degradation test results showed that weight-loss inversely related to the concentration of glutaraldehyde [16]. It was found that the scaffold with GA 0.50% had a more reduction in weight (28.727 ± 0.954). Whereas scaffold with GA 0.75 and 1.00% had a degradation for 28 days of 16.800 ± 0.369 and 8.150 ± 0.315%, respectively. The result is consistent with the research of Wang et al. 2009 that indicates that there is good degradation of the scaffold. As the scaffold begins to degrade, it is replaced by a new bone matrix, which can accelerate the bone regeneration process. When the degradation rate of the scaffold equal with the rate of osteogenesis, the scaffold can accelerate the process of regeneration [21].

The MTT test (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) is based on the conversion of MTT to formazan crystals by living cells, which determines mitochondrial activity. Because for a large part of the cell population, the total mitochondrial activity is related to the number of viable cells [18]. The cytotoxic value was determined based on the IC50 concentration required to achieve 50% growth inhibition compared to the growth of the control [24]. All scaffold synthesized in this study showed an increasing trend of formazan absorbance (Figure 6), thus suggesting an increase in glutaraldehyde concentration by up to 1.00% increased cell proliferation.

Glutaraldehyde is a toxic agent at high concentrations [25]. Several studies that have been conducted by other researchers, including those of Gao et al., stated that the scaffold soaked and washed with the GA cross-link agent concentration of 1 and 2.5% had a toxic effect on chondrocyte cells [26]. The safe and optimal GA concentration is used as a cross-linking agent in the concentration range of 0.5–2% [19]. This study indicated that scaffold with GA 0.50–1.00% does not negatively affect cell proliferation, it can maintain cyto-compatibility properties and achieve good mechanical properties.

Conclusions

Bovine hydroxyapatite-gelatin-alendronate scaffold was fabricated with various concentrations of glutaraldehyde. An increase in GA will increase the scaffold's porosity, which causes a decrease in compressive strength. The swelling test and *in vitro* degradation test are inversely proportional to the increase in GA. All samples showed non toxicity based on cytotoxic assays. Based on these results, the presence of GA in bovine hydroxyapatite-gelatin-alendronate is safe and suitable candidate scaffold for bone regeneration.

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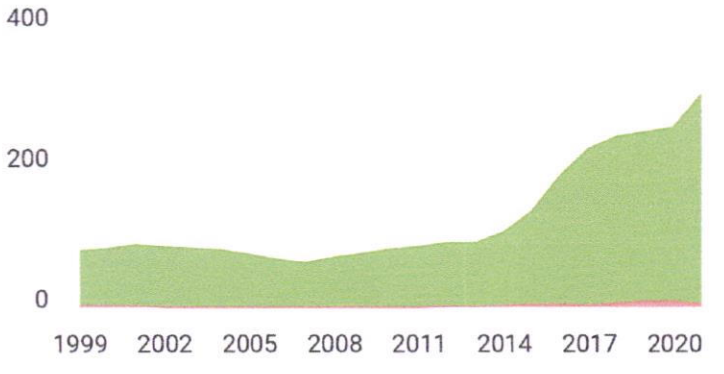

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